Pediatric Dialysis

Bradley A. Warady
Steven R. Alexander
Franz Schaefer
Editors

Third Edition

Springer

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We thank our families for the support they provide us.
We thank our colleagues for the insight they share with us.
We thank our patients for the trust they have in us.

The editors

Preface

The provision of optimal dialysis therapy to children requires a thorough understanding of the multidisciplinary way the pediatric patient is affected by kidney failure. It was based on this philosophy that the inaugural edition of *Pediatric Dialysis* was published in 2004 and the second edition in 2012. Thankfully, the care of pediatric patients requiring dialysis has continued to improve, in large part the result of our ever-increasing understanding of the many factors which play a significant role in defining patient outcomes. We, in turn, believe that enhancement of the content of our text from nearly a decade ago is imperative so that *Pediatric Dialysis* may continue to serve as a contemporary, comprehensive, and authoritative source of information that can not only help facilitate the provision of superb patient care by seasoned clinicians, but can also help meet the demand of our young trainees for the information that they require as a foundation for the future advances that they will surely initiate.

To that end, we have been fortunate once again to successfully enlist the expertise of experts from around the globe to provide superb contributions to the third edition of *Pediatric Dialysis*. One-hundred authors either updated chapters from the second edition or created all new content designed to reflect essential elements of current clinical management strategies. The inclusion of several new chapters on topics such as *Antibiotic Stewardship in the Pediatric Dialysis Unit, Infectious Complications of Hemodialysis in Children, Remote Patient Monitoring in Peritoneal Dialysis, Ethical Decision Making in Children with End-Stage Kidney Disease and The Spectrum of Lived Experience: The Patient Experience* has resulted in a text which remains the most comprehensive source of state-of-the-art information on the dialysis of infants, children, and adolescents currently available. To all the authors, we are eternally grateful for their commitment to this project.

We have been humbled by the encouragement of our colleagues to publish this third edition. However, as clinicians ourselves who have spent many hours over the past four decades on hospital wards, in the intensive care unit, and in the dialysis unit applying what we have learned from the documented experience of others, we know that this text is a unique source of the knowledge and ingenuity exhibited by the global pediatric nephrology community and, as such, cannot help but to serve as a valuable tool with a singular

emphasis on successfully caring for our challenging patient population. If that goal can be achieved through the publication of the third edition of *Pediatric Dialysis* and even one child benefits from our combined efforts, it will all have been worthwhile.

Kansas City, MO, USA — Bradley A. Warady
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Contents

Part V Management of Secondary Complications of Chronic Dialysis

Part VI Drugs and Dialysis

Part VII Outcome of Chronic Dialysis

Part VIII Special Indications, Techniques and Applications

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Part I

Essential Primers

Notes on the History of Dialysis Therapy in Children

1

Steven R. Alexander and Pierre Cochat

Introduction

Prior to the 1950s and 1960s, the study and management of disorders of the kidney was the province of general physicians. As described by Stuart Cameron, along with the introduction of the renal biopsy and its interpretation, the introduction of dialysis was "…an important motor which accelerated the emergence of nephrology as a specialty. Suddenly there was a need for specialist knowledge to apply the complex data from the increasing number of critically ill patients who survived their primary disease only to go into acute renal failure…" [1, 2]. When long-term dialysis became possible in the 1960s, hundreds of adult dialysis units sprang up in North America and Europe, and by the 1970s, nephrology had become "…an autonomous specialty with an uneasy relationship to general internal medicine. There is no doubt that those physicians who chose to make dialysis their principal interest were to some extent a breed apart…" [1].

In contrast, the discipline of pediatric nephrology emerged in response to different drivers. Based in the classic work of pediatric physiologists on fluid and electrolyte metabolism, regulation of intracellular and extracellular fluid, acid-base homeostasis, and parenteral fluid therapy, the first generation of pediatric nephrologists who arose in the 1950s and 1960s were rarely exposed to the care of children with acute or chronic renal failure [3, 4]. It is emblematic that the early starting point of pediatric nephrology as a specialty is traced by many to the organization of the International Study of Kidney Disease in Children (ISKDC) in the 1960s, which was a study of childhood nephrotic syndrome [1]. Early pediatric nephrologists rarely cared for children suffering what is now called acute kidney injury (AKI), a role more often played by pediatric surgeons. Those who cared for children with what is now known as chronic kidney disease (CKD) focused on dietary restrictions and diuretic, antibiotic, and electrolyte therapy, attempting to ease the progression to end-stage kidney disease (ESKD). When ESKD was reached, older children and adolescents often had to look to adult ESKD programs for access to chronic dialysis and transplantation; infants and younger children were frequently offered only palliative care [5].

During the past six decades, the landscape has changed dramatically. Acute and chronic dialysis is now routinely available for children throughout the world, and the study of dialysis therapy and the disordered physiology of the pediatric patient with AKI or ESKD has come to occupy a prominent if not dominant place in pediatric

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nephrology research [4]. Pediatric nephrology training programs worldwide are expected to teach trainees how to dialyze children of all ages, and modern pediatric nephrology training program graduates come equipped with technical skills unimagined by the founders of the specialty. With increasing acceptance of universal access to dialysis therapy for children has come a concomitant growth in the demand for pediatric nephrologists, leading to a steady increase in the size of pediatric nephrology programs. Unlike adult dialysis programs, many of which long ago separated from their academic roots, pediatric dialysis programs remain firmly grounded in university medical centers and medical school-affiliated children's hospitals, a fortunate association that has promoted a culture of scientific inquiry in what easily could have become a purely technical and derivative discipline.

In this chapter we have attempted to briefly review selected high points in the development of dialysis therapy for children, focusing on the ingenuity and resourcefulness of some of these early pioneers. It is an exciting story. We have left a detailed description of these innovations to the chapters that follow. Our goal is to place these advances in historical context, acknowledging the debt owed those pioneering pediatric nephrologists, nurses, engineers, dieticians, and social workers and their young patients and their families. All have helped make a complex and life-sustaining therapy a part of routine medical management for children throughout the world.

Peritoneal Dialysis

The roots of the use of peritoneal dialysis (PD) in children can be traced to the use of the peritoneal cavity to treat dehydration in infants. In 1918, two Johns Hopkins pediatricians, Kenneth Blackfan and Kenneth Maxcy, first described the successful fluid resuscitation of dehydrated infants using intraperitoneal injections of saline solution [6]. At that time, dehydrated infants too small or dehydrated to permit intravenous access were treated by "clysis," injecting fluids into the subcutaneous tissues. Blackfan and Maxcy noted that clysis was often disappointing, because "… absorption from the subcutaneous tissues is often very slow and after repeated injections is almost nil…." Injection of physiologic sodium chloride solution directly into the peritoneal cavity was "…simple…practicable and accompanied by a minimum of risk to the patient…" [6]. These same characteristic features, simplicity, practicality, and safety, have made peritoneal dialysis particularly well suited for use in children for the past 100 years.

The 1949 experience of Henry Swan and Harry H. Gordon should be credited as the first conclusive demonstration of the lifesaving potential of PD when used to treat acute renal failure in children [7]. These pioneering Denver pediatric surgeons employed continuous peritoneal lavage to treat three acutely anuric children, 9 months, 3 years, and 8 years of age. Rigid surgical suction tips covered by metal sheaths with multiple perforations were implanted into the upper abdomen and pelvis allowing large volumes (~33 liters/day) of sterile, physiologic Tyrode's solution to flow by gravity from 20-liter carboys continuously into and out of the abdomen. Ultrafiltration was controlled by adjusting the dextrose concentration between 2% and 4%, while dialysate temperature was regulated by changing the number of illuminated incandescent 60-W light bulbs in a box placed over the inflow tubing. The two older children regained normal renal function and survived after 9 and 12 days of peritoneal lavage; the infant was sustained for 28 days, but did not regain renal function and succumbed to obscure complications. Peritonitis occurred only once and responded to intraperitoneal antibiotics. Removal of urea and maintenance of fluid balance were successful in all three children, although obviously herculean efforts were required to deliver this therapy [7]. Although impractical and technically difficult to deliver, the continuous peritoneal lavage of Swan and Gordon should be credited as the first conclusive demonstration of the lifesaving potential of PD when used to treat acute kidney injury (AKI) in children.

It was more than a decade before the use of PD in children was again reported. During the

1950s and early 1960s, the development of disposable nylon catheters [16] and commercially prepared dialysis solutions led to the replacement of continuous peritoneal lavage techniques with intermittent forms of PD, allowing the routine use of peritoneal dialysis as a treatment for AKI and some intoxications in adults [8–11]. These methods were adapted for use in children in the early 1960s by teams in Indianapolis and Memphis [12, 13] who also showed how PD could be effective in the treatment of the boric acid and salicylate intoxications commonly seen in small children at that time [14, 15]. Subsequent reports established PD as the most frequently employed renal replacement therapy (RRT) for AKI in pediatric patients [16–22]. Compared to hemodialysis (HD), PD appeared ideally suited for use in children. It was intrinsically simple, practical, safe, and easily adapted for use in patients of all ages and sizes, from premature newborn infants to fully grown adolescents. In contrast, HD at this early stage of development required large extracorporeal blood circuits and vascular access that was difficult to achieve and maintain in pediatric patients (see later in this chapter).

Although successful as a treatment for AKI, early PD techniques were poorly suited for the child with ESKD. The need to re-insert the dialysis catheter for each treatment made prolonged use of PD in small patients problematic. In the largest published pediatric series from the disposable catheter period, Feldman, Baliah and Drummond maintained seven children, ages 6–14 years on intermittent peritoneal dialysis (IPD) for 3.5–8 months while awaiting transplantation [23]. Treatments were infrequent, ranging from every 7–12 days to every 4–12 weeks. Although complications were few, at the time of the report, two children had died, two had been transferred to HD, and three remained on PD; no child had been successfully transplanted [23].

More than any other advance, it was the development of a permanent peritoneal catheter that made long-term PD an acceptable form of treatment for pediatric patients. First proposed by Palmer, Quinton, and Gray in 1964 [24] and later refined by Tenckhoff and Schechter in 1968 [25], the permanent PD catheter revolutionized chronic PD for adults and children in the same way the Scribner shunt transformed chronic HD, both making long-term renal support therapy possible. In Seattle, the new permanent peritoneal catheters were combined with an existing automated dialysate delivery system that had been designed by Boen, Mion, Curtis, and Shilipetar for use in the home [26, 27]. In the early 1970s, this work culminated in the establishment in Seattle of the first pediatric chronic home PD program [28]. The success of the Seattle program throughout the 1970s showed that chronic IPD could be a practical option for some children with ESKD [29].

Additional limited experience with chronic IPD was reported from several other pediatric centers [30–33], but enthusiasm for the technique was limited. Chronic IPD seemed to involve many of the least desirable features of chronic HD, including substantial fluid and dietary restrictions, immobility during treatments that lasted many hours, and the need for complex machinery requiring parental or nursing supervision, without providing the efficiency of HD. Moreover, it became clear from efforts to maintain adult ESKD patients on chronic IPD that long-term technique survival was not often achieved [34]. Inadequate dialysis resulting in severe undernutrition and frequent peritonitis were cited as the most common causes of IPD failure in the 1970s, leading to widespread reliance on HD among adult dialysis programs and limited access to chronic dialysis for children, especially infants. Pediatric dialysis and transplant programs at the time routinely excluded infants and small children, reasoning with Hurley that "…although it is technically possible to perform hemodialysis and transplantation in these children, the myriad of well-known problems… should contraindicate such therapy…" [35], and with Reinhart, "…we may find the price the child pays for life too great…" [36]. During a period in which advances in ESKD therapy pushed the upper age limits for successful therapy well into the seventh and eighth decades, the youngest ESKD patients remained therapeutic orphans, considered by many to have severely limited chances for survival [36, 37].

The description of what became known as continuous ambulatory peritoneal dialysis (CAPD) by Robert Popovich and Jack Moncrief and associates in 1976 heralded a new era in the treatment of ESKD in children [38]. As originally described, 2 liters of dialysate were infused into an adult's peritoneal cavity and retained for 4–5 hours, then drained, and repeated a total of five times per day while the patient went about regular daily activities [39]. As early experience with CAPD in adults was analyzed by pediatric nephrologists, it became clear that this new modality offered theoretical advantages to children when compared to HD and IPD that included near steady-state biochemical control, no disequilibrium syndrome, greatly reduced fluid and dietary restrictions, and freedom from repeated dialysis needle punctures. CAPD allowed children of all ages to receive dialysis at home, which offered a more normal childhood. And for the first time, CAPD made it possible to routinely provide chronic dialysis for infants and small children, which meant that this population could now be safely maintained on CAPD until they reached a transplantable age and size.

The first child to receive CAPD was a 3-year-old girl in Toronto in 1978 [40, 41]. Although a number of pediatric dialysis programs in North America [42–45] and Europe [46, 47] quickly followed suit, enthusiasm in many areas was tempered by the availability of dialysis fluid only in 2000-mL containers. In Canada, small-volume plastic dialysis fluid containers were provided by Baxter, Inc. soon after the first pediatric CAPD patients were trained there in 1978, but it would be another 2 years before small-volume containers became available in the United States and the rest of the world [48].

During the 1980s, the popularity of CAPD for children spread worldwide [49]. In Japan, where transplantation was less common due to religious prohibitions on organ donation, Masataka Honda and other pioneers established large CAPD programs that demonstrated the long-term capabilities of the modality in children [50]. Pediatric nephrologists in developing countries soon realized that CAPD was relatively affordable, which meant that ESKD was no longer an inexorably lethal condition for children from families with limited resources [51–53], and throughout the world, the survival of so many more children with ESKD increased demand for the multidisciplinary pediatric specialists required to care for them.

The next big step in the evolution of PD for children was the resurgence of automated cycling machinery. As we have seen, during the 1960s and 1970s, automated PD machinery was used to deliver chronic IPD, but treatments were infrequent, with patients often receiving three PD treatments per week, usually for 12 hours overnight. Following the success of CAPD, in the early 1980s, quality of life issues made a revival of interest in automated PD inevitable in those countries where it could be afforded. The CAPD technique required interruption of daily activities several times each day for dialysis exchanges; how much easier and less intrusive it would be to relegate dialysis to nightly exchanges performed by automated cyclers while the patient and family slept.

The first reports of an automated dialysis fluid cycling device adapted to provide "continuous" cycler PD (CCPD) were published in 1981 by groups in Charlotte, North Carolina, and Houston, Texas [54, 55]. The technique maintained the principle of continuous PD by cycling dialysate exchanges through the night and leaving an exchange in place during the day. CCPD was first shown to work in a pediatric patient by the Houston group in 1981 [55]. Soon, CCPD became extremely popular among pediatric dialysis programs in developed countries worldwide [56–61].

During the late 1980s, improvements in renal transplantation increased renal allograft and patient survival rates so dramatically in children that all forms of dialysis were viewed even more as a bridge to get children safely to or between kidney transplants [56]. The ready availability of potent vitamin D analogues, ESKD-friendly phosphate binders and nutritional supplements and formulas, controlled enteral nutrition via gastrostomy or nasogastric tubes, recombinant human erythropoietin, and recombinant human growth hormone (see Chaps. 26, 27, 28, 29, 30, 31, and 32) gave pediatric nephrologists a power-

ful armamentarium with which to bring the child on chronic dialysis safely to transplantation in relatively good condition. Attention could then be turned to quality of life issues, scholastic and emotional development, and child and family psychosocial adjustment to the rigors of ESKD and chronic dialysis (see Chaps. 34 and 35).

Before 1982, fewer than 100 pediatric patients had been treated with CAPD worldwide, and CCPD for children was virtually unknown. During the ensuing three decades, continuous forms of PD became available in pediatric dialysis centers throughout the world. Regional, national, and international multicenter study groups and registries developed during this period have since added much to our knowledge of peritoneal dialysis in children [57–62]. These efforts have spawned an extensive series of clinical guidelines and treatment options that will be discussed in many of the chapters that follow.

Hemodialysis

The clinical use of an "artificial kidney" was pioneered in 1944 in adult patients suffering from acute renal failure by Willem J. ("Pim") Kolff [63], a Dutch physician in Nazi-occupied Holland during the Second World War. Kolff's interest in dialysis grew from his experiences caring for young patients with renal failure for whom treatment options were essentially nonexistent at that time [64]. Prior to Kolff's remarkable invention, the stage had been set for the introduction of an extracorporeal dialysis device by the availability of two key elements: heparin and cellophane.

Heparin was first purified from an extract of liver tissue in 1916 by a second year medical student at Johns Hopkins, Jay MacLean, working in the laboratory of a prominent hematologist, William H. Howell [65]. Heparin rapidly replaced hirudin, a naturally occurring, but often toxic, anticoagulant extracted from the heads and gullets of leeches.

The basis for cellophane is cellulose, a substance first purified from wood in 1885. Cellophane had been available since 1910 as sheets of cellulose acetate used in the packing industry; in addition, it had the necessary qualities of a good dialysis membrane: it could be easily sterilized without injury to the material and had a long shelf life. When cellophane tubes became widely available as sausage casings in the 1920s, studies in animals showed the casings also made excellent diffusion membranes [66]. Clinical application of cellophane and heparin in the construction of a dialysis device awaited Kolff's invention of the rotating drum kidney in 1944.

Pediatric application of the Kolff artificial kidney was first reported in 1950 by John Merrill and his colleagues in Boston who included a 3 1/2-year-old boy with nephrotic syndrome in their initial series of 42 adult patients dialyzed using a rotating drum machine essentially the same as Kolff's original design [67].

As described by Merrill: "…blood is led from the radial artery by means of an inlying glass cannula through a rotating coupling to the surface of a revolving metal drum. Here it passes through a length of cellophane tubing (~20 meters) wound spirally around the drum, and is carried by the motion of the drum to the distal end. During its course, the blood-filled tubing is passed through a rinsing fluid maintained at a constant temperature of 101 degrees F in a 100 liter container. Into this medium, diffusion from the blood takes place through the cellophane membrane. Distally, the blood is passed through a second rotating coupling, and pumped to inflow flasks, whence it is fed by gravity to a vein in the forearm through another inlying cannula…." [67]

Merrill's pediatric patient received a single 4-hour dialysis treatment and was said to have had "…modest improvement, but of short duration…" [67].

In 1955, FM Mateer, L Greenman, and TS Danowski described their experience at the Children's Hospital of Pittsburgh with eight hemodialysis treatments in five severely uremic children, 7–15 years of age, all of whom were "…either stuporous or confused... overbreathing present in three of the five… (one child) had developed pulmonary edema, and convulsions

had appeared in (two children)…" [68]. Their equipment was built by the Westinghouse Company based on an Alwall coil kidney design [69]. Alwall's coil kidney in effect turned Kolff's rotating drum on its end submerging the coils of cellophane tubing completely in the dialysate bath. Mateer's version of the coil kidney was more compact than the Kolff machine, consisting of ~15 meters of 1 1/8-inch cellophane tubing wound on stainless steel screens submerged in a warmed 32-liter bath of dialysate. An in-line roller pump propelled heparinized blood through the tubing from the radial artery through the cellophane coils to return via the saphenous vein. Dialysate consisted of Pittsburgh tap water to which was added sodium, calcium, chloride, bicarbonate, glucose, and variable amounts of potassium; a fresh batch was mixed every 200 minutes, and with every bath change, an antibiotic (usually oxytetracycline) was injected into the tubing leading to the artificial kidney [68].

For these severely uremic children, hemodialysis was clearly a heroic treatment that was surprisingly effective, if only temporarily. After treatments lasting 2–13 hours, all patients became more alert, pulmonary edema and overbreathing improved, phosphorus levels fell, and blood nonprotein nitrogen levels decreased from an average of 231 to 113 mg/dL. Two of the five children survived, one recovering normal renal function after an episode of what may have been hemolytic uremic syndrome ("...previously well... bloody diarrhea...oliguria, albuminuria, profound anemia..."). Mateer concluded that, while dialysis had been successful in supporting this child's reversible ATN, "...in view of the difficulty in assessing elements of reversibility of renal failure in chronic states, more frequent use of dialysis is indicated in these situations..." [68].

In 1957, Frank H Carter and a team at the Cleveland Clinic that included Willem Kolff, who had emigrated to the United States in 1950, next described eight HD treatments in five children (2–14 years of age) using an improved and disposable Alwall twin coil kidney that could be modified for children <20 kg by using only one of the two coils, thereby reducing the priming volume from 750 ml to 400 ml [70]. The coils sat in the warmed rinsing bath with rinsing fluid circulating over the blood-filled cellophane tubing. Vascular access was via a large-bore polyvinyl catheter inserted into the inferior vena cava via a saphenous vein cutdown with return of dialyzed blood to a large vein in the arm. Roller pump speed was 200–400 ml/min. Catheters remained in place until the child died or recovered sufficient renal function to no longer need dialysis [70].

Four of the five children survived, including a 2-year-old boy with probable acute post-infectious glomerulonephritis who presented anuric with a blood urea nitrogen (BUN) of 322 mg/dL. Carter noted that "...in the hands of a well-trained team, hemodialysis is not only helpful in producing a smoother course in these children, but it may also be lifesaving..." [70].

Unlike the concise and constricted prose demanded by modern journal editors, the papers by Mateer and Carter published more than 60 years ago are wonderfully detailed, conveying the intensity and drama that must have attended these early pediatric HD sessions. While some laboratory testing was available, management decisions relied primarily on clinical judgment. Presaging modern use of aggressive RRT in critically ill children, Mateer concluded that:

"...the relative safety of the procedure (hemodialysis) warrants an increased use in uremic patients whose prognosis has been considered hopeless, with the goal that time will thereby be provided for recovery for those who have reversible lesions...." [68]

Intoxications with salicylates or barbiturates represented another potential use for HD in children [71]. However, while potentially lifesaving in cases of reversible AKI or intoxications, the role of periodic HD in the management of irreversible renal failure in children faced daunting technical challenges, the first of which was the absence of a reusable vascular access. This problem was first solved in 1960 by Belding Scribner and the team in Seattle with the development of a Teflon^{R}-Silastic shunt that still bears his name [72]. The Scribner shunt consisted of Silastic-Teflon^{R} cannulas inserted in the radial artery and

a nearby forearm vein that were connected to each other between dialysis treatments and could be separated and connected to the arterial and venous tubing of a dialysis apparatus. Smaller versions of the Scribner shunt were soon adapted for use in children [73], and by the mid-1960s, the availability of repeated vascular access via these shunts made chronic HD in children a reality.

Using a pumpless system developed for pediatric patients by Robert Hickman and Belding Scribner in Seattle in the early 1960s [74], the first large pediatric chronic HD programs were established in Seattle [75], San Francisco [76], Los Angeles [77], Minneapolis [78], London [79], and Paris [80].

The San Francisco experience is illustrative of the problems encountered and overcome by these pioneering pediatric centers during this early period, so critical to the successful adaptation of chronic HD for children. In a report summarizing their initial experience from 1966 to 1969, Donald Potter and his associates at San Francisco General Hospital described the chronic HD provided to 14 children 2–16 years of age weighing 10–52 kg [76]. Time on dialysis ranged from 1 to 27 months, with five children receiving dialysis at home. For the first 3 years of the pediatric dialysis program, children were selected for dialysis in competition with adult patients by a committee, a stark reminder of the earliest days of chronic HD when the scarcity of this resource forced painful decisions into the hands of so-called Life and Death Committees [81]. By 1969, a separate pediatric unit had been created in San Francisco, and children were accepted "...on a first-come, first served basis if they were medically stable..." [76].

Using the Seattle pumpless method, Potter's patients were dialyzed thrice weekly primarily using the recently introduced flat plate dialyzers and an automated dialysate delivery system. The basic flat plate device, known as a Kiil kidney [82], consisted of two grooved polypropylene plates clamped tightly together and separated by a sheet of cellophane. Blood flowed through the enclosed dialyzer down the grooves on one side of the cellophane membrane across from dialysate flowing in the grooves of the plate on the other side of the membrane in a counter-current direction. One or more of these membrane "sandwiches" could be clamped together to construct the dialyzer. The parents of the children treated at home in the early days of the program were required to construct a Kiil dialyzer for every treatment (Donald Potter, MD, personal communication, 2011).

Vascular access was via an arteriovenous shunt originating in either the radial, brachial, posterior tibial, or femoral artery. Extracorporeal volume during treatment averaged 14% of estimated blood volume, and blood loss with each treatment was 20–40 mL. Transfusions were given when the hematocrit fell to <15%, leading to a mean transfusion requirement of 0.5 unit of packed red blood cells per month. The highest dialyzer clearance available was 128 mL/minute, and because of this low clearance, five of the children were dialyzed 18–27 hours per week. Dialysis prescriptions were adjusted according to the pre-dialysis BUN, which averaged 70–86 mg/dL [76].

There were many complications, including hemodynamic decompensation, shunt clotting and infection, anemia, hypertension, renal bone disease, congestive heart failure, uremic pericarditis, and growth delay. Despite these difficulties, there was only one death, and at the time of the 1970 report, seven children had received a successful kidney transplant. Looking back on his early experience, Potter recalled that although HD in 1970 appeared to be a potentially successful therapy for some uremic children, there were many who doubted its technical problems could be overcome sufficiently to allow its routine use in children. According to Potter, three major subsequent advances turned the tide: (1) improved vascular access with the introduction of arteriovenous fistulas and permanent double-lumen catheters; (2) the introduction of smaller more efficient dialyzers and lower-volume dialysis circuits; and (3) the development of dialysis equipment with more precise ultrafiltration monitoring and control capability (Donald Potter, personal communication, 2011).

The critical problem of ultrafiltration monitoring in infants, most critical due to their small body size and narrow blood volume safety limits, was solved ingeniously by another pioneering pediatric HD program in Minneapolis led by Michael Mauer and Carl Kjellstrand who developed electronic weighing equipment on which the dialyzing infant lay throughout the procedure. The equipment required meticulous calibration but was able to very accurately measure weight changes to within 3 g [83]. In a review published in 1976, Mauer and R.E. Lynch addressed these issues and others in an engaging description of the state of the art of pediatric HD in North America in the early 1970s [84].

Developments in Europe paralleled those in North America. In 1975, the second edition of the famous French textbook of pediatric nephrology was co-edited by Pierre Royer, Renée Habib, Michel Broyer, and Chantal Loirat. There were six pages about HD, stating as follows: "…The management of end-stage renal disease in children is a recent experience, and pediatric maintenance hemodialysis had really begun in 1969-70 in Europe…" [85]. According to these authors, there were three major contraindications to chronic dialysis in children: (i) systemic disease such as lupus, (ii) mental retardation, and (iii) young age, i.e., below 18 months. Vascular accesses included only radial or femoral arteriovenous shunt or fistula, so that such a procedure was limited to children older than 2–3 years. There was no specific device for pediatric dialysis, and children suffered from many uncomfortable/unacceptable side effects (seizures, severe hypotension) during HD sessions. Morbidity primarily consisted of arterial hypertension, renal osteodystrophy, anemia, undernutrition, and poor growth velocity. However, actuarial patient survival was reported to be 90% after 3 years on chronic HD [85].

By the late 1980s, chronic HD for children had become widely available throughout Europe and North America. While the goal was always preparation for a successful kidney transplant, further technical improvements in the delivery of dialysis therapy allowed the focus to shift from simply prolonging life to rehabilitation and the achievement of more normal physical, intellectual, and social development [86].

Among the most recent advances, some have brought significant improvement in HD for children:

- Daily on-line hemodiafiltration allows better nutrition, reduces blood pressure, improves left ventricular size and function, improves calcium × phosphate control, better controls chronic microinflammation, and promotes catch-up growth in children [87].
- The lowest age limit for starting HD in children has dropped to include neonates thanks to specific devices and improvement in general care of such patients [88].
- There is better worldwide knowledge and investigation of cardiovascular risk factors leading to better long-term control and prevention of cardiovascular disease (see Chap. 30).
- The use of on-line monitoring equipment for chemical/physical signals during HD and biofeedback is growing, such as continuous noninvasive monitoring of relative blood volume changes during HD, patient-dialysate sodium gradient assessment, ionic dialysance and plasma conductivity (calculated from on-line inlet and outlet dialysate conductivity measurements), estimation of sodium concentration derived from conductivity, intra-HD urea kinetics and delivered dialysis dose from on-line urea monitors, and dialysate temperature modulation according to blood temperature monitoring [89].

Patient Registries and Multicenter Studies

By the early 1970s, it became clear among pediatric nephrologists in North America and Europe that the care of children with ESKD required separate facilities from those in which adult patients were dialyzed. The concept of specialized pediatric dialysis centers was pioneered in Europe by Michel Broyer, Karl Scharer, Cyril Chantler, RA Donckerwolke, Gianfranco

Rizzoni, and many others who stressed the importance of concentrating pediatric ESKD patients in multidisciplinary pediatric centers specially equipped for children and with the experience and expertise to care for children on dialysis and their families [86]. These units were usually attached to university departments of pediatrics, as was the case in similar units established in North America. However, no single pediatric center in Europe or North America could hope to treat enough patients to properly develop the therapy. As a result, the concept of large national and international patient databases or registries of children receiving dialysis was born.

The first of these was the work of the European Dialysis and Transplant Association (EDTA), which in 1971 published the first report devoted entirely to the care of pediatric dialysis patients [90]. The 1971 report presented data on 296 patients less than 15 years of age at the start of RRT who were receiving treatment at 122 centers, only 5 of which had treated 3 or more pediatric patients, reflecting the practice in Europe at that time of managing children on dialysis in adult units. In 1976, the components of a pediatric dialysis center were rigorously defined by the EDTA to include pediatricians, pediatric nurses, dieticians, social workers, child psychologists, and school facilities, along with a separate children's ward in which therapy was provided away from adult patients [91]. Close association with a transplant program was also prescribed, reflecting early recognition of the critical importance of transplantation as the therapy of choice for children with ESKD. By 1989, nearly 80% of all children receiving dialysis in the countries of the EDTA were cared for in specialized pediatric centers [92].

Pediatric dialysis in Europe was summarized in 2010 with a report on 483 incident and 2512 prevalent pediatric dialysis patients (age <15 years) from 28 countries [93]. In comparison to a previous demographic report of the former EDTA registry 14 years earlier, the authors found a nearly threefold higher incidence and prevalence of RRT among children aged younger than 15 years. They speculated that the difference was likely to be due to underreporting to the previous EDTA registry, the recent achievement of RRT programs for all children in many countries and an increasing acceptance and survival of infants and children with multiple comorbidities in pediatric RRT programs in Europe, resulting in a truly increased incidence and prevalence of RRT [93].

In North America, the success of the EDTA pediatric registry prompted over 60 pediatric ESKD programs to band together in 1987 under the leadership of Amir Tejani, Richard Fine, Steven Alexander, William Harmon and others to form what is now called the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [94]. The NAPRTCS is a voluntary registry restricted to pediatric centers in Canada, the United States, Mexico, and Costa Rica that initially focused on transplant patients. In 1992, the NAPRTCS expanded to include dialysis patients and in 1994 expanded again to include children with chronic kidney disease (CKD). As of July 2019, data have been recorded on 21,316 children entered into the NAPRTCS registry. This includes 10,874 courses of dialysis among 8507 children and 13,611 kidney transplants performed in 12,525 children and young adults. A complete listing of the more than 150 publications based on NAPRTCS data that have appeared since 1990 is available on the NAPRTCS website, as are all of its most recent Annual Data Reports (http://web.emmes.com/study/peds).

The most recent addition to the international pediatric patient registries is the International Pediatric Dialysis Network (IPDN). The IPDN is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic dialysis. Currently, 245 institutions participate in the network from Europe; Scandinavia; North, Central, and South America; and Oceania. The IPDN is composed of the IPPN registry for children on chronic peritoneal dialysis and the IPHN registry for children on hemodialysis. To date 3773 patients have been enrolled in the IPPN registry at 128 contributing centers in 43 countries, and 1005 patients have been enrolled in the IPHN at 85 contributing centers in 36 countries (http://pedpd.org).

Conclusion

The EDTA, NAPRTCS, and the IPDN registries have catalogued and promoted the steady growth and development of RRT for children that has occurred since the 1970s and 1980s. During the last four decades, HD and PD in children have dramatically improved, with the near disappearance of many of the complications that once plagued pediatric hemodialysis; advances in peritoneal dialysis have occurred in parallel with those in hemodialysis for children, although not always at the same pace.

The history of maintenance HD and PD in children has been characterized by a series of major developments, nearly all of which are discussed in the ensuing chapters [95–100]:

- Introduction of more efficient and biocompatible synthetic membranes and peritoneal dialysis solutions (Chaps. 13 and 20)
- Erythropoietin treatment (Chap. 32)
- Growth hormone therapy (Chap. 28)
- The development of new therapeutic approaches to bone disease and calcium-phosphate disorders (Chap. 29)
- Advances in vascular accesses (microsurgery for arteriovenous fistulae, new materials for cuffed tunnelled venous catheters) (Chap. 19)
- Introduction of pediatric data for dialysis adequacy measurement (Kt/V, urea reduction ratio) (Chaps. 13 and 20)
- Novel dialysis strategies (e.g., high-flux dialysis, hemodiafiltration) (Chap. 21)
- Optimizing the use of anticoagulation (low molecular weight heparins, regional trisodium citrate) (Chap. 20)
- Improving dialysis water quality and bacterial safety (ultrapure dialysate)
- Non-invasive investigation of vascular access blood flow
- Using urokinase or tPA for the management of the thrombosed hemodialysis catheter (Chap. 25)
- Improving nutritional assessment and support (Chap. 27)
- Using new machines with precise control of ultrafiltration by volumetric assessment and continuous blood volume monitoring during dialysis sessions
- The availability of specific small-size dialyzers and tubing for infants (Chap. 22)
- The use of sodium modelling

In the meantime, HD and PD practice has benefited from specific medical and staff training, including educational courses, fellowship programs, and congresses. Specific regulations have also been established for HD and PD practice in children. During this period, patient morbidity and mortality have significantly decreased. Worldwide clinical experience has resulted in general practical guidelines for pediatric HD and PD, many of which will be discussed in the chapters that follow.

All these improvements have led to better quality of life, better nutritional status, better neurological development, better psychosocial outcome, and better patient survival for those children who receive chronic dialysis. All have their origins in the work of pioneering medical teams, patients, and families beginning almost a century ago. It has been a truly exciting story that continues to this day. The chapters that follow in this text will address these and other recent advances in dialysis therapy for children.

References

1. Cameron JS. A history of the treatment of renal failure by dialysis. New York: Oxford University Press Inc; 2002. p. 179–85.
2. Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: a paradigm of the forming of nephrology by technology. Am J Nephrol. 1997;17:347–58.
3. Barnett HL, Edelmann CM Jr. Development of pediatric nephrology. Am J Kidney Dis. 1990;16:557–62.
4. Chesney RW. The development of pediatric nephrology. Pediatr Res. 2002;52:770–8.
5. Scharer K, Fine RN. The history of dialysis therapy in children. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht: Kluwer Academic Publishers Inc; 2004. p. 1–11.

6. Blackfan KD, Maxcy KF. The intraperitoneal injection of saline solution. Am J Dis Child. 1918;15:19–28.
7. Swan H, Gordon HH. Peritoneal lavage in the treatment of anuria in children. Pediatrics. 1949;4:586–95.
8. Odel HM, Ferris DO, Power MH. Peritoneal lavage as an effective means of extra-renal excretion. Am J Med. 1950;9:63–77.
9. Fine J, Frank HA, Seligman AM. The treatment of acute renal failure by peritoneal irrigation. Ann Surg. 1946;124:857–75.
10. Weston RE, Roberts M. Clinical use of a stylet catheter for peritoneal dialysis. Arch Intern Med. 1965;15:659–62.
11. Maxwell MH, Rockney RB, Kleeman CR, Twiss MR. Peritoneal dialysis: technique and applications. JAMA. 1959;170:917–24.
12. Segar WE, Gibson RK, Rhamy R. Peritoneal dialysis in infants and small children. Pediatrics. 1961;27:603–13.
13. Etteldorf JN, Dobbins WT, Sweeney MJ, Smith JD, Whittington GL, Sheffield JA, Meadows RW. Intermittent peritoneal dialysis in the management of acute renal failure in children. J Pediatr. 1962;60:327–39.
14. Segar WE. Peritoneal dialysis in treatment of boric acid poisoning. N Engl J Med. 1960;262:708–800.
15. Ettledorf JN, Dobbins WT, Summitt RL, Rainwater WT, Fischer RL. Intermittent peritoneal dialysis using 5 per cent albumin in the treatment of salicylate intoxication in children. J Pediatr. 1961;58:226–36.
16. Lloyd-Still JD, Atwell JD. Renal failure in infancy, with special reference to the use of peritoneal dialysis. J Pediatr Surg. 1966;1:466–75.
17. Manley GL, Collipp PJ. Renal failure in the newborn: treatment with peritoneal dialysis. Am J Dis Child. 1968;115:107–10.
18. Lugo G, Ceballos R, Brown W, Polhill R, Cassady G. Acute renal failure in the neonate managed by peritoneal dialysis: preliminary report of two cases. Am J Dis Child. 1969;118:655–9.
19. Giantantonio CA, Vitacco M, Mendilaharzu J, Mendilaharzu F, Rutty A. Acute renal failure in infancy and childhood: clinical course and treatment of 41 patients. J Pediatr. 1962;61:660–78.
20. Wiggelinkhuizen J. Peritoneal dialysis in children. S Afr Med J. 1971;45:1047–54.
21. Day RE, White RHR. Peritoneal dialysis in children: review of 8 years' experience. Arch Dis Child. 1977;52:56–61.
22. Chan JCM. Peritoneal dialysis for renal failure in childhood. Clin Pediatr. 1978;17:349–54.
23. Feldman W, Baliah T, Drummond KN. Intermittent peritoneal dialysis in the management of chronic renal failure in children. Am J Dis Child. 1968;116:30–6.
24. Palmer RA, Quinton WE, Gray J-F. Prolonged peritoneal dialysis for chronic renal failure. Lancet. 1964;1:700–2.
25. Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. Trans Am Soc Artif Intern Organs. 1968;14:181–7.
26. Boen ST, Mion CM, Curtis FK, Shilitar G. Periodic peritoneal dialysis using the repeated puncture technique and an automatic cycling machine. Trans Am Soc Artif Intern Organs. 1964;10:409–14.
27. Tenckhoff H, Meston B, Shilipetar G. A simplified automatic peritoneal dialysis system. Trans Am Soc Artif Intern Organs. 1972;18:436–40.
28. Counts S, Hickman R, Garbaccio A, Tenckhoff H. Chronic home peritoneal dialysis in children. Trans Am Soc Artif Intern Organs. 1973;19:157–67.
29. Hickman RO. Nine years' experience with chronic peritoneal dialysis in childhood. Dial Transplant. 1978;7:803.
30. Brouhard BH, Berger M, Cunningham RJ, Petrusik T, Allen W, Lynch RE, Travis LB. Trans Am Soc Artif Intern Organs. 1979;25:90–4.
31. Baluarte HJ, Grossman MB, Polinsky MS, Elzouki AY, Prebis JW, Gruskin AB. Experience with intermittent home peritoneal dialysis (IHPD) in children. (Abstract). Pediatr Res. 1980;14:994.
32. Lorentz WB, Hamilton RW, Disher B. Home peritoneal dialysis during infancy. Clin Nephrol. 1981;15:194–7.
33. Potter DE, McDaid TK, Ramirez JA. Peritoneal dialysis in children. In: Atkins RC, Thomson NM, Farrell PC, editors. Peritoneal dialysis. New York: Churchill Livingstone; 1981. p. 356–61.
34. Ahmad S, Gallagher N, Shen S. Intermittent peritoneal dialysis: status re-assessed. Trans Am Soc Artif Intern Organs. 1979;25:86–8.
35. Hurley JK. Kidney transplantation in infants. (Letter). J Pediatr. 1978;93:538.
36. Reinhart JB. The doctor's dilemma: whether or not to recommend continuous renal dialysis or renal homotransplantations for the child with end-stage renal disease. J Pediatr. 1970;77:505.
37. Oreopoulos DG, Katirtzoglou A, Arbus G, Cordy P. Dialysis and transplantation in young children. (Editorial). Br Med J. 1979;2:1033.
38. Popovich RP, Moncrief JW, Dechard JF. The definition of a novel portable/wearable equilibrium dialysis technique (Abstract). Trans Am Soc Artif Intern Organs. 1976;5:64.
39. Moncrief JW, Popovich RP, Nolph KD. The history and current status of continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1990;16:579–84.
40. Oreopoulos DG, Katirtzoglou A, Arbus G, Cordy P. Dialysis and transplantation in young children (Letter). Br Med J. 1979;1:1628–9.
41. Balfe JW, Irwin MA. Continuous ambulatory peritoneal dialysis in pediatrics. In: Legain M, edi-

tor. Continuous ambulatory peritoneal dialysis. Amsterdam: Excerpta Medica; 1980. p. 131–6.
42. Alexander SR, Tseng CH, Maksym KA, Talwalker YA. Clinical parameters in continuous ambulatory peritoneal dialysis for infants and young children. In: Moncrief JW, Popovich RP, editors. CAPD update. New York: Masson Publ; 1981. p. 195–209.
43. Kohaut EC. Continuous ambulatory peritoneal dialysis: a preliminary pediatric experience. Am J Dis Child. 1981;135:270–1.
44. Potter DE, McDaid TK, McHenry K, Mar H. Continuous ambulatory peritoneal dialysis (CAPD) in children. Trans Am Soc Artif Intern Organs. 1981;27:64–7.
45. Salusky IB, Lucullo L, Nelson P, Fine RN. Continuous ambulatory peritoneal dialysis in children. Pediatr Clin N Am. 1982;29:1005–12.
46. Guillot M, Clermont M-J, Gagnadoux M-F, Broyer M. Nineteen months' experience with continuous ambulatory peritoneal dialysis in children: main clinical and biological results. In: Gahl GM, Kessel M, Nolph KD, editors. Advances in peritoneal dialysis. Amsterdam: Excerpta Medica; 1981. p. 203–7.
47. Eastham EJ, Kirplani H, Francis D, Gokal R, Jackson RH. Pediatric continuous ambulatory peritoneal dialysis. Arch Dis Child. 1982;57:677–80.
48. Alexander SR. Pediatric CAPD update-1983. Perit Dial Bull (Suppl). 1983;3:S15–22.
49. Alexander SR, Honda M. Continuous ambulatory peritoneal dialysis for children: a decade of worldwide growth and development. Kidney Int. 1993;43(Suppl):S65–74.
50. Honda M, Itaka K, Kawaguchi H, et al. The Japanese data on CAPD: a ten year experience. A report of the Study Group of the Pediatric PD Conference. Perit Dial Int. 1996;16:269–75.
51. Munoz AR, Salazar GML, Gordillo PG. Adequacy of chronic peritoneal dialysis in low socioeconomic class uremic children. Int J Pediatr Nephrol. 1986;7:81–4.
52. Bakkaloglu SA, Ekim M, Sever L, et al. Chronic peritoneal dialysis in Turkish children: a multicenter study. Pediatr Nephrol. 2005;20:644–51.
53. Grunberg J, Verocay MC, Rebori A, et al. Twenty years' pediatric chronic peritoneal dialysis in Uruguay: patient and technique survival. Pediatr Nephrol. 2005;20:1315–9.
54. Diaz-Buxo JA, Farmer CD, Walker PJ, Chandler JT, Holt KL. Continuous cyclic peritoneal dialysis: a preliminary report. Artif Organs. 1981;5:157–61.
55. Price CG, Suki WN. Newer modifications of peritoneal dialysis: options in treatment of patients with renal failure. Am J Nephrol. 1981;1:97.
56. Seikaly M, Ho PL, Emmett L, Tejani A. The 12th annual report of the North American Pediatric Renal Transplant Cooperative Study: renal transplantation from 1987 to 1998. Pediatr Transplant. 2001;5:215–31.
57. Warady BA, Sullivan EK, Alexander SR. Lessons from the peritoneal dialysis patient database: a report of the North American Pediatric Renal Transplant Cooperative Study. Kidney Int. 1996;49(Suppl):S68–71.
58. Edefonti A, Verrina E, Schaefer F, Fischbach M, Watson A. The European experience with CAPD/CCPD in children. In: Fine RN, Alexander SR, Warady B, editors. CAPD/CCPD in children. Boston: Kluwer Academic Publ; 1998. p. 17–34.
59. Fine RN, Ho M. The role of APD in the management of pediatric patients: a report of the North American Pediatric Renal Transplant Cooperative Study. Semin Dial. 2002;15:427–9.
60. Neu AM, Sander A, Borzych-Dazualka D, Watson AR, Valles PG, Ha IS, Patel H, Azkenazi D, Balasz-Chmielewska I, Lauronen J, Groothoff JW, Feber J, Schaefer F, Warady BA, IPPN investigators. Comorbidities in chronic pediatric peritoneal dialysis patients: a report of the International Pediatric Peritoneal Dialysis Network. Perit Dial Int. 2012;32:410–8.
61. Van der Heijden BJ, van Dijk PC, Vernier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004;19:213–21.
62. Verrina E, Edefonti A, Gianglio B, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pedatr Nephrol. 2004;19:82–90.
63. Kolff WJ, Berk HTH, Ter Welle M, van der Leg JW, van Dijk EC, van Noordwijk J. The artificial kidney: a dialyser with great area. Acta Medica Scand. 1944;117:121–34.
64. Kolff WJ. First clinical experience with the artificial kidney. Ann Intern Med. 1965;62:608–19.
65. MacLean J. The thromboplastic action of cephalin. Am J Phys. 1916;41:250–7.
66. Andrus FC. Use of Visking sausage casing for ultrafiltration. Proc Soc Exp Biol Med. 1919;27:127–8.
67. Merrill JP, Smith S III, Callahan EJ III, Thorn GW. The use of an artificial kidney. II Clinical experience. J Clin Invest. 1950;29:425–38.
68. Mateer FM, Greenman L, Danowski TS. Hemodialysis of the uremic child. Am J Dis Child. 1955;89:645–55.
69. Alwall N. Apparatus for dialysis of the blood in vivo. Acta Med Scand. 1947;128:317–35.
70. Carter FH, Aoyama S, Mercer RD, Kolff WJ. Hemodialysis in children: report of five cases. J Pediatr. 1957;51:125–36.
71. Kallen RJ, Zaltzman S, Coe FL, Metcoff J. Hemodialysis in children: technique, kinetic aspects related to varying body size, and application to salicylate intoxication, acute renal failure and some other disorders. Medicine. 1966;45:1–50.
72. Quinton W, Dillard D, Scribner B. Cannulation of blood vessels for prolonged hemodialysis. Trans ASAIO. 1960;6:104.
73. Morse TS. Synthetic arteriovenous shunts for hemodialysis in children. J Ped Surg. 1970;5:23–31.

74. Hickman RO, Scribner BH. Application of the pumpless hemodialysis system to infants and children. Trans Am Soc Artif Intern Organs. 1962;8:309–14.
75. Hutchings RH, Hickman R, Scribner BH. Chronic hemodialysis in a pre-adolescent. Pediatrics. 1966;37:68–73.
76. Potter D, Larsen D, Leumann E, Perin D, Simmons J, Piel CF, Holliday MA. Treatment of chronic uremia in childhood. II Hemodialysis. Pediatrics. 1970;46:678–89.
77. Fine RN, DePalma JR, Lieberman E, Donnell GN, Gordon A, Maxwell MH. Extended hemodialysis in children with chronic renal failure. J Pediatr. 1968;73:706–13.
78. Mauer SM, Shideman JR, Buselmeier TJ, Kjellstrand CM. Long-term hemodialysis in the neonatal period. Am J Dis Child. 1973;125:269–72.
79. Boulton-Jones JM, Cameron JS, Bewick M, Ogg CS, Meadow SR, Ellis FG. Treatment of terminal renal failure in children by home dialysis and transplantation. Arch Dis Child. 1971;46:457–64.
80. Broyer M, Loirat C, Kleinknecht C. Technical aspects and results of regular hemodialysis in children. Acta Paediat Scand. 1972;61:677–84.
81. Lenzer J. Obituary: Belding Scribner: inventor of shunt dialysis. BMJ. 2003;327(7407):167.
82. Cole JJ, Pollard TL, Murray JS. Studies on the modified polypropylene Kiil dialyser. Trans Am Soc Artif Intern Organs. 1963;9:67–72.
83. Kjellstrand CM, Mauer SM, Shideman JR, Buselmeier TJ. Accurate weight monitoring during pediatric hemodialysis. Nephrom. 1973;10:302–5.
84. Mauer SM, Lynch RE. Hemodialysis techniques for infants and children. Ped Clin N America. 1976;23:843–56.
85. Broyer M. Dialyse et transplantation rénale. In: Royer P, Habib R, Broyer M, Loirat C, editors. Néphrologie Pédiatrique. Paris: Flammarion Médecin-Sciences; 1975. p. 302–13.
86. Broyer M, Chantler C, Donckerwolke R, Rizzoni G. Renal replacement therapy in children. In: Mahaer JF, editor. Replacement of renal function by dialysis. 3rd ed. Boston: Kluwer Academic Publisher; 1989. p. 720–49.
87. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily online haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
88. Shroff R, Wright E, Ledermann S, Hutchinson C, Rees L. Chronic hemodialysis in infants and children under 2 years of age. Pediatr Nephrol. 2003;18:378–83.
89. Locatelli F, Buoncristiani U, Canaud B, Köhler H, Petitclerc T, Zucchelli P. Haemodialysis with on-line monitoring equipments: tools or toys? Nephrol Dial Transplant. 2005;20:22–3.
90. Scharer K, Brunner FP, Gurland HJ, Harlen H, Parsons FM. Combined report on regular dialysis and renal transplantation of children in Europe, 1971. Proc Eur Dial Transplant Assoc. 1972;9:191–200.
91. Chantler C, Donckerwolke RA, Brunner FP, Gurland H, Hathway RA, Jacobs C, Selwood NH, Wing AJ. Combined report on regular dialysis and renal transplantation of children in Europe, 1976. Proc Eur Dial Transplant Assoc. 1977;14:70–112.
92. Ehrich JHH, Rizzoni G, Brunner FP, Brynger H, Gerlings W, Fasbinder W, Raine AEG, Selwood NH, Tufveson G. Combined report on regular dialysis and transplantation of children in Europe, 1989. Nephrol Dial Transplant. 1991;6(Suppl 1):37–47.
93. Van Stralen KJ, Tizard EJ, Verrina E, Schaefer F, Jager KJ, on behalf of the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESRN/ERA-EDTA). Demographics of paediatric renal replacement therapy in Europe: 2007 annual report of the ESPN/ERA-EDTA registry. Pediatr Nephrol. 2010;25:1379–82.
94. Alexander SR, Sullivan EK, Harmon WE, Stablein DM, Tejani A. Maintenance dialysis in North American children: a preliminary report of the NAPRTCS. Kidney Int Suppl. 1993;43:S104–9.
95. Shroff R, Ledermann S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2009;24:463–74.
96. Goldstein SL, Allsteadt A. Ultrasound dilution evaluation of pediatric hemodialysis vascular access. Kidney Int. 2001;59:2357–60.
97. Sheth RD, Brandt ML, Brewer ED, Nuchtern JG, Kale AS, Goldstein SL. Permanent hemodialysis vascular access survival in children and adolescents with end-stage renal disease. Kidney Int. 2002;62:1864–9.
98. Bourquelot P, Raynaud F, Pirozzi N. Microsurgery in children for creation of arteriovenous fistula for renal and non-renal diseases. Ther Apher Dial. 2003;7:498–503.
99. Krause I, Birk E, Davidovits M, Cleper R, Blieden L, Pinhas L, Gamzo Z, Eisentsein B. Inferior vena cava diameter: a useful method for estimation of fluid status in children on haemodialysis. Nephrol Dial Transplant. 2001;16:1203–6.
100. Fischbach M, Edefonti A, Schröder C, Watson A, the European Pediatric Dialysis Working Group. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20:1054–66.

The Biology of Dialysis

2

William R. Clark and Claudio Ronco

Introduction

Dialysis forms the cornerstone of therapy for most patients with chronic kidney disease Stage V (end-stage renal disease; ESRD) and many patients with acute kidney injury (AKI). Consequently, it is imperative that clinicians managing these patients understand the fundamental principles of dialytic therapies, especially those having a biologic basis. In this chapter, many of these principles are reviewed. The topic of uremic toxicity is first addressed, with emphasis on the classification of uremic toxins based on solute molecular weight (MW) and chemical characteristics. The dialytic solute removal mechanisms (diffusion, convection, and adsorption) broadly applicable to all renal replacement therapies are subsequently reviewed. As the major determinant of overall efficiency of hemodialysis (HD), the most commonly applied renal replacement therapy, diffusive solute removal will be rigorously assessed by applying a "resistance-in-series" model to a dialyzer. Moreover, new perspectives on the importance of specific membrane characteristics, including pore size and fiber inner diameter, will be discussed. In much the same way, fluid and mass transfer in peritoneal dialysis will be assessed by examining the elements of the system: peritoneal microcirculation, peritoneal membrane, and the dialysate compartment. Finally, from a kinetic perspective, the differences between intermittent, continuous, and semi-continuous therapies will be discussed, with emphasis on quantification of solute removal.

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Biology of Uremic Toxicity

One of the major functions of the kidney is to eliminate waste products and toxins generated from a variety of metabolic processes [1]. Normal kidney function provides efficient elimination of these solutes, allowing for control of their blood and tissue concentrations at relatively low levels. On the other hand, toxin retention is felt to be a major contributor to the development of uremia in patients with advanced chronic kidney disease and ESRD [2].

In the classic taxonomy, uremic retention compounds are divided into three categories [3]: small solutes, "middle molecules," and protein-bound toxins. Compounds comprising the first category, for which the upper molecular weight limit is generally considered to be 500 Da, possess a high degree of water solubility and minimal or absent protein binding [4]. Despite having

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significant kinetic differences, both urea and creatinine are considered to be representative molecules (surrogates) for the small solute class. Nevertheless, as discussed below, it remains a matter of debate whether these two solutes themselves are toxic per se.

The second category of middle molecules has largely evolved now to be synonymous with peptides and proteins that accumulate in uremia [5]. Although not precisely defined, low molecular weight proteins (LMWP) as a class have a molecular weight spectrum ranging from approximately 500 to 60,000 daltons [6]. Thus, peptides with as few as ten amino acids and proteins nearly as large as albumin comprise this group. In patients with intact kidney function, these compounds are initially filtered by the glomerulus and subsequently undergo catabolism with reclamation of the constituent amino acids at the level of the proximal tubule [7, 8]. While the kidney is not the sole organ responsible for detoxification of these compounds, renal elimination accounts for 30–80% of total metabolic removal.

The final category of uremic retention compounds, one which has received much less attention than the other two, is protein-bound uremic toxins (PBUTs) [9, 10]. As opposed to the above small, highly water-soluble toxins, which are largely by-products of protein metabolism, PBUTs have diverse origins and possess chemical characteristics that preclude the possibility of circulation in an unbound form despite being of low molecular weight (<500 daltons also). These organic molecules typically have ionic and/or hydrophobic characteristics and bind avidly to albumin in the blood. Under conditions of normal kidney function, they are eliminated primarily by organic acid transporters (OATs) residing in the proximal tubule [11, 12]. Uremia is associated with elevated concentrations of both bound and unbound forms of PBUTs, with both reduced renal elimination and impaired albumin binding considered to be important factors [13]. Attention has focused on the metabolic products of the gut microbiome as the source of many PBUTs, including indoxyl sulfate and *p*-cresol [14, 15] (Fig. 2.1). The general topic of uremic toxicity

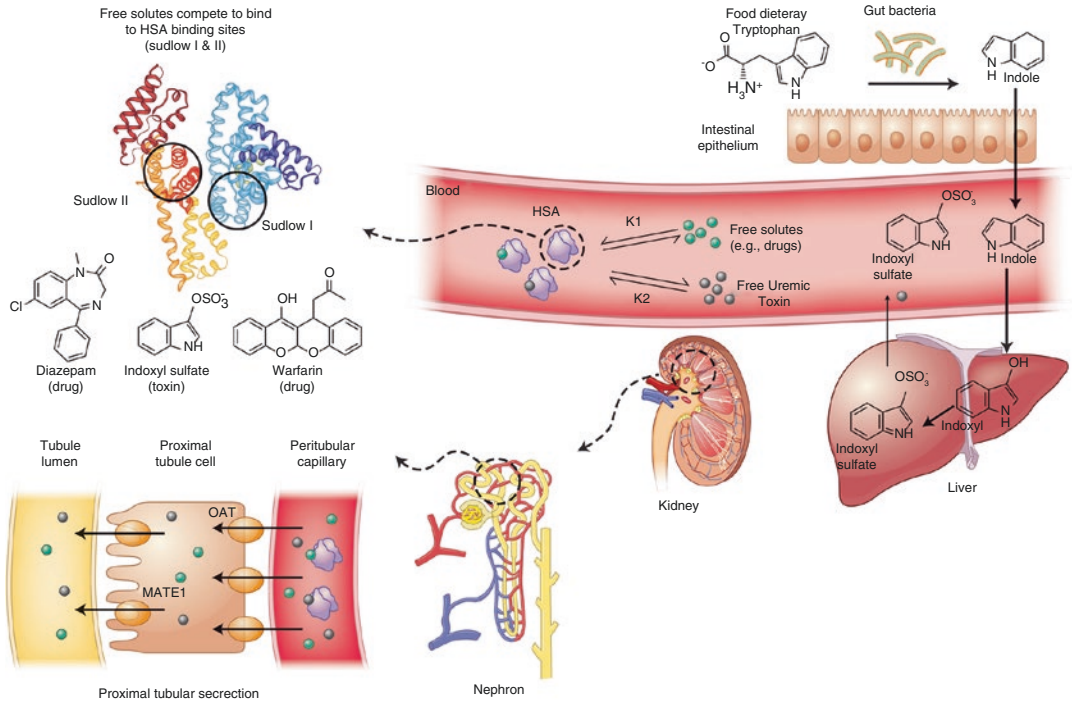

Fig. 2.1 Generation and elimination of gut-derived protein-bound uremic toxins. (Modified from Clark et al. (2019) [15])

has been comprehensively assessed in a recent review by Clark et al. [15].

Solute Removal Mechanisms in Extracorporeal Dialysis

Diffusion

Diffusion involves the mass transfer of a solute in response to a concentration gradient. The inherent rate of diffusion of a solute is termed its diffusivity [16], whether this in solution (such as dialysate and blood) or within an extracorporeal membrane. Diffusivity in solution is inversely proportional to solute MW and directly proportional to solution temperature [17]. Solute diffusion within a membrane is influenced by both membrane thickness (diffusion path length) and membrane diffusivity [18], which is a function of both pore size and number (density).

In hemodialysis (HD), the overall mass transfer coefficient-area product (KoA) is used to quantify the diffusion characteristics of a particular solute–membrane combination under a defined set of operating conditions [19]. The overall mass transfer coefficient is the inverse of the overall resistance to diffusive mass transfer, the latter being a more applicable quantitative parameter from an engineering perspective:

$$K_O = 1/R_O \tag{2.1}$$

The overall mass transfer resistance can be viewed as the sum of resistances in series [20]:

$$R_O = R_B + R_M + R_D \tag{2.2}$$

where R_B, R_M, and R_D are the mass transfer resistances associated with the blood, membrane, and dialysate, respectively. In turn, each resistance component is a function of both diffusion path length (x) and diffusivity (D):

$$R_O = (x/D)_B + (x/D)_M + (x/D)_D \tag{2.3}$$

The diffusive mass transfer resistance of both the blood and dialysate compartments for a hemodialyzer is primarily due to the unstirred (boundary) layer just adjacent to the membrane [21, 22]. Minimizing the thickness of these unstirred layers is primarily dependent on achieving relatively high shear rates, particularly in the blood compartment [23]. For similar blood flow rates, higher blood compartment shear rates are achieved with a hollow fiber dialyzer than a flat plate dialyzer. Indeed, based on the blood and dialysate flow rates (generally at least 250 and 500 mL/min, respectively) achieved in contemporary HD with hollow fiber dialyzers, the controlling diffusive resistance for solutes larger than approximately 200 daltons is that due to the membrane itself [24] (Fig. 2.2).

Another approach to quantifying diffusive mass transfer specifically through an extracorporeal membrane is by use of Fick's law of diffusion [25]:

$$N = D \cdot A(\Delta C/\Delta x) \tag{2.4}$$

where D is the solute diffusivity (area/time), A is the membrane area, ΔC is the transmembrane concentration gradient, and Δx is the diffusion path length. With increasing solute molecular weight, pore size limitations become increasingly important in restricting solute entry and limiting ("hindering") diffusion of molecules that gain pore entry [26, 27]. Thus, for a given concentration gradient across a membrane, the rate of diffusive solute removal is directly proportional to

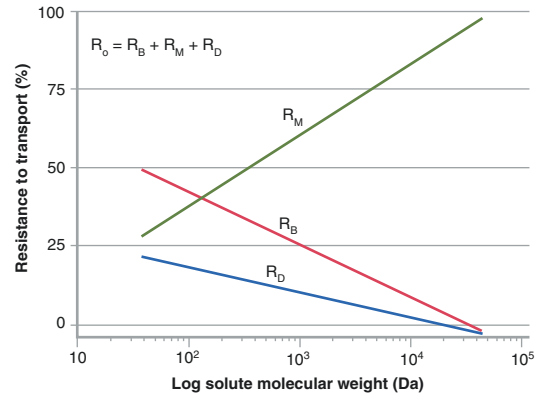

Fig. 2.2 Diffusive mass transfer resistances in a hemodialyzer. (Modified from Ronco and Clark (2018) [24])

the membrane diffusivity and indirectly proportional to the effective thickness of the membrane.

Membrane diffusivity is determined both by the pore size distribution and by the number of pores per unit membrane area (pore density). Based on a model in which a membrane has N (straight) cylindrical pores (per unit membrane surface area) of radius r oriented perpendicular to the flow of blood and dialysate, diffusive solute flux (φ: mass removal rate per unit membrane surface area) can be expressed as [28]:

$$\varphi = \lambda D \rho \Delta C / t \tag{2.5}$$

where λ is the solute partition coefficient, D is solute diffusivity, ρ is membrane porosity, ΔC is the transmembrane concentration gradient, and t is membrane thickness. (While the partition coefficient is essentially unity for solutes such as urea and creatinine, larger solutes with incomplete access to the membrane pores have λ values that are less than one.) Membrane porosity is a function of both pore size and number:

$$\rho = N \pi r^2 \tag{2.6}$$

Equations (2.5) and (2.6) suggest diffusive transport is relatively favorable for low molecular weight (LMW) solutes, due not only to the inverse relationship between MW and diffusivity but also to the greater access of small solutes to the membrane pore structure. Equation (2.5) also indicates diffusive transport is enhanced at low values of membrane thickness.

Diffusive mass transfer rates within a membrane decrease as solute MW increases not only due to effect of molecular size itself but also due to the resistance provided by the membrane pores. The difference in mean pore sizes between low-permeability dialysis membranes (e.g., regenerated cellulose) and high-permeability membranes (e.g., polysulfone, polyacrylonitrile, polyethersulfone) has a relatively small impact on small solute (urea, creatinine) diffusivities. This is related to the fact that even low-permeability membranes have pore sizes that are significantly larger than the molecular sizes of these solutes. However, as solute MW increases, the tight pore structure of the low-permeability membranes plays an increasingly constraining role such that diffusive removal of solutes larger than 1000 daltons is minimal by these membranes. On the other hand, the larger pore sizes which characterize high-flux membranes account for their higher diffusive permeabilities. Nevertheless, as discussed subsequently, the relatively limited ability of conventional high-flux membranes to remove large MW toxins due to pore size restrictions has generated interest in the use of membranes with larger pore dimensions.

Solute Removal by Convection

Convective solute removal is primarily determined by the sieving properties of the membrane used and the ultrafiltration rate [29]. The mechanism by which convection occurs is termed solvent drag. If the molecular dimensions of a solute are such that some degree of membrane permeation can occur, the solute is swept ("dragged") across the membrane in association with ultrafiltered plasma water. Thus, the rate of convective solute removal can be modified either by changes in the rate of solvent (plasma water) flow or in the mean effective pore size of the membrane.

Hydraulic flux (water permeability), the most common criterion traditionally used to classify dialysis membranes [16], is an important determinant of convective solute removal. The clinical parameter used to quantify water permeability is the ultrafiltration coefficient (Kuf), which is derived from the relationship between ultrafiltration rate (Qf) and TMP over a clinically relevant range of TMP. As suggested previously, a common first-order approximation of dialysis membrane pore structure is to assume that all pores are parallel and have the same radius, which results in ultrafiltrate flow that is perpendicular to the flow of blood and dialysate [30]. According to the Hagen–Poiseuille law [31], the rate of ultrafiltrate flow is proportional to the fourth power of the pore radius (i.e., r^4) at constant TMP. Thus, the membrane parameters that have the most substantial influence on water flux are the average

pore size and, to a lesser extent, the pore density per unit surface area.

The sieving coefficient is classically used to define the convective transport properties of a membrane for a specific solute. In Eq. (2.7), the sieving coefficient (SC) is the ratio between the solute concentration in the filtrate (Cf) and the solute concentration in the plasma water (Cp) [25, 29]:

$$SC = Cf / Cp \tag{2.7}$$

The observed (measured) SC values are influenced by interactions between the membrane and blood elements during dialysis. The nonspecific adsorption of a plasma protein layer, variously known as the secondary membrane, gel, or protein cake, reduces effective membrane permeability immediately upon exposure to blood [32–35] in a process known as fouling. In the convective removal of specific solutes, the influence of secondary membrane formation is directly proportional to solute molecular weight. The proteins found in the highest concentrations in the plasma, such as albumin, fibrinogen, and immunoglobulins, are the predominant components of the secondary membrane. This layer of proteins, by serving as an additional resistance to mass transfer, effectively reduces both the water and solute permeability of an extracorporeal membrane. Evidence of this is found in comparisons of solute sieving coefficients determined before and after exposure of a membrane to plasma or other protein-containing solution [36]. In general, the extent of secondary membrane development and its effect on membrane permeability is directly proportional to the membrane's adsorptive tendencies (i.e., hydrophobicity). Therefore, this process tends to be most evident for high-flux synthetic membranes, such as polysulfone and polymethylmethacrylate.

Both the water and solute permeability of a membrane used for therapies which involve relatively high ultrafiltration rates are influenced not only by secondary membrane formation but also concentration polarization [29] (Fig. 2.3). Although concentration polarization primarily pertains to plasma proteins, it is distinct from secondary membrane formation. Concentration polarization specifically relates to ultrafiltration-based processes and applies to the kinetic behavior of an individual protein. Accumulation of a plasma protein that is predominantly or completely rejected by a membrane used for ultrafiltration of plasma occurs at the blood compartment membrane surface. This surface accumulation causes the protein concentration just adjacent to the membrane surface (i.e., the submembranous concentration) to be higher than the bulk (plasma) concentration. In this manner, a submembranous (high) to bulk (low) concen-

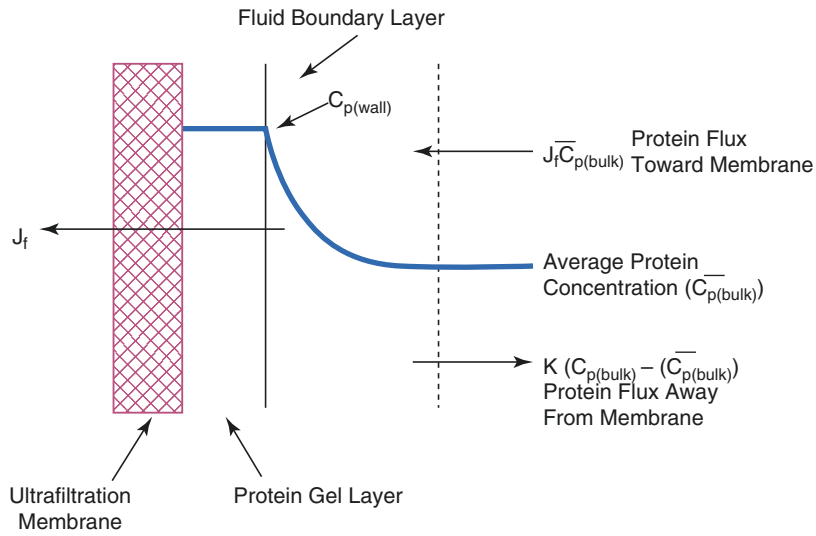

Fig. 2.3 Secondary membrane and concentration polarization phenomena in convective therapies. The protein gel layer corresponds to the secondary membrane while the fluid boundary layer represents concentration polarization. (Modified from Henderson (1996) [29])

tration gradient is established, resulting in "backdiffusion" from the membrane surface out into the plasma. At steady state, the rate of convective transport to the membrane surface is equal to the rate of backdiffusion. The polarized layer of protein is the distance defined by the gradient between the submembranous and bulk concentrations. This distance (or thickness) of the polarized layer, which can be estimated by mass balance techniques, reflects the extent of the concentration polarization process.

Conditions which promote concentration polarization are high ultrafiltration rate (high rate of convective transport), low blood flow rate (low shear rate), and the use of post-dilution (rather than pre-dilution) replacement fluids (increased local protein concentrations) [37]. By definition, concentration polarization is applicable in clinical situations in which relatively high ultrafiltration rates are used. Therefore, in the chronic dialysis setting, this phenomenon is potentially important in convective therapies (hemofiltration and hemodiafiltration).

The extent of the concentration polarization process determines its effect on actual solute (protein) removal. In general, the degree to which the removal of a protein is influenced correlates directly with that protein's extent of rejection by a particular membrane. In fact, concentration polarization actually enhances the removal of a MW class of proteins (30,000–70,000 daltons) that otherwise would have minimal convective removal. This is explained by the fact that the pertinent blood compartment concentration subjected to the ultrafiltrate flux is the high submembranous concentration primarily rather than the much lower bulk concentration. Therefore, the potentially desirable removal of certain proteins in this size range (e.g., β2M in ESRD patients) has to be weighed against the undesirable increase in convective albumin losses.

On the other hand, the use of very high ultrafiltration rates in conjunction with other conditions favorable to protein polarization may significantly impair overall membrane performance. The relationship between ultrafiltration rate and transmembrane pressure (TMP) is linear for relatively low ultrafiltration rates, and the positive slope of this line defines the ultrafiltration coefficient of the membrane. However, as ultrafiltration rate further increases, this curve eventually plateaus [38]. At this point, maintenance of a certain ultrafiltration rate is only achieved by a concomitant increase in TMP. At sufficiently high TMP, gelling of the membrane with denatured proteins may occur, and an irreversible decline in solute and water permeability of the membrane ensues. Therefore, the ultrafiltration rate (and associated TMP) used for a convective therapy with a specific membrane needs to fall on the initial (linear) portion of the UFR vs. TMP relationship with avoidance of the plateau region.

Solute Removal by Internal Filtration

Conventional membranes that are used in hemodialysis generally provide high clearance rates for small solutes such as urea and creatinine, irrespective of flux. However, membranes in current use, even those that are traditionally considered to be highly permeable, provide limited clearance of compounds >10 kDa for several reasons. Although these membranes have relatively large mean pore sizes (at least in comparison to unmodified cellulosic membranes), they still offer substantial mass transfer resistance to the diffusive removal of large solutes. Furthermore, fouling has a considerable effect on convective solute clearances, especially for molecules >10 kDa [35]. These constraints are particularly relevant in conditions involving high ultrafiltration rates, which promote secondary membrane formation by more effectively delivering plasma proteins to the membrane surface through convection (versus lower ultrafiltration rates). In typical hemodialysis operating conditions, the water permeability characteristics for a standard high-flux dialyzer result in a fairly large drop in the blood compartment axial (i.e., arterial end to venous end) pressure during treatment. The pressure drop is sufficiently

large that, at some point along the length of the dialyzer, the blood compartment pressure is less than the dialysate compartment pressure in normal operating conditions. Thus, especially considering the oncotic effects of plasma proteins in the blood compartment, there is a point at which the ultrafiltrate begins to be driven from the dialysate to the blood, as opposed to the "standard" (blood–dialysate) direction in the more proximal part of the dialyzer (Fig. 2.4). In fact, this combination of filtration and "backfiltration" [39–41] is considered to be the predominant mechanism by which larger compounds are removed during standard high-flux hemodialysis [42, 43], as explained further below.

The concentration of a molecule that is removed from the blood by convection in the proximal part of a high-flux dialyzer is substantially reduced once it crosses the membrane owing to the combination of sieving and the diluting effect of dialysate flow. When a portion of the dialysate is reinfused back into the blood as backfiltrate in the distal segment of the dialyzer, the amount of solute reinfused by solvent drag is negligible compared with that removed in the proximal part of the dialyzer owing to the blood–dialysate concentration difference, even if the filtration and backfiltration rates are similar. In fact, the reinfused fluid can be considered an "internal" substitution fluid because the concentration of the solute of interest is essentially zero. As such, in the context of high-flux hemodialysis, this mechanism has been termed "internal hemodiafiltration" or, more commonly, internal filtration. Maximizing the extent of internal filtration during high-flux hemodialysis through a combination of increased membrane permeability (increased pore size) and higher axial blood compartment resistance (decreased hollow fiber inner diameter) (44–46; see below) can provide clinically meaningful increases in large solute clearance. Internal filtration rates are estimated to be as high as 60 ml/min (~3.5 l/h) [40], and new membrane designs may be able to extend this range. However, strict control of dialysate quality is clearly of paramount importance in high-flux hemodialysis, especially when using such membranes.

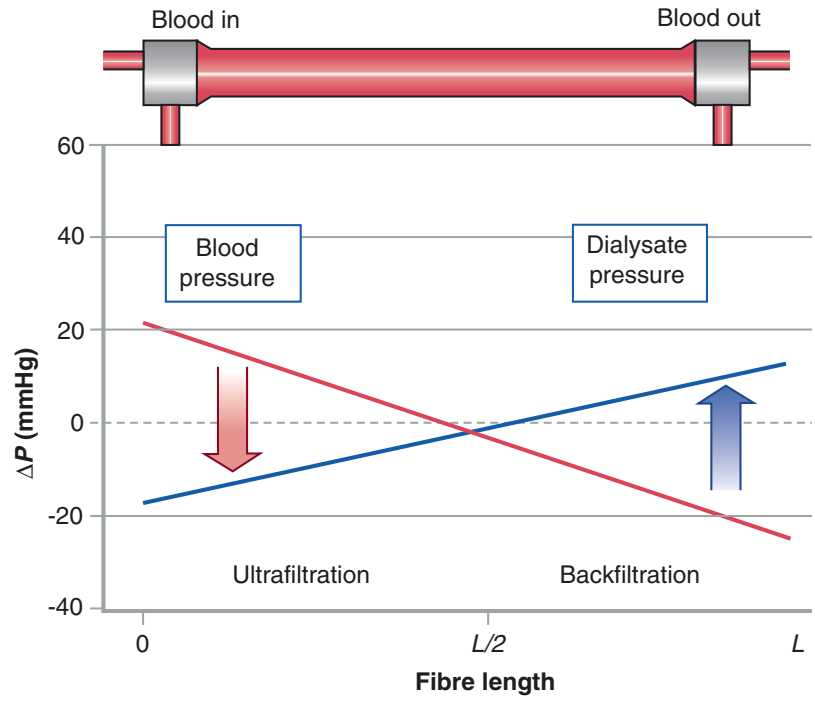

Fig. 2.4 Concept of internal filtration. (Modified from Ronco and Clark (2018) [24])

New Membrane Designs for Enhanced Removal of Large Toxins

While dialyzer classification has been based traditionally on water permeability (flux), new schemes that focus more on solute permeability properties have been proposed. These new classification systems acknowledge the importance of larger MW uremic toxins and the need to incorporate additional membrane classes that have extended removal spectra. High-flux and "protein-leaking" membranes have been defined on the basis of a combination of water permeability, β2m removal parameters (sieving coefficient or clearance), and albumin parameters (sieving coefficient or amount removed) [47]. In this system, the high-flux class is defined by a water permeability of 20–40 ml/h/mmHg/m^2, a β2m SC of 0.7–0.8, and albumin loss of <0.5 g (on the basis of a 4 h hemodialysis treatment), whereas the same parameters defining a protein-leaking membrane are >40 m/h/mmHg/m^2, 0.9–1.0, and 2–6 g, respectively. Although not explicitly stated, the Kuf and β2m SC values correspond to "virgin" membrane performance and do not reflect potential diminutions during treatment as a result of secondary membrane effects. Two new membrane classes, medium cut-off (MCO) and high cut-off (HCO), have been proposed, extending the earlier classification scheme [24]. The HCO class is characterized by a substantial increase in water permeability (relative to both the high-flux and the protein-leaking classes) and a virgin β2m SC of 1.0 [48]. However, the high albumin loss rates associated with this membrane class generally preclude their long-term use for patients with ESRD [49].

Thus, the design challenge is to maximize the removal of large uremic toxins while also maintaining albumin losses in a clinically acceptable range for long-term treatment of patients with ESRD. MCO membranes incorporate high-retention onset (HRO) properties, and this class may hold promise in addressing the challenge of achieving acceptable albumin losses. In comparison to HCO membranes, the MCO class is intended to preserve the β2m sieving characteristics and to improve the clearance of other large molecular weight solutes (e.g., free antibody light chains) while demonstrating a marked reduction in albumin permeability (Fig. 2.5).

Solute Removal by Adsorption

For certain HD membranes, adsorption (binding) may be the dominant or sole mechanism by which some hydrophobic compounds (e.g., peptides

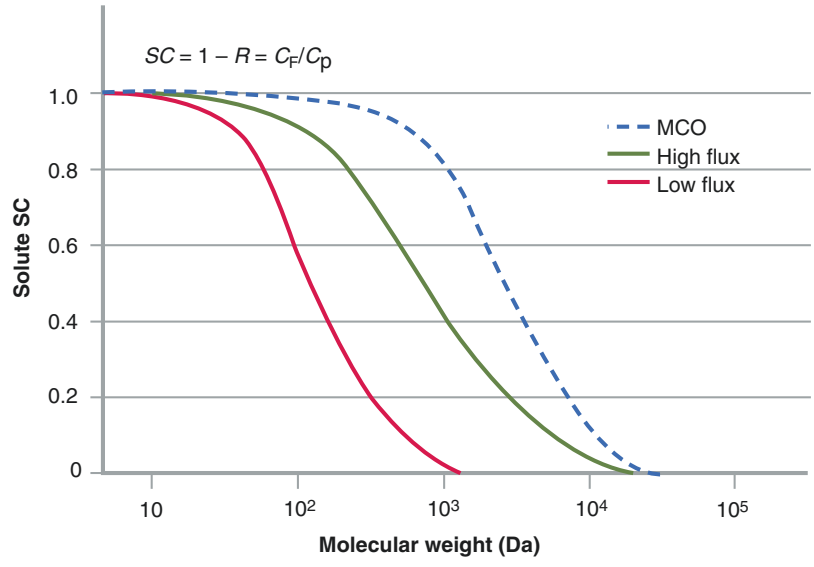

Fig. 2.5 Sieving coefficient curves for low-flux, standard high-flux, and medium cut-off (MCO) dialyzers. (Modified from Ronco and Clark (2018) [24])

and proteins) are removed [50–52]. The adsorptive surface area of a membrane resides primarily in the pore structure rather than the nominal surface area. As such, the adsorption of a LMW protein is highly dependent on access of the protein to a membrane's internal pore structure [53]. Consequently, adsorption of peptides and LMW proteins, such as β2M, to low-flux membranes is not expected to be clinically significant, at least in comparison to that which occurs to high-flux membranes. The adsorption affinity of certain high-flux synthetic membranes for proteins and peptides is particularly high, generally attributable to the relative hydrophobicity of these membranes [54].

Peritoneal Dialysis: Biologic and Mass Transfer Considerations

The peritoneal dialysis system has three major components: (1) the peritoneal microcirculation, (2) the peritoneal membrane, and (3) the dialysate compartment that includes the composition of the solution and the modalities of delivery. All these three components may have an important impact on the final performance of the technique [55].

Factors Affecting Solute Transport

The Dialysate Compartment In Fig. 2.6, urea clearance is plotted against dialysate flow rate. The curve identifies three specific regions. The first region includes the dialysate flow rates typical for continuous ambulatory peritoneal dialysis (CAPD) involving three to five exchanges/day. In this region, the correlation is very steep, and clearance displays significant changes even in response to minimal changes in the dialysate flow. This region is therefore dialysate flow dependent or flow limited, since the volume of the dialysate per day is the factor that chiefly limits the clearance value. In this region, it would be simple theoretically to increase the dialysate flow by a few mL/day to achieve much higher clearances and, consequently, significant increases in Kt/V. However, while theoretically possible this would not be feasible in practice since it would mean carrying out six to ten exchanges/day. Therefore, a typical CAPD technique is basically dialysate flow limited. The only possible way to increase the dialysate flow without increasing the number of exchanges is to increase the volume of solution per exchange.

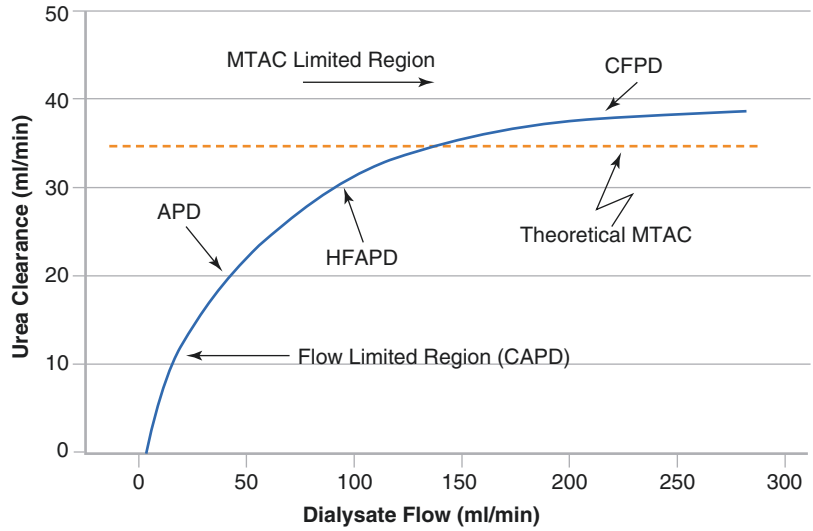

Fig. 2.6 Plot of urea clearance vs. dialysate flow rate in peritoneal dialysis. (Modified from Ronco and Clark (2001) [17])

The second part of the curve is the typical region of automated or intermittent peritoneal dialysis. The dialysate flows may vary significantly due to a variation of the dwell time (from 30 min to 0) and on the number of exchanges per day. Assuming a 30 min dwell time and 20 min for influx and outflow, 12 2 liter exchanges can be performed overnight for an overall duration of 10 h. Finally, the third part of the curve of Fig. 2.6 is the region where the plateau is reached, and further increases in dialysate flow rates do not result in parallel increases in clearance. This region has been explored experimentally utilizing continuous flow peritoneal dialysis (CFPD) performed with double lumen peritoneal catheters [56] and theoretical mathematical models based on mass transfer-area coefficient (MTC) calculations [57]. The value of the mass transfer coefficient is a function of the product of the overall permeability of the peritoneum and the available surface area of the membrane. This parameter is based on the calculation made for each single subject of the maximal clearance theoretically achievable at infinite blood and dialysate flow rates (i.e., at a constantly maximal gradient for diffusion).

The abovementioned regions of the curve describe the relationship between dialysate flow and solute transport. Other factors such as dialysate temperature, intraperitoneal volume, and dialysate osmolality represent further factors affecting solute transport either by increasing the diffusion process or by adding some convective transport due to increased ultrafiltration rates.

The Peritoneal Dialysis Membrane The peritoneal dialysis membrane is a living structure that can be considered more a functional barrier than a precisely defined anatomical structure. Based on the flow/clearance curve described above, a question may arise: Why is the value of the MTC so low in peritoneal dialysis compared with other dialysis treatments, and is the membrane involved in such limitations?

The three-pore model has been proposed by Rippe et al. to explain the peculiar behavior of the peritoneal membrane in relation to macromolecules, micromolecules, and water transport [58]. According to this model, human peritoneum appears to behave as a membrane with a series of differently sized pores: large pores of 25 nm (macromolecule transport), small pores of 5 nm (micromolecule transport), and ultrasmall pores (water transport). The anatomical structure of these ultrasmall pores corresponds to the water channels created by a specific protein (aquaporin) acting as a carrier for water molecules.

This model locates the main resistance to transport at the level of the capillary wall, considering all other anatomical structures as a negligible site of resistance. Only recently, the interstitium has been included as an additional site of resistance. A controversial opinion is offered by the "distributed model" of Flessner et al. [59]. In this model, the main resistance to transport is apparently located in the interstitial tissue. This anatomical entity consists of a double density material, containing water and glycosaminoglycans in different proportions. The interstitial matrix seems to act as the main site of resistance to solute and water transport from the blood stream to the peritoneal cavity. The solute diffusivity in free water is greater than that in the tissue by more than one order of magnitude. Accordingly, not only the structure of the interstitium but also the thickness of the glycosaminoglycan layer may play an important role in restricting the diffusive transport of solutes. There is a certain discrepancy between the two models, and overall transport process is probably governed by a more complex and integrated series of events, each with a remarkable but not absolute importance.

The Peritoneal Microcirculation Despite several lines of evidence suggesting that peritoneal blood flow should be high enough to avoid any limitation in solute clearances and ultrafiltration, the real impact of effective blood flow on the efficiency of the peritoneal dialysis system is still controversial [60]. Experimental work has in fact suggested that peritoneal ultrafiltration and solute clearances might be blood flow limited at least in some conditions [61].

Although mesenteric blood flow averages 10% of cardiac output, peritoneal capillary blood flow seems to vary between 50 and 100 mL/min. "Effective" flow involved in peritoneal exchanges is, however, unknown and it could be much lower. Gas clearance studies have suggested that peritoneal blood flow may be as high as 68–82 mL/min [62], while other studies have suggested much lower values of effective blood flow [63]. Gas clearance studies were based on the assumption that peritoneal gas clearance is equivalent to effective blood flow, but this assumption may not necessarily represent the actual condition. In recent studies, we have obtained an indirect measure of effective blood flow of between 25 and 45 mL/min [64].

When peritoneal dialysis is carried out with short exchanges and high dialysate flows, solute clearances and ultrafiltration rate are still rather low if compared with extracorporeal HD. Some authors have hypothesized these parameters to be limited mostly by the permeability of peritoneal mesothelium or by the peritoneal membrane as a whole (vascular endothelium, interstitium, and mesothelium). As an alternative, we have proposed that peritoneal blood flow might be the major limiting factor in rapid peritoneal dialysis exchanges [63, 65, 66].

The results obtained by a study in which a fragment of human peritoneum was perfused in a closed vascular loop displayed a linear correlation between the inlet blood flow and the rate of ultrafiltration, with a stable value of the filtration fraction [61]. The linear correlation between small solute clearance and blood flow, even at these high blood flows, seems to suggest that small solute clearance in peritoneal dialysis is probably limited more by the low effective blood flow than by the low permeability of the peritoneal membrane [67]. For larger solutes such as inulin, the low diffusion coefficients of the molecule may represent the most important limitation to transport. All these observations led to the formulation of the "nearest capillary hypothesis" [68].

Considering the peritoneal microvasculature as a network of capillaries with a three-dimensional distribution and different distances from the mesothelium, the diffusion distances of solutes as well as the glucose backdiffusion distances may be different in different populations of capillaries. In this condition, the capillary situated closest to the mesothelium would experience a greater osmotic effect compared with those located further away, presenting a filtration fraction much higher compared with the others. The final effect would be represented by an average value of clearance and ultrafiltration to which proximal and distant capillaries are differently contributing. Clearance and ultrafiltration could be limited by low blood flow at least in the capillaries closest to the peritoneal mesothelium. While in distant capillaries blood flow could be enough to avoid significant limitations, the effective blood flow in the capillaries closest to mesothelium might be too low. The vascular reserve, represented by the most distant capillaries, would only participate partially in the peritoneal exchanges because of the greater distance to the mesothelium and the interference of the interstitial surrounding tissue. In such a condition, the central role of the interstitium becomes evident as well as its hydration state.

Relationship Between Clearance and Mass Removal Rate Among Various Renal Replacement Therapies

Quantification of solute removal by RRT is complicated by the confusion relating to the relationship between clearance and mass removal for different therapies. Exploring this relationship for the renal handling of urea at differing levels of native kidney function is an instructive first step. By definition [69], solute clearance (K) is the ratio of mass removal rate (N) to blood solute concentration (C_B):

$$K = N / C_B \tag{2.8}$$

From this relatively simple expression, it is clear that a defined relationship between clear-

ance and mass removal rate is not necessarily expected to exist. The assumption of a steady-state condition in this situation implies that overall removal of a solute is exactly balanced by its generation to produce a constant blood concentration. Therefore, for two patients with widely different levels of native kidney function but the same rate of urea generation (i.e., dietary protein intake), steady state is characterized by equivalent mass removal rates but significantly different urea clearance and BUN values.

The situation is more complicated in renal failure patients treated with various forms of RRT. As discussed by Henderson et al. [70], the mass removal rate of small solutes like urea is very high during the early stage of an intermittent HD treatment due to a favorable transmembrane concentration gradient for diffusion at this time. However, as this gradient dissipates, mass removal rate declines despite a constant dialyzer urea clearance (assuming dialyzer function is preserved during the treatment) (Fig. 2.7a). A different time-dependent relationship between instantaneous clearance and mass removal rate is observed during a typical CAPD exchange. As also described by Henderson et al. (Fig. 2.7b), instantaneous clearance progressively falls during the course of an exchange concomitant with a decreasing transmembrane concentration gradient. Therefore, both mass removal rate and clearance, derived by measuring solute mass in the effluent dialysate collected over

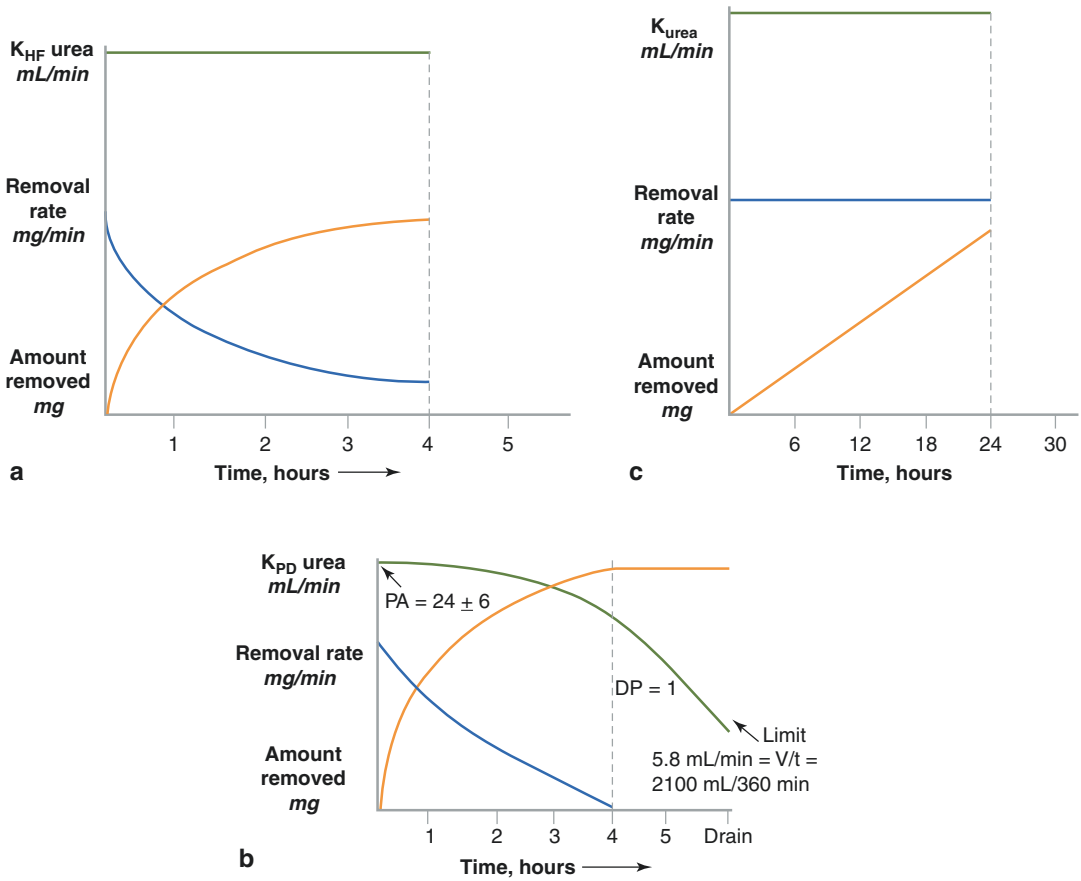

Fig. 2.7 Relationship between clearance and mass removal rate for intermittent hemodialysis (**a**), peritoneal dialysis (**b**), and continuous renal replacement therapy (**c**). (Modified from Clark and Henderson (2001) [71])

an entire exchange, are actually time-averaged parameters. Finally, continuous RRT (CRRT) used in AKI provides additional proof that the relationship between clearance and mass removal rate is therapy specific. In Fig. 2.7c, this relationship for CRRT operated at steady state with respect to BUN (in a patient with a constant protein catabolic rate) is shown [71]. In this situation, as long as urea clearance by the hemofilter is constant, mass removal rate is also constant such that the two parallel one another, and cumulative removal is related to time in a linear manner.

Clearance as a Dialyzer Performance Parameter

Whole-Blood Clearance

For a hemodialyzer, mass removal rate is simply the difference between the rate of solute mass (i.e., product of flow rate and concentration) presented to the dialyzer in the arterial bloodline and the rate of solute mass leaving the dialyzer in the venous blood line. This mass balance applied to the dialyzer results in the classical (i.e., arteriovenous) whole-blood dialyzer clearance equation [72]:

$$K_B = \left[\left(Q_{Bi} * C_{Bi}\right) - \left(Q_{Bo} * C_{Bo}\right)\right] / C_{Bi} + Q_F * \left(C_{Bo} / C_{Bi}\right) \tag{2.9}$$

In this equation, K_B is whole-blood clearance, Q_B is blood flow rate, C_B is whole-blood solute concentration, and Q_F is net ultrafiltration rate. [The subscripts "i" and "o" refer to the inlet (arterial) and outlet (venous) blood lines.]

It is important to note that diffusive, convective, and possibly adsorptive solute removal occur simultaneously in HD. For a non-adsorbing solute like urea, diffusion and convection interact in such a manner that total solute removal is significantly less than what is expected if the individual components are simply added together. This phenomenon is explained in the following way. Diffusive removal results in a decrease in solute concentration in the blood compartment along the axial length (i.e., from blood inlet to blood outlet) of the hemodialyzer. As convective solute removal is directly proportional to the blood compartment concentration, convective solute removal also decreases as a function of this axial concentration gradient. On the other hand, hemoconcentration resulting from ultrafiltration of plasma water causes a progressive increase in plasma protein concentration and hematocrit along the axial length of the dialyzer. This hemoconcentration and resultant hyperviscosity causes an increase in diffusive mass transfer resistance and a decrease in solute transport by this mechanism. The effect of this interaction on overall solute removal has been analyzed rigorously by numerous investigators. The most useful quantification has been developed by Jaffrin [73]:

$$K_T = K_D + Q_F * T_r \tag{2.10}$$

In this equation, K_T is total solute clearance, K_D is diffusive clearance under conditions of no net ultrafiltration, and the final term is the convective component of clearance. The latter term is a function of the ultrafiltration rate (Q_F) and an experimentally derived transmittance coefficient (T_r), such that:

$$T_r = S\left(1 - K_D / Q_B\right) \tag{2.11}$$

where S is solute sieving coefficient. Thus, T_r for a particular solute is dependent on the efficiency of diffusive removal. At very low values of K_D/Q_B, diffusion has a very small impact on blood compartment concentrations, and the convective component of clearance closely approximates the quantity S^*Q_F. However, with increasing efficiency of diffusive removal (i.e., increasing K_D/Q_B), blood compartment concentrations are significantly influenced. The result is

a decrease in T_r and, consequently, in the convective contribution to total clearance.

Blood Water and Plasma Clearance

An implicit assumption in the determination of whole-blood clearance is that the volume from which the solute is cleared is the actual volume of blood transiting through the dialyzer at a certain time. This assumption is incorrect for two reasons. First, in both the erythron and plasma components of blood, a certain volume is comprised of solids (proteins or lipids) rather than water. Second, for solutes like creatinine and phosphate which are distributed in both the erythron and plasma water, slow mass transfer from the intracellular space to the plasma space (relative to mass transfer across the dialyzer) results in relative sequestration (compartmentalization) in the former compartment [74–76]. This reduces the *effective* volume of distribution from which these solutes can be cleared *in the dialyzer*. As such, whole-blood dialyzer clearances derived by using plasma water concentrations in conjunction with blood flow rates, a common practice in dialyzer evaluations, result in a significant overestimation of actual solute removal. The more appropriate approach is to employ blood water clearances, which account for the above hematocrit-dependent effects on effective intradialyzer solute distribution volume [77]:

$$Q_{BW} = 0.93 * Q_B \left[1 - \mathrm{Hct} + K\left(1 - e^{-\alpha t}\right)\mathrm{Hct} \right] \tag{2.12}$$

where Q_{BW} is blood water flow rate. In this equation, for a given solute, K is the RBC water/plasma water partition coefficient for a given solute, α is the transcellular rate constant (units: time^{-1}), and t is the characteristic dialyzer residence time. Estimates for these parameters have been provided by numerous prior studies and have been summarized by Shinaberger et al. [78]. (The factor 0.93 in Eq. (2.12) corrects for the volume of plasma occupied by plasma proteins and lipids.) Finally, K_{BW} can be calculated by substituting Q_{BW} for Q_B in Eq. (2.9).

Although the distribution volume of many uremic solutes approximates total body water, it is much more limited for other toxins, particularly those of larger MW. For example, the distribution space of β2M and many other LMW proteins is the extracellular volume. Consequently, when using Eq. (2.2) to determine β2M clearance, plasma flow rates (inlet and outlet) should replace blood flow rates in the first term of the right-hand side of the equation.

The distinction between whole blood, blood water, and plasma clearances is very important when interpreting clinical data. However, clearances provided by dialyzer manufacturers are typically in vitro data generated from experiments in which the blood compartment fluid is an aqueous solution. Although these data provide useful information to the clinician, they overestimate actual dialyzer performance that can be achieved clinically (under the same conditions). This overestimation is related to the inability of aqueous-based experiments to capture the effects of red blood cells (see above) and plasma proteins (see below) on solute mass transfer.

Dialysate-Side Clearance

As indicated in Eq. (2.8), solute clearance is the ratio of mass removal rate to blood concentration. Although blood-side measurements are typically used to determine solute mass removal rate, clearance can also be estimated from dialysate-side measurements:

$$K_D = Q_{Do} * C_{Do} / C_{Bi} \tag{2.13}$$

In this equation, dialysate-side solute clearance (K_D) is determined by measuring the rate of mass appearance in the effluent dialysate stream (Q_{Do}*C_{Do}). Dialysate-side measurements provide more accurate mass transfer information than do blood-side determinations and are generally considered the "gold standard" dialyzer evaluation technique. Relative to dialysate-side values, whole-blood clearances substantially overestimate true dialyzer performance [77]. Blood water clearances also moderately overestimate dialyzer

performance, although the agreement between these and simultaneous dialysate-side values (for non-adsorbing solutes) is usually within 5% under rigorous test conditions. The major disadvantage of dialysate-based clearance techniques is the need to assay solute concentrations at very low concentrations. For some solutes (e.g., phosphate), these dilute concentrations may be difficult to assay with standard automated chemistry devices.

Whole-Body Clearance

The discussion to this point has focused on clearance of a solute by the dialyzer but has not focused on the effects of solute compartmentalization on effective dialytic removal. As discussed above, one compartment in which solute sequestration occurs is the red blood cell water. Compartmentalization may also occur during HD within other organ systems or anatomical spaces. During HD, direct removal of a particular solute can only occur from that portion of its volume of distribution which actually perfuses the dialyzer, and sequestration of solute occurs in the remaining volume of distribution. Solute compartmentalization involves an interplay between dialyzer solute clearance and patient/solute parameters, such as compartment volumes and intercompartment mass transfer resistances [79]. Even if solute removal by the dialyzer is relatively efficient, overall (effective) solute removal may be limited by slow intercompartment mass transfer within the body.

To account for these effects of "intracorporeal" solute compartmentalization on overall solute removal, many clinicians prefer to use whole-body rather than dialyzer clearance, as the former is felt to be a better measure of overall treatment efficacy [80]. Whole-body clearance methodologies employ blood samples obtained before and after the HD treatment. An example of a widely used whole-body clearance approach is the second-generation Daugirdas equation [81]. In this approach, a logarithmic relationship between delivered urea Kt/V and the extent of the intradialytic reduction in the BUN is assumed. Two issues complicate the use of these methodologies. One is the assumed distribution volume of the solute for which the clearance is being estimated and whether or not this volume is multi-compartmental. The second important consideration, incorporation of the effects of post-HD rebound, is closely tied to multi-compartment kinetics [79].

References

1. Upadhyay A, Inker LA, Levey AS. Chronic kidney disease: definition, classification, and approach to management. In: Turner NN, et al., editors. Oxford textbook of nephrology. 4th ed. Oxford: Oxford University Press; 2015.
2. Clark WR, Gao D. Determinants of uremic toxin removal. Nephrol Dial Transplant. 2002;17(Suppl 3):30–4.
3. Vanholder R, Argiles A, Baurmeister U, et al. Uremic toxicity: present state of the art. Int J Artif Organs. 2001;24:695–725.
4. Depner TA. Uremic toxicity: urea and beyond. Sem Dial. 2001;14:246–51.
5. Clark WR, Gao D. Low-molecular weight proteins in end-stage renal disease: potential toxicity and dialytic removal mechanisms. J Am Soc Nephrol. 2002;13:S41–7.
6. Chmielewski M, Cohen G, Wiecek A, Carrero JJ. The peptidic middle molecules: is molecular weight doing the trick? Semin Nephrol. 2014;34:118–34.
7. Carone FA, Peterson DR, Oparil S, Pullman TN. Renal tubular transport and catabolism of proteins and peptides. Kidney Int. 1979;16:271–8.
8. Maack T, Johnson V, Kau ST, Figueiredo J, Sigulem D. Renal filtration, transport, and metabolism of low-molecular weight proteins: a review. Kidney Int. 1979;16:251–70.
9. Sirich TL, Meyer TW, Gondouin B, Brunet P, Niwa T. Protein-bound molecules: a large family with a bad character. Semin Nephrol. 2014;34:106–17.
10. Vanholder R, Schepers E, Pletinck A, Nagler E, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. J Am Soc Nephrol. 2014;25:1897–907.
11. Nigam SK, Wu W, Bush KT, Hoenig MP, Blantz RC, Bhatnagar V. Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. Clin J Am Soc Nephrol. 2015;10:2039–49.
12. Nigam SK, Bush KT, Martovetsky G, et al. The organic anion transporter (OAT) family: a systems biology perspective. Physiol Rev. 2015;95:83–123.
13. Lowenstein J, Grantham JJ. Residual renal function: a paradigm shift. Kidney Int. 2017;91:561–5.
14. Mair RD, Sirich TL, Plummer NS, Meyer TW. Characteristics of colon-derived uremic solutes. Clin J Am Soc Nephrol. 2018;13:1398–404.

15. Clark WR, Laal Dehghani N, Narsimham V, Ronco C. New perspectives on extracorporeal renal replacement therapy for end-stage renal disease: (I) uremic toxins. Blood Purif. 2019;48:299–314.
16. Clark WR. Quantitative characterization of hemodialyzer solute and water transport. Semin Dial. 2001;14:32–6.
17. Ronco C, Clark WR. Factors affecting hemodialysis and peritoneal dialysis efficiency. Semin Dial. 2001;14:257–62.
18. Clark WR, Ronco C. Determinants of hemodialyzer performance and the effect on clinical outcome. Nephrol Dial Transplant. 2001;16(Suppl 3):56–60.
19. Clark WR, Shinaberger JH. Effect of dialysate-side mass transfer resistance on small solute removal in hemodialysis. Blood Purif. 2000;18:260–3.
20. Clark WR, Hamburger RJ, Lysaght MJ. Effect of membrane composition and structure on performance and biocompatibility in hemodialysis. Kidney Int. 1999;56:2005–15.
21. Colton CK, Lowrie EG. Hemodialysis: physical principles and technical considerations. In: Brenner BM, Rector FC, editors. The kidney. 2nd ed. Philadelphia: Saunders; 1981. p. 2425–89.
22. Huang Z, Clark WR, Gao D. Determinants of small solute clearance in hemodialysis. Semin Dial 2005;18:30–35.
23. Bird RB, Stewart WE, Lightfoot EN. Velocity distributions in laminar flow. In: Bird RB, Stewart WE, Lightfoot EN, editors. Transport phenomena. 1st ed. New York: Wiley; 1960. p. 34–70.
24. Ronco C, Clark WR. Haemodialysis membranes. Nat Rev Nephrol. 2018;14:394–410.
25. Ronco C, Ghezzi PM, Brendolan A, Crepaldi C, La Greca G. The haemodialysis system: basic mechanisms of water and solute transport in extracorporeal renal replacement therapies. Nephrol Dial Transplant. 1998;13(Suppl. 6):3–9.
26. Villarroel F, Klein E, Holland F. Solute flux in hemodialysis and hemofiltration membranes. Trans Am Soc Artif Organs. 1977;23:225–32.
27. Zydney AL. Bulk mass transport limitations during high-flux hemodialysis. Artif. Organs. 1993;17:919–24.
28. Lysaght MJ. Hemodialysis membranes in transition. Contrib Nephrol. 1988;61:1–17.
29. Henderson LW. Biophysics of ultrafiltration and hemofiltration. In: Jacobs C, Kjellstrand C, Koch K, Winchester J, editors. Replacement of renal function by dialysis. Dordrecht: Springer; 1996. p. 114–45.
30. Takeyama T, Sakai Y. Polymethylmethacrylate: one biomaterial for a series of membranes. Contrib Nephrol. 1988;125:9–24.
31. Bird RB, Stewart WE, Lightfoot EN. In: Bird RB, Stewart WE, Lightfoot EN, editors. Transport phenomena. 1st ed. New York: Wiley; 1960. p. 34–70.
32. Huang Z, Gao D, Letteri JJ, Clark WR. Blood-membrane interactions during dialysis. Semin Dial. 2009;22:623–8.
33. Langsdorf LJ, Zydney AL. Effect of blood contact on the transport properties of hemodialysis membranes: a two-layer model. Blood Purif. 1994;12:292–307.
34. Morti SM, Zydney AL. Protein-membrane interactions during hemodialysis: effects on solute transport. ASAIO J. 1998;44:319–26.
35. Rockel A, et al. Permeability and secondary membrane formation of a high flux polysulfone hemofilter. Kidney Int. 1986;30:429–432.4.
36. Henderson LW. Pre vs. post dilution hemofiltration. Clin Nephrol. 1979;11:120–4.
37. Ofsthun NJ, Zydney AL. Importance of convection in artificial kidney treatment. Contrib Nephrol. 1994;108:53–70.
38. Kim S. Characteristics of protein removal in hemodiafiltration. Contrib Nephrol. 1994;108:23–37.
39. Fiore GB, Guadagni G, Lupi A, Ricci Z, Ronco C. A new semiempirical mathematical model for prediction of internal filtration in hollow fiber hemodialyzers. Blood Purif. 2006;24:555–68.
40. Lorenzin A, Neri M, Clark WR, Ronco C. Experimental measurement filtration of internal rate for a new medium cut-off dialyzer. Contrib Nephrol. 2017;191:127–41.
41. Ronco C, Brendolan A, Lupi A, Bettini MC, La Greca G. Enhancement of convective transport by internal filtration in a modified experimental dialyzer. Kidney Int. 1998;54:979–85.
42. Fiore GB, Ronco C. Principles and practice of internal hemodiafiltration. Contrib Nephrol. 2007;158:177–84.
43. Mineshima M. New trends in HDF: validity of internal filtration-enhanced hemodialysis. Blood Purif. 2004;22(Suppl. 2):60–6.
44. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58:809–17.
45. Ronco C, La Manna G. Expanded hemodialysis: a new therapy for a new class of membranes. Contrib Nephrol. 2017;190:124–33.
46. Ronco C. The rise of expanded hemodialysis. Blood Purif. 2017;44:I–VIII.
47. Ward RA. Protein-leaking membranes for hemodialysis: a new class of membranes in search of an application? J Am Soc Nephrol. 2005;6:2421–30.
48. Boschetti-de-Fierro A, Voigt M, Storr M, Krause B. Extended characterization of a new class of membranes for blood purification: the high cut-off membranes. Int J Artif Organs. 2013;36:455–63.
49. Rousseau-Gagnon M, Agharazii M, De Serres SA, Desmeules S. Effectiveness of haemodiafiltration with heat sterilized high-flux polyphenylene HF dialyzer in reducing free light chains in patients with myeloma cast nephropathy. PLoS One. 2015;10:e0140463.
50. Jorstad S, Smeby L, Balstad T, Wideroe T. Removal, generation, and adsorption of beta-2-microglobulin during hemofiltration with five different membranes. Blood Purif. 1988;6:96–105.
51. Jindal KK, McDougall J, Woods B, Nowakowski L, Goldstein MB. A study of the basic principles deter-

mining the performance of several high-flux dialyzers. Am J Kidney Dis. 1989;14:507–11.
52. Klinke B, Rockel A, Abdelhamid S, Fiegel P, Walb D. Transmembrane transport and adsorption of beta2-microglobulin during hemodialysis using polysulfone, polyacrylonitrile, polymethylmethacrylate, and cuprammonium rayon membranes. Int J Artif Organs. 1989;12:697–702.
53. Clark WR, Macias WL, Molitoris BA, Wang NHL. ß$_2$-microglobulin membrane adsorption: equilibrium and kinetic characterization. Kidney Int. 1994;46:1140–6.
54. Clark WR, Macias WL, Molitoris BA, Wang NHL. Plasma protein adsorption to highly permeable hemodialysis membranes. Kidney Int. 1995;48:481–7.
55. Ronco C, Brendolan A, La Greca G. The peritoneal dialysis system. Nephrol Dial Transplant. 1998;13(Suppl 6):94–9.
56. Amerling R, Ronco C, Levin NW. Continuous flow peritoneal dialysis. Perit Dial Int. 2000;20(Suppl 2):S178–82.
57. Ronco C. Limitations of peritoneal dialysis. Kidney Int. 1996;50(Suppl 56):S69–74.
58. Rippe B, Simonsen O, Stelin G. Clinical implications of a three pore model of peritoneal transport. Perit Dial Int. 1991;7:3–9.
59. Dedrick RL, Flessner MF, Collins JM, Schulz JS. Is the peritoneum a membrane? ASAIO J. 1982;5:1–8.
60. Ronco C, Feriani M, Chiaramonte S, Brendolan A, Milan M, La Greca G. Peritoneal blood flow: does it matter? Perit Dial Int. 1996;16(Suppl 1):70–5.
61. Ronco C, Brendolan A, Crepaldi C, Conz P, Bragantini L, Milan M, La Greca G. Ultrafiltration and clearance studies in human isolated peritoneal vascular loops. Blood Purif. 1994;12:233–42.
62. Aune S. Transperitoneal exchanges II: peritoneal blood flow estimated by hydrogen gas clearance. Scand J Gastroenterol. 1970;5:99–102.
63. Ronco C, Borin D, Brendolan A, La Greca G. Influence of blood flow and plasma proteins on ultrafiltration rate in peritoneal dialysis. In: Maher JF, Winchester JF, editors. Frontiers in peritoneal dialysis. New York: Friedrich and Associates; 1986. p. 82–6.
64. Ronco C, Feriani M, Chiaramonte S, La Greca G. Pathophysiology of ultrafiltration in peritoneal dialysis. Perit Dial Int. 1990;10:119–26.
65. Waniewski J, Werynski A, Lindholm B. Effect of blood perfusion on diffusive transport in peritoneal dialysis. Kidney Int. 1999;56:707–13.
66. Kim M, Lofthouse J, Flessner MF. A method to test blood flow limitation of peritoneal blood transport. J Am Soc Nephrol. 1997;8:471–4.
67. Kim M, Lofthouse J, Flessner MF. Blood flow limitations of solute transport across the visceral peritoneum. J Am Soc Nephrol. 1997;8:1946–50.
68. Ronco C. The nearest capillary hypothesis: a novel approach to peritoneal transport physiology. Perit Dial Int. 1996;16:121–5.
69. Henderson L. Why do we use clearance? Blood Purif. 1995;13:283–8.
70. Henderson L, Leypoldt JK, Lysaght M, Cheung A. Death on dialysis and the time/flux trade-off. Blood Purif. 1997;15:1–14.
71. Clark WR, Henderson LW. Renal vs. continuous vs. intermittent therapies for removal of uremic toxins. Kidney Int. 2001;59(Suppl 78):S298–303.
72. Clark WR, Shinaberger JH. Clinical evaluation of a new high-efficiency hemodialyzer: polysynthane (PSN™). ASAIO J. 2000;46:288–92.
73. Jaffrin MY. Convective mass transfer in hemodialysis. Artif Organs. 1995;19:1162–71.
74. Katz M, Hull A. Transcellular creatinine disequilibrium and its significance in hemodialysis. Nephron. 1974;12:171–7.
75. Slatsky M, Schindhelm K, Farrell P. Creatinine transfer between red blood cells and plasma: a comparison between normal and uremic subjects. Nephron. 1978;22:514–21.
76. Schmidt B, Ward R. The impact of erythropoietin on hemodialyzer design and performance. Artif Organs. 1989;13:35–42.
77. Lim V, Flanigan M, Fangman J. Effect of hematocrit on solute removal during high efficiency hemodialysis. Kidney Int. 1990;37:1557–62.
78. Shinaberger J, Miller J, Gardner P. Erythropoietin alert: risks of high hematocrit hemodialysis. ASAIO Trans. 1988;34:179–84.
79. Clark WR, Leypoldt JK, Henderson LW, Mueller BA, Scott MK, Vonesh EF. Quantifying the effect of changes in the hemodialysis prescription on effective solute removal with a mathematical model. J Am Soc Nephrol. 1999;10:601–10.
80. Clark WR, Rocco MV, Collins AJ. Quantification of hemodialysis: analysis of methods and relevance to clinical outcome. Blood Purif. 1997;15:92–111.
81. Daugirdas JT. Second-generation estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–13.

The Demographics of Dialysis in Children

3

Jeffrey J. Fadrowski and Lesley Rees

Introduction

The use of chronic dialysis to sustain the lives of children with end-stage kidney disease (ESKD) has been available in developed countries since the 1970s [1, 2]. Advances in technology have made long-term dialysis a viable treatment option for pediatric ESKD patients of all ages, from newborns to adolescents [2, 3]. While a successful kidney transplant remains the treatment of choice for all pediatric ESKD patients, almost three-fourths of these children require chronic dialysis while awaiting transplantation for periods ranging from a few months to several years [4, 5].

The pediatric dialysis population is remarkably heterogeneous in many ways, as will be described in this chapter. Unlike adult dialysis populations in which the primary kidney disease diagnoses tend to cluster within a narrow range of etiologies, pediatric dialysis populations display a variety of different primary kidney disorders, many of which must still be considered in overall patient management, despite having reached end-stage levels of kidney function [6].

In this chapter, we have attempted to broadly describe the pediatric dialysis patient population by examining available data on such basic demographic characteristics as age at presentation, primary kidney disease diagnosis, and dialysis modality choice. Comprehensive data on the demographics of a region's or a nation's pediatric dialysis patient population are available from several large ESKD patient registries and a few published reviews [7–13]. Our objective is not to attempt a precise accounting of these data, nor is it to systematically compare findings from one pediatric ESKD registry to another. While the methodology required for such rigorous cross-registry analyses exists, it would require access to data elements beyond the summaries published in available registry reports. Rather, we have attempted to use and interpret available information to provide a snapshot of pediatric chronic dialysis as it has been practiced around the world during the early decades of the twenty-first century.

Sources of Demographic Data on Pediatric Dialysis Patients

The European Dialysis and Transplant Association – European Renal Association (EDTA) The importance of differences that characterize pediatric dialysis patient

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demographics when compared to adult patients was first understood as a result of the pioneering efforts of the EDTA, which has published an annual report containing pediatric summary data from a group of European countries for more than 20 years. Many of the survey techniques and conventions piloted and refined by the EDTA were later adopted by pediatric registries in other regions. During the past few decades, the work of the EDTA with regard to pediatric dialysis was supplanted by the development of national ESKD patient registries, some of which have focused on pediatric issues. From its new coordinating center at the University of Amsterdam, the EDTA resumed publication of an annual report in 1998. The latest ERA-EDTA 2016 Report, available at https://www.era-edta-reg.org/index.jsp, contains summary data from 36 European countries on patients of all ages in which information on children is largely reported in aggregate for the age group 0–19 years.

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) The NAPRTCS is a voluntary collaborative data-sharing and research effort supported by more than 140 pediatric kidney treatment centers in the United States, Canada, Mexico, and Costa Rica. Founded in 1987 to study kidney transplantation, the NAPRTCS expanded in 1992 to include children receiving dialysis in participating NAPRTCS transplant centers. NAPRTCS enrolls dialysis patients up to their 21st birthday and thus describes a slightly older cohort than the other registries. Information was obtained for the present review from the NAPRTCS 2011 and 2014 Annual Data Reports, available at https://web.emmes.com/study/ped/annlrept/annlrept.html [9, 14].

The United States Renal Data System (USRDS) The USRDS provides a different perspective on pediatric dialysis in the United States from that seen in the NAPRTCS. The USRDS pediatric data are compiled from reports submitted to the US government healthcare funding agency on all dialysis patients eligible for government support, which includes almost all pediatric patients. Thus, while the NAPRTCS contains pediatric data compiled only in specialized pediatric kidney centers in four North American countries, the USRDS includes data on children treated in both adult and pediatric centers in the United States. In addition, patients are included in USRDS pediatric reports only if they initiated dialysis prior to their 19th birthday. The 2018 USRDS Annual Data Report is available on the Internet at https://www.usrds.org/adr.aspx [15].

The International Pediatric Peritoneal Dialysis Network (IPPN) IPPN started as a database for peritoneal dialysis (PD) but has now expanded to include hemodialysis (HD) patients as well so that its new name is the *International Pediatric Dialysis Network (IPDN)*. The network is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic dialysis. To date, 3582 patients have been enrolled in the PD registry at 126 contributing centers in 43 countries, and 864 patients have been enrolled in the HD registry at 82 contributing centers in 36 countries (http://www.pedpd.org).

The International Pediatric Nephrology Association (IPNA) IPNA is currently developing a new global registry, the aim being to improve knowledge about the incidence and outcomes of pediatric renal replacement therapy (RRT) around the globe. By use of a questionnaire to its members, so far 94 countries (representing 86.2% of the world childhood population) have responded, and 84 countries report they have the means to provide RRT to children. Among the 84 countries providing RRT, 51 (60.7%) had national registries for both dialysis and transplantation, 9 (10.7%) had either a dialysis or a transplant registry, 6 participated in international registries only (7.1%), and in 18 (21.4%), children on RRT were not followed in any registry (Fig. 3.1). A systematic search of the literature related to this study identified 92 pediatric RRT registries, primarily national registries located in Europe, North America, and Asia [7].

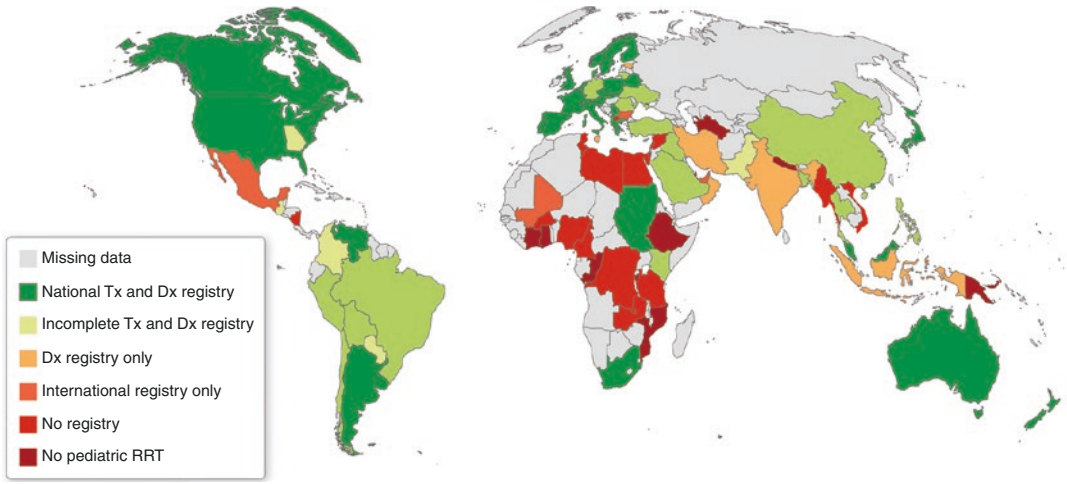

Fig. 3.1 Countries with national pediatric RRT registries in place according to survey. Tx Transplantation, Dx dialysis. (Source: Adapted from Ploos van Amstel/Pediatric Nephrology) [7]

Incidence and Prevalence

Access to Dialysis Around the World

Significant variations in the incidence of RRT in children exist in the world. Figure 3.2 shows the incidence of RRT in children in 2008 by country [16]. There are huge disparities in access to dialysis for children around the world (Fig. 3.3) [7, 17]. Management of the child with ESKD is labor-intensive and costly and is restricted in countries where resources are limited. Indeed, over three quarters of children on RRT live in Europe, North America, or Japan, where such treatment is available to the majority of children. However, children in the rest of the world are not so advantaged: a recent meta-analysis of studies and reports from sub-Saharan African countries found that most children with ESKD remain undiagnosed and untreated and die. Among those who were dialyzed, 61% received one or more dialysis sessions, and only 35% remained on dialysis for at least 3 months. One-third died or were presumed to have died without transplantation. The most likely explanation for the inability to commence or continue treatment was that families were unable to pay [18].

The IPDN looked at the impact of economic conditions on chronic PD practices and outcomes in 33 countries around the world. Compared to higher-income countries, in low-income countries, the dialysis populations had a smaller fraction of children younger than 3 years of age at dialysis initiation and were less likely to have comorbidities in addition to kidney disease. Children on PD in low-income countries were also found to be approximately 1 standard deviation shorter and had worse survival compared to those in wealthier countries [19].

Differences in access to and outcomes of RRT have also been described in developed countries. The incidence of pediatric RRT between 2007 and 2011 varied widely between countries in Europe, with the lowest incidence in Eastern Europe (3.6 per million children [pmc]) and the highest incidence in Northern Europe (8.1 pmc). There was not much variation in the occurrence of specific kidney diseases by region. Among countries that were wealthier and spent more on healthcare and where patients pay less out of pocket for healthcare, rates of RRT were higher. Thus, differences in the macroeconomics of the countries, which limit equal access to healthcare services, are speculated to be the primary driver of the varation in pediatric RRT rates in Europe [20].

In the United States, Medicare, a national health insurance program, pays for dialysis in children and adults if private insurance is not

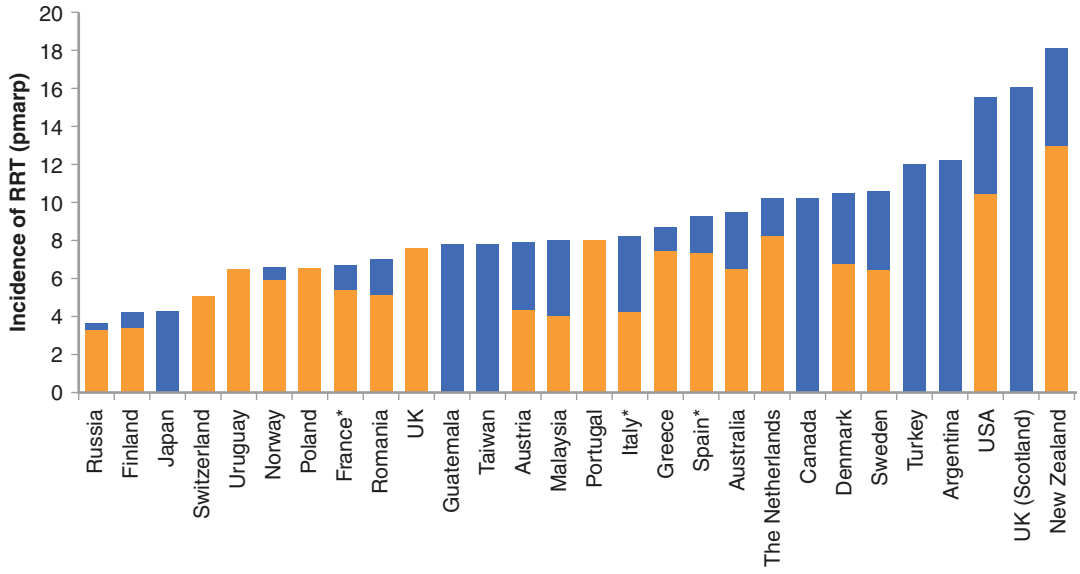

Fig. 3.2 Incidence of RRT in children in 2008 by country. The orange bars correspond to incidence in children aged 0–14 years; the sum of the orange and blue bars corresponds to the incidence in children aged 0–19 years. Pmarp, Per million age-related population. *France 16 out of 26 regions, Italy 13 out of 20 regions, Spain 4 out of 18 regions in the 15- to 19-year-old age group. (Source: Adapted from Harambat/Pediatric Nephrology) [16]

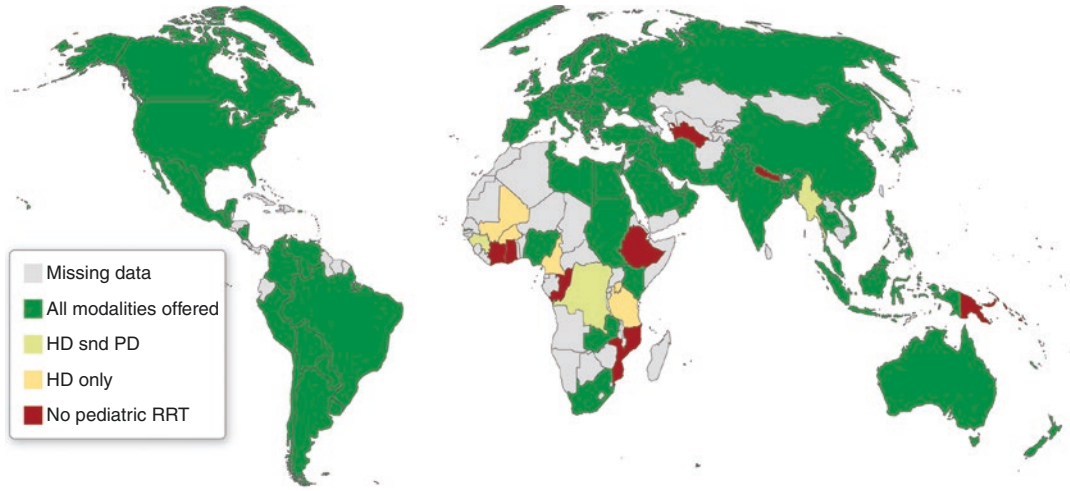

Fig. 3.3 Countries where pediatric RRT (HD, PD, and/or transplant) is offered according to survey of 94 countries. (Source: Adapted from Ploos van Amstel/Pediatric Nephrology) [7]

available. However, differences in access to therapies for ESKD exist. Time to first RRT was examined among African American and non-African American children with CKD with a median age of 10 years. Times to dialysis were shorter among African American children even when accounting for socioeconomic status, yet access to kidney transplant occurred later [21]. Disparity in access to kidney transplant is thought to underly the increased risk of mortality observed in non-Hispanic black children compared to white children on dialysis [22]. Among children with CKD in the USRDS, GFR decline was similar across income groups, but better blood pressure control and correction of height deficits were observed among the highest-income group (≥$75,000/year) compared to the lower groups [23]. Efforts to improve universal access to RRT

are needed globally, and particularly in nations with less economic advantages.

Effect of Era on the Incidence and Prevalence of ESKD in Children

The incidence of ESKD per million population in the United States has declined slightly over the past decade (Fig. 3.4), although the prevalence has been stable (Fig. 3.5) [15]. In Europe, the incidence of ESKD in children aged 0–19 years per million age-related population in 2015–2016 was 8.4. From 2011 to 2016, neither the age ranges nor the proportion of children managed by PD, HD, or transplant has changed (Fig. 3.6) [10].

Effect of Age on the Incidence of RRT and Treatment Modality

The breakdown of patients according to age and treatment modality in Europe is also shown in Fig. 3.6. The USRDS also provides incidence data by age group. In 2015, there were 237 cases in those aged 0–4 years, 115 aged 5–9, 165 aged 10–13, 336 aged 14–17, and 547 aged 18–21 years, for a total of 1400 children in the United States with incident ESKD. Within these age-based cohorts, incidence rates in 2015 were 11.4 per million population (PMP) per year for 0–4-year-olds, 5.0 for 5–9-year-olds, 9.3 for 10–13-year-olds, 19.3 for 14–17-year-olds, and 31.6 for 18–21-year-olds. PD was the most common initial ESKD treatment modality for children aged 9 years and younger. Hemodialysis was the most common initial modality for patients aged 10 years and older (Fig. 3.7). Similar relationships are shown by patient weight, with PD most commonly prescribed as the initial modality in small children weighing less than 20 kg, and initiation with HD becoming more common with increasing patient weight [15]. In Australia and New Zealand from 2008 to 2013, PD was the most common mode of initial RRT among children 0–9 years of age (59%), and HD was the most common among those 10–17 years of age (45%) [24].

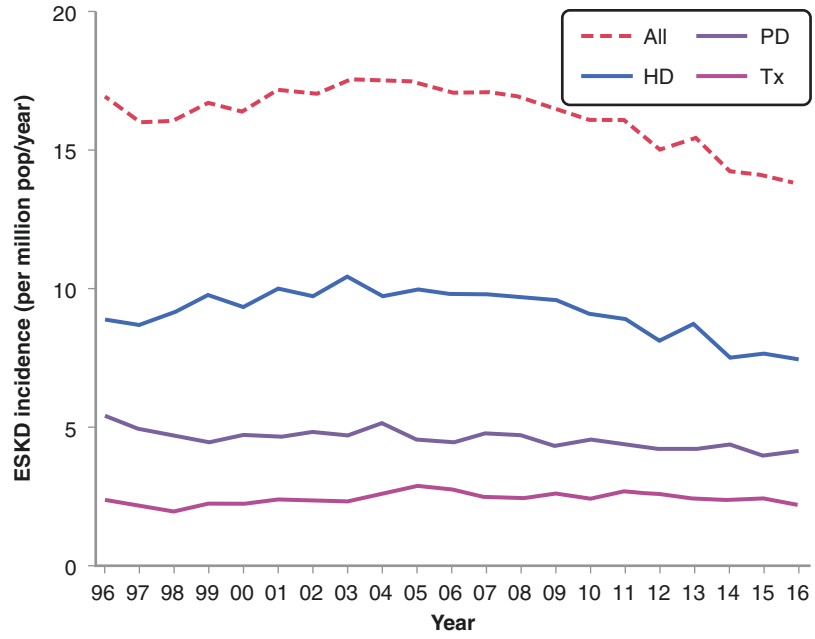

Fig. 3.4 Incidence of ESKD among pediatric patients (aged 0–21 years) per million US population per year by modality, 1996–2016. (Source: Adapted from USRDS 2018 Annual Data Report) [15]

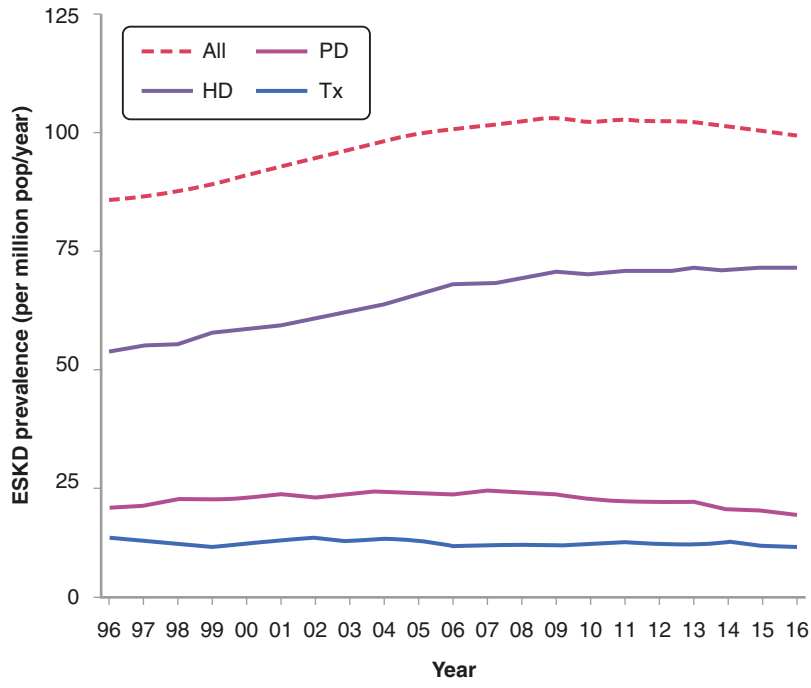

Fig. 3.5 Prevalence of ESKD among pediatric patients (aged 0–21 years) per million US population per year by modality, 1996–2016. (Source: Adapted from USRDS 2018 Annual Data Report) [15]

Cohort	All			0-4			5-9			10-14			15-19		
	HD Pmarp	PD Pmarp	Tx Pmarp	HD Pmarp	PD Pmarp	Tx Pmarp	HD Pmarp	PD Pmarp	Tx Pmarp	HD Pmarp	PD Pmarp	Tx Pmarp	HD Pmarp	PD Pmarp	Tx Pmarp
2011 - 2012	3.8	3.0	2.0	2.5	6.5	0.6	1.3	1.4	2.3	3.4	2.2	3.3	8.1	2.0	1.9
2013 - 2014	3.6	2.5	2.1	1.4	4.9	0.7	2.2	1.3	2.4	4.0	1.6	2.6	6.9	2.3	2.6
2015 - 2016	4.2	2.3	2.5	2.2	4.3	1.1	2.2	0.9	1.3	3.5	1.8	4.1	8.9	2.3	3.6
2011 - 2012*	3.9	2.2	1.8	2.2	4.6	0.7	1.4	0.9	1.6	3.4	1.5	2.4	8.5	1.6	2.5
2013 - 2014*	3.9	2.0	1.8	1.3	3.8	0.9	2.1	1.3	1.5	4.1	1.2	2.2	8.2	1.6	2.6
2015 - 2016*	4.3	1.9	2.1	2.6	3.8	0.8	2.0	0.8	1.4	4.1	1.2	3.0	8.5	1.9	3.3
2013 - 2016* †	4.0	2.0	1.9	2.0	4.0	0.8	1.8	1.0	1.5	3.9	1.3	2.5	8.4	1.7	2.8

** Including data from Estonia since 2013, France (coverage ranging from 99.4% in 2011 to 100% from 2012 onwards), Romania (coverage from 100% in 2011 to 97.8% in 2016), Serbia since 2016, Spain (region of Murcia) since 2012, Switzerland (coverage 99.9% in 2015 and 100% in 2016) since 2016, and the Netherlands (coverage 100% prior to 2016 and 96% in 2016)*
† For 22 patients information opn treatment modality at start was unavailable

Fig. 3.6 Incidence ESKD per million age-related European population by age and treatment modality, 2011–2016. (Source: Adapted from ESPN/ERA-EDTA Registry) [10]

Primary Kidney Disease Diagnosis

Data from Chile, India, Italy, Japan, Kuwait, Nigeria, and the NAPRTCS (United States, Canada, Mexico, Costa Rica) on selected primary kidney diagnoses are summarized in Table 3.1 [5, 25–31]. Data from Chile, India, and Nigeria represent children with advanced chronic kidney disease and ESKD. The Kuwaiti, Italian, and NAPRTCS data describe the primary kidney disorders of prevalent dialysis patients, whereas the data from Japan are from all ESKD patients. The Indian, Kuwaiti, and Nigerian data were obtained from a single center in each country, although in Kuwait at least, the center provided virtually all of the pediatric nephrologic care in the country. Data from the other countries represent multiple centers. Only major diagnostic categories are included. Note the similarities among the registries for many primary kidney disorders. Whereas differences do exist, some are likely due to the lack of uniform coding among registries. The distinction between dysplasia/hypoplasia and vesicoureteral reflux appears particularly variable by registry.

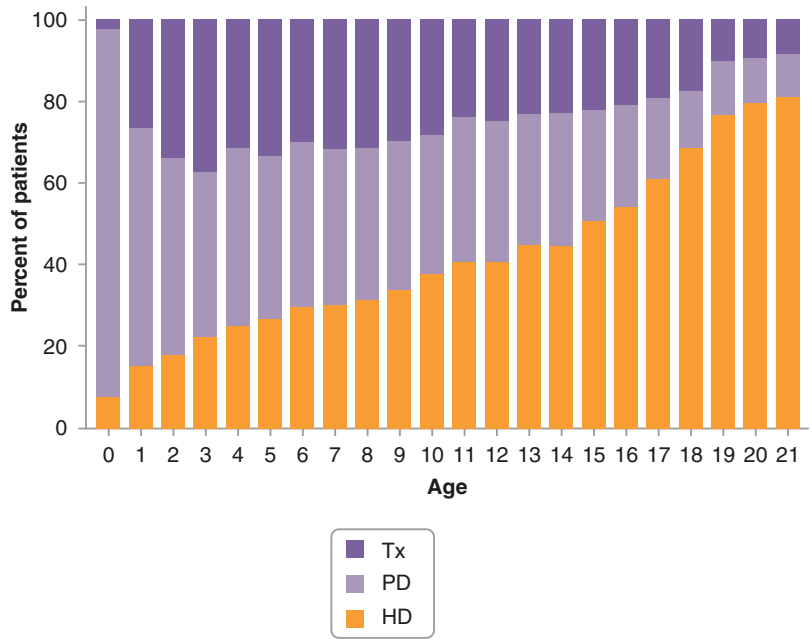

Fig. 3.7 Distribution in pediatric ESKD modality at initiation in the United States by age, 1996–2016. (Source: Adapted from USRDS 2018 Annual Data Report) [15]

Table 3.1 Primary kidney diagnoses as percent of total prevalent patients in seven different areas of the world

Diagnosis	Chile	India	Italy	Japan	Kuwait	Nigeria	NAPRTCS
Aplasia/dysplasia/hypoplasia	20.7	4.9	23.8	28.9	18.7	–	14.2
Glomerulonephritis/FSGS	16.3	27.5	19.7	27.1	6.3	53.3	29.6
Obstructive uropathy/neurogenic bladder	22.0	36.3	13.8	1.7	16.6	28.9	12.6
Congenital nephrotic syndrome	0.004	–	–	5.8	4.2	–	2.6
Polycystic kidney disease	7.5	–	2.2	2.5	8.3	–	2.9
Hemolytic uremic syndrome	7.5	1.6	5.2	2.2	2.1	4.4	3.1
Nephronophthisis	1.8	–	9.0	4.0	2.1	–	–
Reflux nephropathy	16.7	16.7	5.9	5.2	16.6	–	3.5

The distribution of primary kidney diagnoses is also different depending on the age at time of ESKD presentation, as shown in Fig. 3.8 from the United Kingdom's Renal Registry [32]. The predominance of renal dysplastic syndromes and obstructive uropathy seen in Table 3.1 clusters in the younger age groups, whereas older patients are more likely to present with glomerular diseases.

Mortality Risk

The overall 5-year survival rate for 6473 patients under 19 years of age from 36 European countries for the years 2000 through 2013 starting on dialysis was 89.5%. The mortality rate was 28.0 deaths per 1000 patient years overall. The mortality rate was highest (36.0/1000) during the first year of dialysis and in the 0- to 5-year age group (49.4/1000). Children who were selected to start on HD had an increased mortality risk compared with those on PD (adjusted HR 1.39). Compared to PD, those on HD had a higher risk of death in the first year of dialysis (adjusted HR 1.70), when starting at older than 5 years of age (adjusted HR 1.58) and when children had been seen by a nephrologist for only a short time before starting dialysis (adjusted HR 6.55). Selection bias may explain the higher mortality risk in the HD population [33].

Survival for a cohort of 2995 North American pediatric dialysis patients is shown in Fig. 3.9. Data collection was initiated in

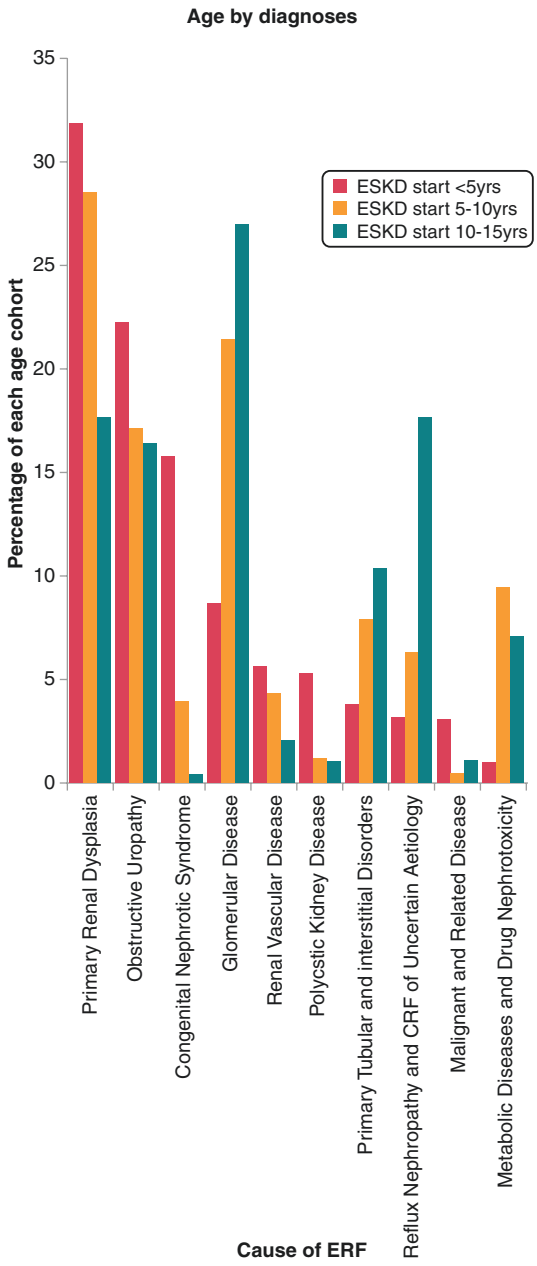

Fig. 3.8 Distribution of primary kidney diagnoses by age of initiation of RRT in the United Kingdom. ERF, End-stage renal failure (ESKD). (Source: Adapted from 2002 Report of the United Kingdom Renal Registry) [32]

1992 [5]. Survival has improved over time in this cohort, with later year of entry into the registry associated with decreased risk of mortality (HR 0.95, $P < 0.001$) after adjusting for patient age. Patient survival curves in Fig. 3.10 show that survival varies significantly by age, with the youngest patients having the lowest survival estimates.

Similar to NAPRTCS data, the USRDS has also revealed that the 5-year survival probability for children initiating dialysis therapy between 2007 and 2011 was lowest in the youngest patients (Fig. 3.11) [15]. Survival has also been shown to improve by era in the USRDS. In a study of 1723 infants in the USRDS database who initiated chronic peritoneal dialysis at ≤12 months of age between 1990 and 2014, there was an increased risk of mortality in all infants in the earlier initiation era (1990–1999) versus the later era (2000–2014) (adjusted HR 1.95, $P < 0.0001$). An increased risk of mortality was also observed for female versus male infants (aHR 1.43, $P = 0.0003$) and for those with a primary diagnosis of cystic kidney diseases versus congenital anomalies of the kidney and urinary tract (aHR 1.84, $P < 0.0001$) [34]. USRDS data also reveal that, remarkably, the expected remaining lifetime in years of the prevalent pediatric dialysis population is exceedingly poor when compared to the data of the general US population and prevalent transplant recipients (Fig. 3.12) [15].

The most common causes of death (mortality rate per 1000 patient years of risk) among prevalent pediatric dialysis patients listed in the USRDS include cardiac arrest (7.1), septicemia (2.1), cerebrovascular disease (1.5), withdrawal from dialysis (2.8), and other/unknown/missing causes (12.7) [15]. The main causes of death among European children with ESKD included cardiovascular events (18.3%) and infections (17.0%) [33]. In Japan, infections (39.5%) and cardiovascular disease (17.9%) were also the most common [31].

Fortunately, most children in the United States terminate a course of dialysis due to transplantation, not death (Fig. 3.13) [5]. Complications associated with a dialysis modality, and patient/family choice, lead to a switch in modality for almost 20% of pediatric dialysis patients. Median time from incident dialysis to first kidney transplant was approximately 12 months in the United States in 2015. For

Patient suvival by era
from first dialysis initiation to last NAPRTCS follow-up

Year of dialysis initiation	N	12 Months		24 Months		36 Months	
		% survival	SE	% survival	SE	% survival	SE
1992 - 1994	1404	95.9	0.5	92.9	0.7	90.8	0.8
1995 - 1997	1444	95.7	0.6	92.9	0.7	90.8	0.8
1998 - 2000	1181	96.2	0.6	94.6	0.7	93.1	0.8
2001 - 2003	906	98.1	0.5	96.4	0.7	94.1	0.9
2004 - 2006	787	97.6	0.6	95.0	0.9	93.4	1.1
2007 - 2010	578	98.8	0.6	96.9	1.0	--	--

Fig. 3.9 Patient survival by era in North American cohort of children on dialysis. (Source: Adapted from 2011 North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS] Annual Report) [32]

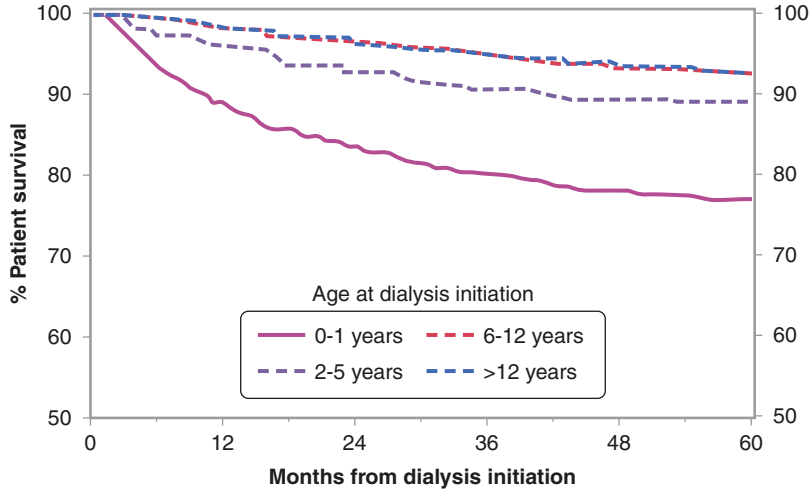

Fig. 3.10 Overall patient survival by age in North American cohort of children on dialysis. (Source: Adapted from 2011 North American Pediatric Renal Trials and Collaborative Studies [NAPRTCS] Annual Report) [32]

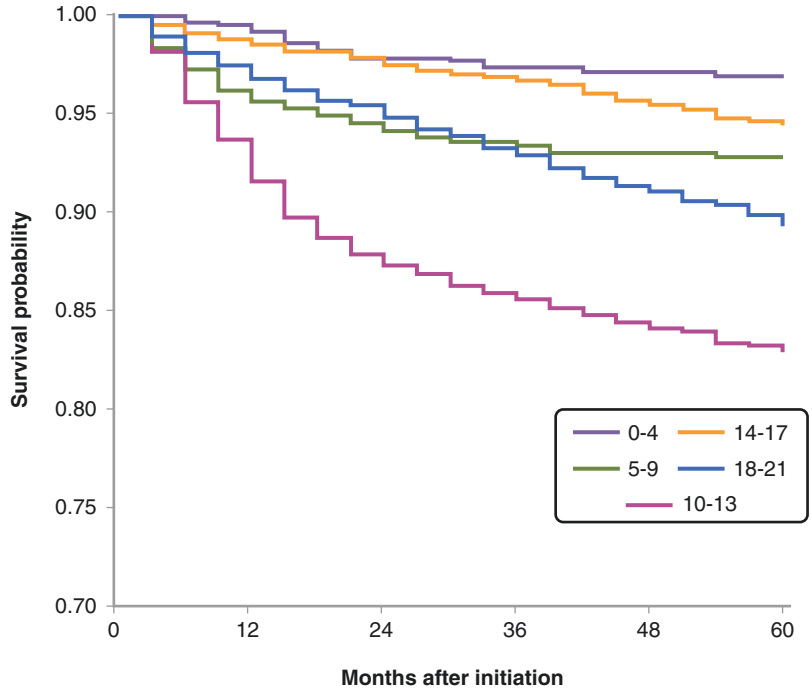

Fig. 3.11 Adjusted 5-year survival in incident pediatric patients (aged 0–21 years) from day 1, by age, in the United States. (Source: Adapted from USRDS 2018 Annual Data Report) [15]

Age group	Dialysis patients	Transplant patients	General population
0-4	22.0	57.7	77.0
5-9	22.8	56.2	72.1
10-13	23.3	52.1	67.6
14-17	20.6	48.9	63.7
18-21	17.6	45.6	59.8
22-29	15.7	42.3	54.1

Fig. 3.12 Expected remaining lifetime in years of prevalent US patients by initial ESKD modality, 2015. (Source: Adapted from USRDS 2018 Annual Data Report) [15]

	All Index Courses after 01/01/92	
	N	%
Terminated Dialysis Courses	**4929**	**100.0**
Reason for Termination		
Patient Transplanted	3412	69.2
Change of Modality	870	17.7
Death	116	2.4
Kidney Function Returned	143	2.9
Other/Unknown	388	7.9
Courses Changing Modality	**870**	**100.0**
Reason for Modality Change		
Excessive infection	265	30.5
Patient/family choice	178	20.5
Access failure	86	9.9
Inadequate ultrafiltration	45	5.2
Inadequate solute clearance	21	2.4
Excessive hospitalization (Dialysis-related)	17	2.0
Excessive hospitalization (Other)	4	0.5
Other (medical)	112	12.9
Other (non-medical)	40	1.6
Unknown	102	11.7

Fig. 3.13 Reasons for termination of dialysis course in cohort of North American children. (Source: North American Pediatric Renal Trials and Collaborative Studies 2011 Annual Data Report) [5]

children age 0–4 years, the median time to transplant was closer to 18 months [15].

Survival data for children on dialysis has been published for other areas of the world over the last 20 years [11, 18, 35–42].

Conclusion

We have reviewed the most current demographic data available to describe pediatric dialysis patients treated around the world. Similarities and differences among patient populations have been described. It must be stressed that comparisons between patient groups can at best be considered qualitative. Rigorous analysis of data summaries reported by different registries is impossible due to fundamental differences in coding, patient grouping, referral patterns, data collection, and availability of complete datasets. The trend toward national registries is likely to further interfere with comparison efforts, unless the approach to pediatric ESKD patient data reporting and analysis is standardized [7].

There is no doubt, however, that regional and national pediatric patient registries can continue to serve important functions. Demographic data can provide information vital to national healthcare planning and resource allocation. Registries are also adept at identifying trends in therapy, and perhaps most important, they can provide the context and stimulus for clinical research by properly framing questions and hypotheses. Finally, with the pediatric ESKD and dialysis population small in the context of the global ESKD patient number, it is hoped that collaborative efforts among national registries will be encouraged and will in turn result in improved patient outcomes.

Notice: Some data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

References

1. Chesney RW. The development of pediatric nephrology. Pediatr Res. 2002;52(5):770–8.
2. Rees L, et al. Chronic dialysis in children and adolescents: challenges and outcomes. Lancet Child Adolesc Health. 2017;1(1):68–77.
3. Sanderson KR, Warady BA. End-stage kidney disease in infancy: an educational review. Pediatr Nephrol. 2018;35(2):229–40.
4. Fadrowski JJ, et al. Patterns of use of vascular catheters for hemodialysis in children in the United States. Am J Kidney Dis. 2009;53(1):91–8.
5. North american pediatric renal trials and collaborative studies (NAPRTCS) 2011 annual report. Online at: https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf. Accessed 15 Dec 2018.
6. Weaver DJ Jr, et al. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
7. van Amstel SP, et al. Renal replacement therapy for children throughout the world: the need for a global registry. Pediatr Nephrol. 2018;33(5):863–71.
8. Hamilton AJ, et al. UK renal registry 19th annual report: chapter 4 demography of the UK paediatric renal replacement therapy population in 2015. Nephron. 2017;137(Suppl 1):103–16.
9. North american pediatric renal trials and collaborative studies (NAPRTCS) annual reports. Online at: https://web.emmes.com/study/ped/annlrept/annlrept.html. Accessed 2 Dec 2018.
10. ESPN/ERA-EDTA registry. european registry for children on renal replacement therapy. Links to national and regional registries collecting paediatric data. Online at: https://www.espn-reg.org/index.jsp?p=lnk. Accessed 2 Dec 2018.
11. Grunberg J, et al. Twenty years' pediatric chronic peritoneal dialysis in Uruguay: patient and technique survival. Pediatr Nephrol. 2005;20(9):1315–9.
12. Ferris M, et al. Hemodialysis outcomes in a global sample of children and young adult hemodialysis patients: the PICCOLO MONDO cohort. Clin Kidney J. 2016;9(2):295–302.
13. Konstantyner T, et al. Pediatric chronic Dialysis in Brazil: epidemiology and regional inequalities. PLoS One. 2015;10(8):e0135649.
14. North american pediatric renal trials and collaborative studies (NAPRTCS) 2014 Annual transplant report. Online at: https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf. Accessed 2 Dec 2018.
15. U.S. Renal Data System, USRDS 2018 annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 2018. Online at: https://www.usrds.org/adr.aspx. Accessed 2 Dec 2018.
16. Harambat J, et al. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27(3):363–73.
17. Harambat J, Ekulu PM. Inequalities in access to pediatric ESRD care: a global health challenge. Pediatr Nephrol. 2016;31(3):353–8.
18. Ashuntantang G, et al. Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. Lancet Glob Health. 2017;5(4):e408–17.
19. Schaefer F, et al. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry. Perit Dial Int. 2012;32(4):399–409.
20. Chesnaye NC, et al. Disparities in treatment rates of paediatric end-stage renal disease across Europe: insights from the ESPN/ERA-EDTA registry. Nephrol Dial Transplant. 2015;30(8):1377–85.
21. Ng DK, et al. Racial differences in renal replacement therapy initiation among children with a nonglomerular cause of chronic kidney disease. Ann Epidemiol. 2016;26(11):780–7, e1.
22. Ku E, et al. Racial and ethnic disparities in survival of children with ESRD. J Am Soc Nephrol. 2017;28(5):1584–91.
23. Hidalgo G, et al. Association of income level with kidney disease severity and progression among children and adolescents with CKD: a report from the Chronic Kidney Disease in Children (CKiD) Study. Am J Kidney Dis. 2013;62(6):1087–94.
24. ANZDATA Registry. 37th report, chapter 11: Paediatrics. Australia and New Zealand dialysis and transplant registry, Adelaide, Australia. 2015. Available at: http://www.anzdata.org.au
25. Hari P, et al. Chronic renal failure in children. Indian Pediatr. 2003;40(11):1035–42.
26. Lagomarsimo E, et al. Chronic renal failure in pediatrics 1996. Chilean survey. Pediatr Nephrol. 1999;13(4):288–91.
27. Al-Eisa AA, Samhan M, Naseef M. End-stage renal disease in Kuwaiti children: an 8-year experience. Transplant Proc. 2004;36(6):1788–91.
28. Verrina E, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19(1):82–90.
29. Anochie I, Eke F. Chronic renal failure in children: a report from Port Harcourt, Nigeria (1985-2000). Pediatr Nephrol. 2003;18(7):692–5.
30. Hattori S, et al. The 1998 report of the Japanese National Registry data on pediatric end-stage renal disease patients. Pediatr Nephrol. 2002;17(6):456–61.
31. Hattori M. Current trend of pediatric renal replacement therapy in Japan. Contrib Nephrol. 2018;196:223–8.
32. The renal association. UK renal registry. The fifth annual report. December 2002. Online at: https://www.renalreg.org/reports/2002-the-fifth-annual-report/. Accessed 15 Dec 2018.
33. Chesnaye NC, et al. Mortality risk in European children with end-stage renal disease on dialysis. Kidney Int. 2016;89(6):1355–62.
34. Sanderson KR, et al. Outcomes of infants receiving chronic peritoneal dialysis: an analysis of the USRDS registry. Pediatr Nephrol. 2018;34(1):155–62.

35. Hooman N, et al. The outcome of Iranian children on continuous ambulatory peritoneal dialysis: the first report of Iranian National Registry. Arch Iran Med. 2009;12(1):24–8.
36. Tsai TC, et al. Incidence and renal survival of ESRD in the young Taiwanese population. Clin J Am Soc Nephrol. 2014;9(2):302–9.
37. Chang HJ, et al. Outcomes of chronic dialysis in Korean children with respect to survival rates and causes of death. Korean J Pediatr. 2014;57(3):135–9.
38. Samuel SM, et al. Survival in pediatric dialysis and transplant patients. Clin J Am Soc Nephrol. 2011;6(5):1094–9.
39. Mong Hiep TT, et al. Etiology and outcome of chronic renal failure in hospitalized children in Ho Chi Minh City, Vietnam. Pediatr Nephrol. 2008;23(6):965–70.
40. Sumboonnanonda A, et al. Chronic renal failure in Thai children: etiology, cost, and outcome. J Med Assoc Thail. 2000;83(8):894–901.
41. Gulati S, et al. Etiology and outcome of chronic renal failure in Indian children. Pediatr Nephrol. 1999;13(7):594–6.
42. El-Reshaid K, et al. Pediatric dialysis and renal transplantation in Kuwait over the past 11 years. Pediatr Nephrol. 1999;13(3):259–64.

Chronic Dialysis in Developing Countries

4

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Introduction

Worldwide, the number of end stage renal disease (ESRD) patients has been rapidly increasing, with more than a million patients receiving dialysis therapy. Coverage of renal replacement therapy (RRT) is usually directly related to country-specific gross national income (GNI). In pediatrics, global data from the International Pediatric Peritoneal Dialysis Network (IPPN) showed that dialysis patient survival was associated with GNI status, being significantly higher in high-income economies (94.1% at 5 years), compared to middle- and low-income countries combined (88.7%). The provision of RRT, funding, dialysis modality, ESRD etiology, technical resources and trained healthcare professionals also show important variation across regions around the world, most of the cases directly related to economic and cultural factors. The IPPN data also showed that these differences do have an impact on growth, nutrition, biochemical status and dialysis-related complications such as peritonitis, especially in children with chronic kidney disease in the developing world. This chapter provides an analysis of the differences in RRT around the world, allowing a better understanding of the ways to improve dialysis programs for children and adolescents in developing regions.

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Economic Indicators

Since more than 30 years ago, chronic dialysis has become the cornerstone of the treatment for patients with end-stage renal disease (ESRD). However, access to dialysis is limited in several regions of the world due to a lack of financial resources and technical development [1]. The coverage of renal replacement therapy (RRT) is far from being uniform around the world, and usually is directly related to country-specific gross national income (GNI). According to the World Bank (WB) 2019 data [2], countries/economies are classified into 4 income groups, low, lower-middle, upper-middle, and high-income countries. Low-income economies are defined as those with a GNI per capita of US$ 995 or less; lower-middle-income economies are those with a GNI per capita between US$ 996 and 3895; upper-middle-income economies are those with a GNI per capita between US$ 3896 and 12,055, and high-income economies are those with a GNI per capita of US$12,056 or more. Of note, the developing world which includes the low-income and lower-middle-income economies is estimated to account for 80% of the global population.

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Epidemiology of Renal Replacement Therapy in Developing Countries

Worldwide, the number of ESRD patients has been rapidly increasing. A decade ago, more than 1 million patients were reported to receive dialysis therapy, with an annual estimated growth rate of 7% [3, 4]. Among the main factors associated with this growth are the longer life expectancy, an increasing survival rate of ESRD patients, and a growing access of younger patients to RRT therapies in developing countries, where the access has been previously limited. A large survey sharing a global dialysis company program representing more than 90% of the global population, and which included 122 countries with a wide range of socioeconomic levels, was published more than a decade ago [3]. The prevalence ESRD values per million population (pmp) showed important differences between regions. The high-income regions, North America (1505 ESRD patients pmp/1030 on dialysis pmp), Europe (585/400 pmp), and Japan (2045/1945 pmp), showed a higher prevalence rate for ESRD and dialyzed patients, compared to Latin America (380/320 pmp), Middle East (190/140 pmp), and Asia and Africa (70/70 pmp), respectively. The prevalence dialysis data showed that 52% of the global dialysis population was located in four countries, namely, the United States of America, Japan, Germany, and Brazil, with the first three belonging to the high-income WB classification. However, these countries accounted for only around 11% of the world population. Given that the survey included mostly adult data, hemodialysis (HD) was the most common RRT modality. The prevalence values for HD vs peritoneal dialysis (PD) therapy showed higher rates in Japan (1865/80 pmp), North America (940/95 pmp), and Europe (360/40 pmp), followed by Latin America (240/75 pmp), Middle East (130/10 pmp), and Africa (65/<5 pmp).

In developing regions, there exists an important heterogeneity among countries, which makes it difficult to obtain representative data for ESRD and RRT therapies. Most of these countries belong to the low and low-middle GNI classification [5–10]. In Latin America, the prevalence of ESRD was 119 patients pmp in 1991, increasing to 669 patients pmp in 2013, according to a global survey involving both adult and pediatric patients [6]. Of these, 442 patients pmp were on HD and 67 pmp on PD. Argentina, Brazil, Chile, Mexico, Puerto Rico, and Uruguay were the countries reporting the highest rates of ESRD in the region, between 707 and 1846 patients pmp.

The number of ESRD patients undergoing dialysis is growing rapidly, especially in the developing world, with a variable predominance between PD and HD. A large study [11] including adults and children from 130 countries showed that 195,555 patients were treated with PD, 58% of them in developing countries and 42% in developed countries. In contrast, HD was less frequently used in developing versus developed countries, 32% versus 68%, respectively, for a total of 1,550,000 patients. Nevertheless, the authors found an important variation in PD use across countries. Mexico, China, and Brazil were the most important countries using PD in the developing world, whereas the United States, Japan, and South Korea were the main countries treating patients with PD in the developed world. On the other hand, 24 countries from the developing world did not offer PD as a treatment modality to ESRD patients. When the prevalence of PD during the last decade was analyzed for 67 developing and 30 developed countries, an increase in both groups was observed, 10.0–34.9 pmp in developing regions, versus 69.7–91.5 pmp in the developed countries, with no significant difference between them. The prevalence of HD, obtained from 51 developing and 30 developed countries showed a similar HD increase in developed countries from 347.8 to 605.8 pmp, versus 128.5 to 309.2 pmp in developing countries [11]. Results from that survey confirm that the number of patients pmp treated with PD in both developing and developed countries has increased over the last decade, although the overall proportion of dialysis patients treated with PD is declining in the developed world. Data from years 1997 to 2008 showed an absolute change of −5.3% (20.6–15.3%, 95% CI −6.7%, −3.8%). Similar data was presented in

another large survey from 122 countries comprising approximately 99% of all treated ESRD patients worldwide at the end of year 2004 [3]. The global distribution of patients under HD and PD between the developed world, the United States, Japan, and Europe, versus all other countries together, was 62% for HD and only 42% for PD. The authors highlighted that 58% of PD patients were from developing countries where 80% of the world's population reside. Although PD therapy in these countries is increasing rapidly, with a 2.5-times increase in PD prevalence over 12 years of follow-up, global data on the type of dialysis confirmed that HD remains the most common treatment modality in all regions of the world, when adults and children are included [3]. Worldwide, 89% of 1,371,000 patients were undergoing HD therapy, in contrast to 11% of patients treated by PD. In that survey, Mexico, Korea, and the United Kingdom had a higher proportion of patients undergoing PD, while HD was the predominant treatment modality in each of the 15 major countries analyzed. In 111 of the 122 countries evaluated, the percentage of dialysis patients on HD exceeded 66% of the ESRD population.

Pediatric ESRD patients represent a small proportion of the global ESRD population [3, 6, 9, 12, 13]. In North America, pediatric ESRD patients represented less than 2% of the chronic kidney disease (CKD) population [12]. Pediatric ESRD registries are scarce and lack global information, as most data are geographically limited and imprecise, mostly due to economic development differences, environmental, racial, and cultural factors. One of the most important pediatric dialysis registries, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), started as a transplant registry in 1987, and included dialysis data since 1992 [14]. The registry includes data from the United States, Canada, Mexico, and Costa Rica, the last 2 belonging to the upper-middle-income economies, and describes important genetic, cultural, and social differences among those 4 countries. A recent analysis of NAPRTCS [15] comparing dialysis data from the decade 1992–2001 with the decade 2002–2011 showed a total of 6482 patients, of whom 4373 enrolled from 1992 to 2001 and 2109 from 2002 to 2011. In this analysis, a significant increase in the use of HD as the initial dialysis modality was observed between cohorts, with 36% of patients starting renal replacement therapy on HD in the first period, compared to 42% in the later decade. Conversely, 64.4% of patients were started on PD in the first decade, and 57.9% in the last evaluated period. Although the registry suggested that this trend was related in part to increased availability of pediatric HD facilities, data separated by country or GNI classification were not provided. As stated by the authors, because the NAPRTCS registry is a voluntary database, sampling bias could be present and results should be interpreted cautiously, considering that the prevalence of ESRD and dialysis therapy are directly related to country GNI.

Global data on pediatric RRT mostly comes from the International Pediatric Peritoneal Dialysis Network (IPPN) [1, 9, 16]. The registry is an international consortium of pediatric dialysis centers that prospectively collects dialytic and clinical information for PD children. A comprehensive report on the impact of global economic disparities on pediatric PD therapy was published in 2012 [1]. Eighty-three countries were included, of which 47% of patients were from high-income, 11% from upper-middle-income, 34% from lower-middle-income, and 8% from low-income countries. Low-income countries, representing more than 70% of the sample when analyzed in terms of country population, showed a low proportion of PD in patients under 3 years of age, as well as a low percentage of patients with comorbidities and cognitive/motor deficits. With regard to PD modality, continuous ambulatory PD was inversely correlated with GNI, while automated PD, in particular night intermittent PD was associated with a higher income GNI level. Despite differences in PD mode and GNI status, a non-significant variation was found in urea clearance and PD technique survival between countries, as well as PD function at 5 years, reflecting successful therapy implementation in the IPPN participating countries. GNI status was associated with patient survival, which was

significantly higher in high-income economies (94.1% at 5 years), compared to middle- and low-income countries combined (88.7%).

Demographics of the ESRD Population in Developing Countries

The etiology of CKD in children differs according to the economic status despite being in the same region [1, 14, 17, 18], with low-income countries having a higher proportion of unknown ESRD etiology. In low-income countries, CKD risk factors include low birth weight, reflux nephropathy, and glomerulonephritis secondary to infectious diseases such as human immunodeficiency virus and hepatitis B. In contrast, etiological factors in middle-income countries approach those found in the developed world [6]. Congenital anomalies of the kidney and urinary tract accounted for at least 50% of the causes of CKD in high-income countries due to active antenatal detection programs and comprehensive post-natal management. Another important factor that is now recognized as a possible cause of progressive CKD in adulthood is acute kidney injury (AKI) occurring during infancy and childhood [19]. In high-income countries, the etiologies of AKI are commonly hospital acquired, including multi-organ failure, post-cardiac surgery, solid organ, or bone marrow transplantation. On the other hand, in low- and low-middle-income countries, infections with sepsis and dehydration, severe malaria, toxins, or snake bites are common causes of AKI requiring RRT.

Data from the IPPN registry showed that children with CKD from low-income regions had lower stature with one standard deviation score (SDS) below patients from developed countries, higher parathyroid hormone levels, lower plasma calcium and hemoglobin values, and lower use of calcium-free phosphate binders and cinacalcet to treat mineral bone disorder [1]. A recent report from the IPPN registry focused on nutritional differences among countries [16]. Data included 1000 PD incident patients from 85 nephrology centers in 35 countries. Nutritional status was recorded at PD initiation, with 8.9%, 71.4%, and 19.7% reported as underweight, normal weight, and overweight/obesity, respectively. Overweight/obese children belonged in general to higher GNI countries, namely, the United States and Middle East. Underweight children were most prevalent in South and Southeast Asia, followed by countries from Central Europe and Turkey. In a multivariate analysis, body mass index SDS at the time of initiation of dialysis showed a positive correlation with glomerular filtration rate (GFR), as well as the use of gastrostomy feeding, with no significant relationship to GNI. Patients with low GFR are at more nutritional and biochemical risk; hence this positive association with GFR highlights the importance of an opportune referral to start RRT in these patients [1, 8, 12, 20–22]. IPPN data represents a remarkable source of information, but it should be cautiously interpreted, considering that a high proportion of low-income countries do not have reliable registries nor access to pediatric PD programs and hence do not participate in global surveys on dialysis in children.

Challenges Faced by Developing Countries in the Provision of Pediatric RRT

Inequities in health care delivery are especially magnified in low- and low-middle-income countries. Because funding and resources for RRT in such economies are generally limited, access to RRT may be restricted to certain groups of the population. Additionally, low- and low-middle-income countries have complex logistic issues, geographical and cultural factors, as well as inadequate numbers of trained healthcare professionals who can provide RRT to children. In such situations, RRT is generally not available to pediatric patients unless they are in the late adolescent age group where RRT can be performed in adult dialysis centers [5, 7, 8, 19, 23–25]. In a recent comprehensive review of dialysis services in Africa [23], only 29 of 54 countries representing approximately 82% of the total population reported dialysis programs with widely variable levels of development and maintenance. Only 8

countries had implemented national dialysis programs, defined as dialysis therapy for at least 100 dialysis patients pmp. According to this survey, Egypt, Morocco, Libya, Tunisia, Mauritius, South Africa, Algeria, and Gabon gave full coverage to dialysis programs in state hospitals. In Sub-Saharan countries, PD has been selected as the first option to treat ESRD patients, in contrast to the North African countries where PD is seldom used. In countries like Tanzania, one of the poorest countries in the world, where two-thirds of the population live in poverty and in rural areas, PD programs have been implemented successfully with the support of the International Society of Nephrology (ISN), but only for AKI patients. The cost of chronic dialysis appears to be prohibitive in view of the limited resources in these countries [24–26].

Pending questions on the sustainability of PD in low-income countries are the high reported rates of infection and the cost of importing dialysis solutions and supplies for treatment. Patients from low-income countries tend to present late in the course of CKD, and hence an urgent start for dialysis is often required [20, 21]. Advantages of PD as the modality of choice especially in children in developing countries would include difficulties and infectious complications associated with central venous catheter insertion, and less requirements for highly trained dialysis personnel as well as expensive equipment and electricity [27–30]. Thailand, a low-middle-income country in South-East Asia, launched its PD First Policy in 2008 [31], despite the prevailing popularity of HD in the country due to economic reasons. This resulted in an increase in the incidence and prevalence of ESRD from 68.34 pmp and 419.9 pmp in 2007 prior to the implementation of the program, to 249.06 pmp and 1072 pmp in 2013, respectively. Such a policy allows for cost containment on a national level with reduction in the cost of the dialysate bags, community support for the PD patients including assistance to establish a clean environment in the home to perform PD exchanges, and organizations helping with transportation to district PD centers for routine visits and emergencies. These measures resulted in successful implementation of a nation-wide PD program, which is a good model for developing countries. The success of this program is seen in the more than 20,000 ESRD patients in Thailand undergoing PD, including pediatric patients.

In a global survey of children on chronic PD, patient mortality was strongly affected by GNI stratum independent of patient age and number of co-morbidities present, a finding also corroborated by others [1, 19, 21]. The country-specific peritonitis incidence rates did not differ significantly according to GNI strata; however, this may be due to the lack of data from countries where chronic PD was done on an ad hoc basis in adult units rather than in a pediatric dialysis center [28]. However, the lower GNI groups did show an increased incidence of culture-negative peritonitis episodes. More importantly, the mortality in patients from low-income countries was mainly due to infections unrelated to the PD process.

Another challenge facing the developing world is AKI in children. Recent initiatives have been aimed at AKI prevention, one of the major factors leading to advanced CKD in these areas. As noted by Lilje, et al., children's access to kidney care is based on 5 key actions [19]. Firstly, AKI prevention programs in particular should include good access to a clean water supply to reduce pre-renal damage secondary to diarrheal illness such as the Easy Water for Everyone Initiative (https://www.easywaterforeveryone.org). Secondly, health education campaigns, such as the World Kidney Day (https://www.worldkidneyday.org), are critical efforts directed at the general public and health community in low-resource regions to improve the knowledge of kidney care at a primary level. Thirdly, access to computer and database information systems by the medical team in order to collect patients' data and identify the magnitude of the problem of AKI, especially that leading to CKD, is important for health care planning. Emerging countries show the highest incidence of AKI illness, resulting in 1.4 million deaths per year in low- and low-middle-income countries, a burden that the 0by25 initiative (https://www.theisn.org/all-articles/616-0by25) has proposed to eliminate worldwide by 2025. Fourthly, health care

workforce training, including pediatricians, nurses, dietitians, and other health care workers, will improve the care of CKD children in some settings where pediatric nephrologists are not available. The Saving Young Lives project is a partnership established in 2012 involving the ISN, International Pediatric Nephrology Association (IPNA), International Society of Peritoneal Dialysis (ISPD), and Sustainable Kidney Care Foundation (SKCF). Since then almost 200 clinicians have been trained to recognize AKI and perform acute PD across 15 centers in sub-Saharan Africa and Southeast Asia, with a plan to extend this program to South America. Successful recovery has been documented from acute PD treatment in more than 400 AKI children, at a reported cost of less than US$25 per therapy. Finally, development of more affordable dialysis modalities has been advocated for use by local health authorities. Given that in most low-middle-income countries there is no national system for paying for dialysis, the authors proposed the use of makeshift catheters (such as nasogastric tubes) and homemade PD solutions as practical and low-cost options "that bypass potential corruption and bureaucracy that can affect the importation of dialysis supplies". 19) The Affordable Dialysis Project led by the George Institute for Global Health (https://www.georgeinstitute.org/projects/the-affordable-dialysis-project) could provide ambulatory dialysis therapies with machines that can be used in up to 5 people for US$850.

Conclusion

Developing countries are dependent on a combination of government funding and private charity organizations to provide RRT facilities for their populations. Access to such programs tends to be limited to the adult population, with pediatric chronic dialysis care being limited to metropolitan centers in the low-middle-income countries. Key strategies in the provision of chronic RRT to children in the low-income countries lie in the availability of cheaper forms of dialysis such as PD [32–34]. However, the ultimate reality is whether these children will be able to obtain a living-related kidney transplant with the use of cheaper generic immunosuppressants, as deceased donor kidney transplantation is largely unavailable and long-term dialysis is unsustainable in these low-income countries.

References

1. Schaefer F, Borzych-Duzalka D, Azocar M, Loza MR, Sever L, Aksu N, et al. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the international pediatric peritoneal dialysis Network Registry. Perit Dial Int. 2012;32:399–409.
2. The World Bank. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Last visit 8 Feb 2020.
3. Grassmann A, Gioberge S, Moeller S, Brown G. ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. Nephrol Dial Transplant. 2005;20:2587–93.
4. Barsoum R. Overview: end-stage renal disease in the developing world. Artif Organs. 2002;26(9):737–46.
5. Jha V, Chugh KS. The practice of dialysis in the developing countries. Hemodial Int. 2003;7(3):239–49.
6. Cusumano AM, Rosa-Diez GJ, Gonzalez-Bedat MC. Latin American dialysis and transplant registry: experience and contributions to end-stage renal disease epidemiology. World J Nephrol. 2016;5:389–97.
7. Pecoits-Filho R, Sola L, Correa-Rotter R, Claure-Del GR, Douthat WG, Bellorin-Font E. Kidney disease in Latin America: current status, challenges, and the role of the ISN in the development of nephrology in the region. Kidney Int. 2018;94:1069–72.
8. Odetunde O, Okafor H, Uwaezuoke N, Ezeonwu B, Ukoha O. Renal replacement therapy in children in the developing world: challenges and outcome in a tertiary hospital in southeast nigeria. Sci World J. 2014;2014:903151. https://doi.org/10.1155/2014/903151.
9. Van Amstel P, Noordzij M, Warady B, Cano F, Craig JC, Groothoff JW, et al. Renal replacement therapy for children throughout the world: the need for a global registry. Pediatr Nephrol. 2018;33(5):863–71.
10. Nayak KS, Prabhu M, Sinoj K, Subhramanyam SV, Sridhar G. Peritoneal dialysis in developing countries. Contrib Nephrol. 2009;163:270–7.
11. Jain A, Blake P, Cordy P, Garg A. Global trends in rates of peritoneal dialysis. J Am Soc Nephrol. 2012;23:533–44.
12. Warady B, Chadha V. Chronic kidney disease in children: the global perspective. Ped Nephrol. 2007;22:2999–3009.
13. Van Stralen K, Tizard E, Verrina E, Schaefer F, Jager K. Demographics of paediatric renal replace-

ment therapy in Europe: 2007 annual report of the ESPN/ERA-EDTA registry. Pediatr Nephrol. 2010;25:1379–82.
14. The North American Pediatric Renal Trials and Collaborative Studies. https://naprtcs.org/system/files/2011_Annual_Dialysis_Report.pdf. Last visit 12 Feb 2020.
15. Weaver D, Somers M, Martz K, Mitsnefes M. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Ped Nephrol. 2017;32:2319–30.
16. Schaefer F, Benner L, Borzych-Dużałka D, Zaritsky J, Xu H. Global variation of nutritional status in children undergoing chronic peritoneal dialysis: a longitudinal study of the international pediatric peritoneal dialysis network. Sci Rep. 2019;9:4886.
17. Nayak KS, Prabhu MW, Sinoj KA, Subhramanyam SV, Sridhar G. Peritoneal dialysis in developing countries. In: Ronco C, Crepaldi C, Cruz DN, editors. Peritoneal dialysis – from basic concepts to clinical excellence. Contrib nephrol, vol. 163. Basel: Karger; 2009. p. 270–7.
18. Warady B, Chadha V. Chronic kidney disease in children: the global perspective. Pediatr Nephrol. 2007;22:1999–2009.
19. Lalji R, Francis A, Johnson DW, McCulloch M. Health disparities in access to kidney replacement therapy amongst children and adolescents with end stage kidney disease in low- and lower-middle income countries. Kidney Int. 2020;97(3):463–5. https://doi.org/10.1016/j.kint.2019.11.030.
20. Schaefer F, Warady B. Peritoneal dialysis in children with end-stage renal disease. Nat Rev Nephrol. 2011;7:659–68.
21. Chesnaye NC, Schaefer F, Bonthuis M, Holman R, Baiko S, Baskin E, et al. ESPN/ERA-EDTA Registry Committee. Mortality risk disparities in children receiving chronic renal replacement therapy for the treatment of end-stage renal disease across Europe: an ESPN-ERA/EDTA registry analysis. Lancet. 2017;389:2128–37.
22. Li P, Chow KM, Van de Luijtgaarden M, Johnson D, Jager K, Mehrotra R, Naicker S, Pecoits-Filho R, Yu X, Lameire N. Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol. 2017;13(2):90–103.
23. Barsoum R. Fifty years of dialysis in Africa: challenges and progress. Am J Kidney Dis. 2015;65(3):502–12.
24. Just P, De Charro F, Tschosik E, Noe L, Bhattacharyya S, Riella M. Reimbursement and economic factors influencing dialysis modality choice around the world. Nephrol Dial Transplant. 2008;23:2365–73.
25. Mushi L, Marschall P, Fleßa S. The cost of dialysis in low and middle income countries: a systematic review. BMC Health Serv Res. 2015;15:506. https://doi.org/10.1186/s12913-015-1166-8.
26. Crews D, Bello A, Saadi G. For the world kidney day steering committee. Burden, access, and disparities in kidney disease. Kidney Int Rep. 2019;4:372–9.
27. Van den Berg H, O'Hagan S, Hurter D. Percutaneous placement of peritoneal dialysis catheters in resource-limited developing countries as an alternative to conventional placement methods. Afr J Rad. 2015;19(1):8. https://doi.org/10.4102/sajr.v19i1.707.
28. Schaefer F, Feneberg R, Aksu N, Donmez O, Sadikoglu B, Alexander SR, et al. Worldwide variation of dialysis-associated peritonitis in children. Kidney Int. 2007;72:1374–9.
29. Awuah K, Finkelstein S, Finkelstein F. Quality of life of chronic kidney disease patients in developing countries. Kidney Int. 2013;S3:227–9.
30. Moloi MW, Kaiawo S, Noubiap JJ, Mbah IO, Ekrikoo U, Kengne AP, et al. Prevalence of peritonitis and mortality in patients treated with continuous ambulatory peritoneal dialysis (CAPD) in Africa: a protocol for a systematic review and meta-analysis. BMJ Open. 2018;8:e020464. https://doi.org/10.1136/bmjopen-2017-020464.
31. Chuengsaman P, Kasemsup V. PD first policy: Thailand's response to the challenge of meeting the needs of patients with end-stage renal disease. Semin Nephrol. 2017;37(3):287–95.
32. Burki T. Tanzania's model peritoneal dialysis programme. Lancet. 2015;395:1935–6.
33. Isla RA, Mapive D, Swanepoel CR, Rozumyk N, Hubahib JE, Okpechi IG. Continuous ambulatory peritoneal Dialysis in Limpopo PROVINCE, South Africa: predictors of patient and technique survival. Perit Dial Int. 2014;34:518–25.
34. Yao Q, Duddington M. Peritoneal Dialysis in China. Perit Dial Int. 2013;34:529–30.

5 Organization and Management of a Pediatric Dialysis Program

Amy Nau

Introduction

The organization and management of a pediatric dialysis unit is a multi-faceted endeavor which requires a unique mindset and perspective for services provided. The environment of care is not an outpatient clinic or a critical care ward, but rather a merging of the two. Providing safe and effective patient care that enhances the life experiences of patients, their families, and staff is the ultimate goal of care and treatment in the pediatric dialysis unit. This chapter will review operational management – culture, organization, regulatory, physical space, human factors influences, and staffing – as well as components of care implementation, modality selection, patient/family education, patient care plans, patient/family support, quality improvement, infection prevention, and safety.

Operational Management

Facility Culture and Organization

In today's environment, an organization's culture and environment play an ever-increasing role of importance influencing all aspects of the dialysis unit – from patient care to staffing to billing and reimbursement. Each organization has the opportunity to foster their own unique cultural ideals. In recent years, cultural focus has shifted in many organizations to include patient and staff satisfaction, as well as financial efficiencies. Balancing these somewhat conflicting priorities remains a delicate and complicated task.

Common themes among organizations that successfully recruit and retain staff are an overarching commitment to shared values, support of employee work-life balance, and encouraging top of license practice with an autonomous staff all while providing safe and effective patient care [1, 2].

In healthcare settings, patient outcomes are linked with workplace culture; positive environments are associated with increased patient satisfaction, decreased patient re-admissions, and decreased volume of treatment complications. An essential factor in creating a positive workplace culture and environment is the tone of interactions between members of the healthcare team. In fact, a positive nurse-physician relationship is one of the biggest predictors of a safe and positive healthcare work environment for patients and staff [1]. This relationship has been shown to influence nurse retention in healthcare facilities with nurses remaining in their professions longer when positive nurse-physician relationships are present [1, 3]. Additionally, a positive nurse-physician relationship is associated with decreased infection and complication rates among patients [4].

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Another aspect which must be considered and which, in the US *pediatric* population, is unique to dialysis facilities is the influence of the Centers for Medicare and Medicaid Services (CMS) on culture, organization, and function. CMS is the regulatory agency responsible for administering the ESRD payment program for all patients covered by Medicare insurance. US dialysis facilities are required to be licensed by CMS in order to bill Medicare for services provided to dialysis patients. CMS requirements, otherwise known as Conditions for Coverage, are well defined and available via the CMS ESRD website [5]. The imperatives of dialysis care defined by CMS do not dictate organizational culture. However, the way an organization incorporates these requirements does play a large role in defining culture in a dialysis unit.

Physical Space Needs

Pediatric dialysis units are places where children with dialysis-dependent ESRD will spend a great deal of time. On average, a child requiring in-center hemodialysis will be present in the unit a minimum of 15 hours each week. The few children who require in-center peritoneal dialysis may spend up to 50 hours per week inside the dialysis unit. Because of this, it is important to consider the physical environment as a component of the treatment being provided. The space must be designed as an element of a healing environment that alleviates anxiety through distraction, age-appropriate play, and inclusion of a patient's support system (such as a parent or other caregiver). In contrast to the traditional design of an adult-centered healthcare facility where the emphasis is on functionality, a pediatric center demands a unique approach to design and aesthetics including the use of bright colors, integration of friendly characters or other artwork, and opportunities for interactive play. These elements work to reduce patient/family stress and enhance the care experience including helping to bolster the interpersonal relationships between the patient/family and the medical team [6] (Fig. 5.1).

The most important and basic factor in designing a physical space is the ability to perform a dialysis treatment. At a minimum, a dialysis treatment area should include the following:

1. Treatment station: There are no standard recommendations for minimum square footage for a dialysis treatment station. A treatment station must have enough space for the machine, a patient chair, electrical access, a

Fig. 5.1 Child-friendly artwork in the pediatric dialysis unit at Children's Mercy Kansas City. (Copyright © 2019. The Children's Mercy Hospital. All rights reserved. Used with permission)

place for liquids to drain, and a water source (for hemodialysis). Additionally, the treatment station must provide "sufficient space" as defined by CMS for the performance of emergency procedures (such as CPR) and to allow for patient privacy and the prevention of cross-contamination between treatment stations [7]. The layout and design of the treatment station space should consider human factors influences, meaning the design should be such that it is easy and convenient to follow policies and provide safe treatments within the space.

2. Handwashing sink: An easily accessible handwashing sink should be designated as a "clean" area and should be plumbed with both hot and cold water [5]. Ideally, handwashing sinks should have a hands-free mechanism for turning the water on/off, and there should be a visible clock in the line of sight to help facilitate proper handwashing duration and procedure.
3. Patient restroom: Patients need a place to use the restroom before or after their treatments. Some patients are required to perform bladder catheterization before or after treatment, and a space is needed for this.
4. Scale: Dialysis treatment settings are often weight-based. A scale is needed to record pre-treatment weights to determine treatment goals. Post-treatment weights are needed to evaluate treatment effectiveness and assist with establishing a future plan of care.
5. Medication preparation: Dialysis facilities should have a clean space designated for medication preparation. This space should be established after consultation with the facility's pharmacy and infection control and prevention departments.
6. Visibility: Irrespective of the number of treatment stations in a unit, each station must always be visible by the nursing staff. If a unit has a station which is not visible from the place a staff person is working (such as a central nursing station), a patient cannot receive treatment in that station. In order to utilize that station, workflow modifications are required to ensure a staff member always has an unobstructed view of the station.
7. Storage: Dialysis units require a variety of supplies. Depending on the services provided by a unit (inpatient, outpatient, in-center, home, hemodialysis, or peritoneal dialysis), the list of supplies can seem endless. From dressing change supplies to machine tubing to dialysate bags, it all needs a clean and dry place to be stored. Having supplies ready and available on the unit can involve storage of all supplies in a storage room within the dialysis unit or can involve storing a small amount of supplies in the dialysis unit and having the bulk of supplies stored in a centralized materials management area elsewhere in the facility. Either way, supplies must be routinely checked to ensure that out of date supplies are removed from the stock and disposed of.
8. Training/meeting space. A dialysis program should have a designated place within or nearby the unit for patient and family training to occur. Dialysis, regardless of modality, is a life-altering therapy. It requires patients and families to undergo education and training to learn how to keep themselves or their loved ones healthy and safe. Additionally, patients in the USA are required by CMS to have formal care plan meetings with the dialysis team at 30 days and 90 days post-dialysis initiation and then annually thereafter [7]. These meetings can also take place in the designated training/meeting space.

For infection control purposes, it is ideal if equipment is not shared between treatment stations. Every item that enters a treatment station must be wiped down and thoroughly cleaned upon exiting a treatment station. Each unit should consult their infection control and prevention team for guidance on ways to ensure infection control practices are initiated and maintained.

As mentioned previously, hemodialysis treatment stations do require a water source. Depending upon the size of the unit, this can be a portable system or a permanent loop system. Individual units can contract with a local dialysis

water professional to determine the ideal setup for the size and volume of the unit. While uncommon in pediatrics, if dialyzer reuse is practiced, a reuse processing plan would also be required.

Each unit will encounter specific challenges and needs. It is advisable for unit administrators to familiarize themselves with the CMS Conditions for Coverage and ESRD Interpretive Guidelines [5, 7] in order to collaborate with organizational architects, planners, and human factors engineers when creating a new dialysis space or repurposing an existing space.

Staffing the Unit

The American Nephrology Nurses' Association (ANNA) Nephrology Nursing Scope and Standards of Practice recommends a team approach to dialysis unit staffing and patient care. Dialysis teams should encompass a variety of multidisciplinary team members to provide a robust and comprehensive plan of care for each patient. In general, the dialysis care team should include medical directors, physicians, nurses, technicians (dialysis, biomedical, and patient care), social workers, dietitians, and the patient/family [8]. Additionally, for the pediatric population, the American Society of Pediatric Nephrology (ASPN) recommends that the team include child life specialists, teachers, and psychologists. This interdisciplinary approach encourages a holistic plan of care that fosters the growth and development of the child who is receiving chronic dialysis care.

A challenge to dialysis unit leaders is the lack of standardized staffing ratios in the dialysis unit. To date, there are no universally accepted standards or guidelines regarding staff to patient ratios in pediatric units. Guidance provided by CMS simply states there must be enough staff to provide a safe environment. This is a subjective statement and leaves much open to interpretation. Some states have established their own staffing guidelines for *adult* dialysis units. Staffing in pediatric units is complex and is made more so by the inclusion of infants in the patient population as well as by the inclusion of inpatient *and* outpatient services including, in some cases, continuous renal replacement therapy (CRRT) or plasmapheresis. All facility administrators are responsible for adhering to state guidelines and regulations, if applicable. Units should collaborate with organizational leadership to establish acceptable staffing ratios and should document these ratios in a unit specific structure standards document. This document outlines the function and form of a unit and provides standard guidance for daily management as well as the definition of unit roles and responsibilities. Examples of role definition can be found in Table 5.1. Facilities that are part of a larger organization may have a specific structure standards template to use when developing unit specific structure standards. As a reference for free-standing units or units without an established template, the components of a comprehensive structure standards document can be found in Table 5.2.

Along with staffing ratios, another important staffing challenge for dialysis unit leaders is staff retention. Gone are the days when employees worked long hours in the same job for 30 years. Individuals in the modern workforce seek opportunity for growth, new challenges, and the ever-elusive work-life balance.

Recent workforce data from the RN Work Project found that 18.1% of newly licensed nurses leave their first employer within the first year of employment. That number jumps to 26.2% when looking at the number of newly licensed nurses who leave their employer with 2 years of employment [14]. This trend presents an important challenge for unit leaders as the financial impact of staff turnover can dominate a unit's budget and prevent dollars from being spent in other areas. It is estimated that between $20,000 and $40,000 is spent on recruitment, hiring, and training when new nurses are added to a unit [9, 10]. In the pediatric dialysis setting, leaders should expect this figure to lean toward the high end of that range due to long orientation periods and the need to attract and recruit highly skilled staff.

While the financial impact of nurse turnover is significant, the effect this turnover has on patient care and outcomes cannot be overlooked. Nursing

Table 5.1 Examples of role definition

Service line director/facility administrator	The nephrology service line director (SLD) manages division-based patient care services including personnel, financial management, and development of programs and services. Participates in department and hospital performance improvement activities
Nurse manager	The dialysis unit nurse manager (NM) manages unit-based patient care services and department performance improvement activities. The nurse manager promotes family-centered patient care that is based on scientific theory and is outcome oriented
Dialysis unit educator	The dialysis unit educator uses the principles of adult education to provide appropriate education and training for all nursing and technical support personnel, as well as patient families. The educator develops and facilitates ongoing education to help start and maintain their skills. The educator utilizes nursing processes and knowledge of scientific principles to provide comprehensive nursing care for patients
Dialysis registered nurse	The dialysis registered nurse utilizes nursing process and knowledge of scientific principles to provide comprehensive nursing care for patients, to include providing dialysis treatments and/or case management services to patients. The nurse assists with the supervision of non-professional personnel as necessary and demonstrates commitment to maintaining and improving department/unit standards
Quality improvement coordinator	The quality improvement coordinator (QIC) assists with development and implementation of the unit QAPI plan. The QIC oversees the collection, organization, and presentation of QAPI data
Dialysis technician	The dialysis technician is responsible for a variety of clinical, technical, and clerical tasks as directed by the SLD or NM. The dialysis technician assists in the maintenance of a safe environment and promotes efficiency of operations
Social worker	The social worker is responsible to evaluate and provide resources for psychosocial and financial needs or concerns of ESRD patients and families while demonstrating commitment to quality improvement activities of the unit
Psychologist	The ESRD psychologist works with the interdisciplinary team to provide psychological support and guidance for patients undergoing dialysis treatments and their families
Administrative assistant	The dialysis administrative assistant acts as a receptionist and performs a variety of clerical functions and assists in the maintenance of a safe environment and promotes efficiency of operations
Registered dietitian	The dialysis registered dietitian is responsible for evaluating and overseeing nutritional requirements for patients undergoing dialysis. The dietitian monitors growth and weight of patients for appropriateness and provides nutritional interventions and education to patients and their families
Biomedical technician	The dialysis biomedical technician is responsible for maintaining hemodialysis machines and equipment
Advanced practice registered nurse	The dialysis advanced practice registered nurse (APRN) utilizes the nursing process and knowledge of scientific principles to provide comprehensive care to the dialysis patient/family
Child life specialist	The child life specialist (CLS) utilizes principles of neurocognitive and physical development to provide age-appropriate education and enrichment for patients undergoing dialysis
Dialysis unit teacher	The dialysis unit teacher is a hospital-based school teacher who works to ensure dialysis patients are able to stay current in their school studies while spending time out of the classroom and in the dialysis unit

units with higher turnover rates show an increase in patient complications and adverse events and a decrease in patient satisfaction and loyalty [11].

Interestingly, data shows that the driving factors for nurse retention and intention to stay in a position do not include salary considerations. The American Association of Critical-Care Nurses identified six standards for establishing and sustaining healthy work environments. The standards of skilled communication, true collaboration, effective decision-making, appropriate staffing, meaningful recognition, and authentic leadership [18] fall in line with data showing that the most important positive influences on nurse retention are often relationship based. The relationships a nurse develops with peers, leaders,

Table 5.2 Structure standards components

General description
(a) Type of unit
(b) Location/size of unit
(c) Narrative-physical space
Administration/organization
(a) Mission/vision statement
(b) Department organization
(c) Program goals and objectives
Hours of operation
(a) Regular operating hours
(b) After hours operation
(c) Emergency dialysis services
Utilization of the area
(a)Admission criteria
(b) Follow-up care
(c) Services provided
(d) Transfer/discharge criteria
Staffing
(a) Delivery of care methodology
(b) Role definitions
(c) Staffing ratios

physicians, and patients, as well as the ability to maintain relationships with family and friends outside of work, have been found to be a predictor of a nurse's intent to stay in a position [10, 11]. Thus, it should be a primary focus of a dialysis unit leader to encourage and foster the growth and development of these relationships. Team building exercises, the provision of supplies, space and education needed to do their jobs, and a leadership style that encourages open and honest communication are of utmost importance to developing and maintaining meaningful relationships in the workplace.

Billing and Regulatory Guidelines

In the USA, dialysis centers are heavily regulated by the federal government via CMS. As mentioned previously, pediatric dialysis patients in the USA are eligible to receive health insurance coverage through Medicare, and thus, dialysis centers are able to receive reimbursement for dialysis services by submitting bills to Medicare. However, Medicare has very specific rules and regulations that must be followed in order for a center to be eligible for reimbursement. These regulations and requirements can be found in the CMS ESRD Conditions for Coverage documents. Facility administrators and leaders should consult these documents for guidance on program requirements.

Care Implementation

Modality Selection

Patient modality selection is an integral part of providing dialysis services. Patients must be presented with all treatment options, including the expectations and requirements for each, in a way that utilizes the principles of health literacy so they are able to provide meaningful input into the modality selection process. Modality selection is best approached as a team effort between patients, families, and the healthcare providers as outlined by the Renal Physicians Association (RPA) Clinical Practice Guidelines [19]. Each modality has specific care requirements and regulations that the center and the patient/family must comply with. For example, it is recommended by the International Society for Peritoneal Dialysis (ISPD) that families of pediatric patients choosing to perform at-home peritoneal dialysis have the physical dexterity to perform dialysis treatments and dressing changes [12, 13]. Program-specific requirements may expand upon that to say a home patient must meet additional requirements such as the ability to provide a physically and emotionally stable and safe treatment environment or the availability of two caregivers able to commit time to complete the program's training requirements. Each dialysis candidate and their caregivers should be evaluated to assess their ability to meet all program-specific criteria before an ultimate decision on modality choice is made.

Modality choices at many centers include in-center hemodialysis or home peritoneal dialysis. Less common choices offered at some centers include home hemodialysis or in-center peritoneal dialysis. In-center peritoneal dialysis may be offered as an option when patients would benefit

most from peritoneal dialysis, but the parents/caregiver do not have the capacity to conduct the treatments at home.

Considerations for modality selection include type of kidney disease, age of the patient, location of the patient, parental preference, and family support system [24]. The goal of the nephrology team is to provide information, education, and support for the modality preferred by the family. For example, a family who is interested in home dialysis will benefit from a home visit before the final modality selection to evaluate if any environmental changes or modifications are needed before starting home therapy. This allows the family to be fully informed of the program requirements for the home environment prior to committing to a home therapy solution.

Patient/Family Education

So much of what we do as dialysis professionals relies on the patient/family to be a partner in the care being provided. A center's outcomes are a result of a combination of the medical team's effort and patient/family participation. Because of this, it is important to ensure proper emphasis is given to the development of patient/family education programs and materials. Patients should receive initial education and training upon diagnosis and treatment initiation but also should receive on-going, regularly scheduled education during their time as a dialysis patient/family. The SCOPE (Standardized Care to Improve Outcomes in Pediatric Endstage Renal Disease) Collaborative recommends at least monthly education for patients/families on dialysis therapies to ensure ongoing compliance with treatment protocols and to provide opportunities for open dialog between staff and patients/families regarding barriers or problems they may be experiencing. Since the implementation of the SCOPE bundles for patient care and education, the collaborative has seen a collective 41% reduction in the rate of peritonitis across all 44 participating centers.

Education materials should be developed by employing the principles of health literacy as defined by the Agency for Healthcare Research and Quality (AHRQ). Studies show that utilizing these principles increases readability and comprehension for people of all abilities and education levels [15, 16]. It is important never to assume a person will be able to understand and apply information based upon their level of formal education. Making this assumption disadvantages all learners by providing them with learning opportunities that may not be appropriate for their learning style or comfort level with the educational material. For this reason, it is wise to perform a health literacy and learning style assessment on all new learners to a program. This assessment can help educators identify the ways in which a learner best learns (visual, hands-on, written, or auditory) to provide education in a format that best suits the needs of the learner. Common examples of these assessment tools include the STOFHLA, BRIEF, and REAM. The STOFHLA tool is recommended for use in dialysis programs by the CKiD (Chronic Kidney Disease in Children) Study because it is a quick and simple tool which has been validated in both English and Spanish.

Upon completion of a health literacy assessment, the educator should employ principles of education that are designed to optimize the learning experience of parents/caregivers by customizing the way content is provided in combination with adult learning strategies or other developmentally appropriate approaches.

For written materials, health literacy experts emphasize evaluating both the readability (the length of words and sentences) and the understandability (word choice and format) of the content. Recommendations from the CDC and AHRQ include maintaining a fifth or sixth grade reading level, giving the most important information first, limiting the number of messages being conveyed at one time, telling the reader what actions they need to take, and utilizing pictures and white space to provide relief to the eye and give the brain an opportunity to process the information provided [17].

Authors of patient education materials can use online tools such as the Fry formula, SMOG, or the Flesch-Kincaid assessment to determine

readability of written materials. Understandability can be assessed using the AHRQ PEMAT, the CDC Clear Communication Index, or the SAM evaluation. More information and resources regarding health literacy and patient communication can be found online utilizing the CDC's health literacy web page.

Patient Care Plans

Services provided by a dialysis facility include evaluating and monitoring the whole patient. Dialysis care not only encompasses the actual dialysis treatments of the patient but also includes attention to growth, development, nutrition, cardiovascular health, bone and mineral disease, and psychosocial health. These components of dialysis care are addressed during the patient care plan process.

Patient care plans are designed to provide a patient and their family a clear representation of the current status of the patient's health and well-being, as well as defined goals for medical care. In the USA, this occurs at a minimum at 30 days and 90 days post-dialysis initiation and then annually thereafter. However, care plan meetings can occur at any time at the request of the patient/family or the medical team. Engaging patients and families in the care plan process allows them to be active participants in their care. Research suggests that patient and family participation in care leads to better medical outcomes as well as an increased sense of control, awareness, and self-esteem [20].

While the development of care plans and the implementation of care is largely an interdisciplinary effort, the role of the nurse in the process is vital to success. The dialysis nurse serves as a coordinator of care for these patients. This unique role allows the patient/family to have one point of contact for dialysis care and allows the medical team to identify one individual to be responsible for ensuring all follow-up tasks are assigned and/or completed. Patients requiring dialysis care have complex medical and psychosocial needs, and it is near impossible to ensure that all needs are met without a designated care coordinator. This coordination of care occurs at the care plan meetings as previously mentioned but also at the regular dialysis patient clinic visits, during phone calls with patients/families which should occur at least every 2 weeks (and more frequently with young patients), during interdisciplinary care conferences, and as needed to follow up on lab results, radiologic testing, and treatment/medication changes.

Patient and Family Support

The care of the child requiring dialysis often extends beyond the child to include familial and environmental care, so as to ensure a safe and stable environment for the child. Families who are thrust into the realities of living with a child who has ESRD can be surprised or caught off guard by the complexities of caring for a loved one with ESRD. It is essential for pediatric dialysis programs to offer education and support for the families facing this challenge. It is not uncommon for families or caregivers to experience a feeling of loss of control or even to go through a period of grieving and mourning as the realization of this life-altering diagnosis sets in.

According to PedsQL data, patients with kidney disease rate themselves as having a significantly lower quality of life than their healthy peers. This stems from a variety of factors including the decreased interaction with peers (from missing school to attend dialysis treatments), the dietary limitations of a renal diet, the uncertainty of the future (will they receive a transplant?), activity restrictions (bathing, swimming, sports), and body image concerns. Knowing quality of life is an impactful factor in longevity and future success, we must be prudent in providing opportunities for these patients/families to participate in meaningful experiences that work to enhance the quality of life and overall growth and development of the patients and their families [21]. Examples of such activities that should be incorporated into the organization of a dialysis program include involving patients/families in unit advisory boards or engaging them in open forums to allow patients/families to give input and feed-

back into unit operations and practices. The perspective of the patient/family is often different than that of a healthcare provider. Asking them to provide input helps them become more independent and allows them to feel more in control of what is happening to them.

Another opportunity that allows growth and development, encourages independence, and enhances the experience patients and families have is summer camp. As dialysis patients, children are not able to experience traditional summer camps alongside their friends from school or church because of their medical needs. Encouraging children to attend a summer camp specifically for children with kidney disease allows them to spend time with other children facing the same challenges they face. ESRD in children is relatively rare, and children requiring dialysis may not actually know any other children in their community who also have kidney disease. Allowing children to come together in the camp setting gives the kids a sense of normalcy. They experience the joys of being a kid without having to worry about what others are thinking about their catheter, their scars, or their handful of medications [22]. This time also affords the families much needed respite time. Families and caregivers of children with ESRD experience burnout and need time to recharge and focus on taking care of themselves. Providing a safe place for their child with ESRD to go and be cared for is an unexpected gift for parents and caregivers. Dialysis programs can support the efforts of their own camp, or a camp operated by another program, by incorporating the camp experience into the culture and expectations for program staff. Some patients may be reluctant to participate in an overnight camp away from their caregivers. Staff who are invested in the camp experience will encourage these patients to participate and will help them to receive the benefits of the camp experience.

Transition and Transfer of Care

Pediatric dialysis programs are designed to meet the needs of children requiring dialysis and their families. There comes a time when children grow into adults and therefore must transfer to an adult care provider. The age at which this happens ranges from 18 years to 22 years depending on the program and facility rules. Transition and transfer of care are often used interchangeably, but the reality is they refer to two very different processes. Transition is defined as the preparation leading up to and immediately after the transfer. Transfer of care is the actual act of shifting care from one provider to another (such as from the pediatric to adult provider). Ideally, the transfer of care occurs once the process of transition is complete. Because dialysis programs care for children from diagnosis until adulthood, it is necessary to establish and implement a transition curriculum to educate and prepare children for the transfer of care to an adult provider. The transition education curriculum should utilize the principles of health literacy and should focus on helping children learn about their kidney disease and how they can help keep themselves healthy. The material should arm the children with the knowledge needed to live a long and productive life with kidney disease. Ideally, this education should begin when a patient is 12 years of age with the slow accumulation of knowledge and skills over many years. Examples of topics which may be included in the education modules are anemia, bone disease, lab values, the functions of a kidney, and information about a patient's dialysis access. Patient knowledge and retention should be tracked utilizing a transition readiness tool which can provide information to help the medical team identify areas of educational need (Table 5.3).

Centers should also define a process for the actual transfer of care. Approaches to this event vary. Anecdotally, successful transfers of care have occurred when both the giving and receiving medical teams work in concert with each other. Some centers choose to host joint clinics with both providers present, while some choose to arrange a post-transfer visit with the pediatric provider to allow the patient and family to debrief after visiting the adult center. Regardless of the approach to integrating the transfer process into the program, it is beneficial for pediatric dialysis programs to establish and cultivate a relationship

Table 5.3 Transition Patient Readiness Tool, Children's Mercy Kansas City ESRD Transition Readiness Tool

Patient name:	Date:		
Transition Patient Readiness Tool			
Instructions: Read the question to the patient, and mark the choice that best describes the patient's response			
1. Chronic kidney disease	Ready	Approaching	Not Ready
What is the name of your kidney disease?			
What is your GFR, creatinine, or stage of kidney disease?			
Does a kidney transplant last a lifetime?			
What are the treatment options if your transplant fails?			
Why is it important to save your veins?			
What is the preferred arm to have labs drawn from or IVs placed?			
2. Rx: Medications	Ready	Approaching	Not Ready
Do you carry a list of your medications?			
What could happen if you do not take your medication?			
Are there any medications you should not take?			
Can you tell me what each of your medications is for?			
Do you have a system to organize your medication?			
What would you do if you ran out of refills?			
3. Lab information	Ready	Approaching	Not Ready
What time do you take your immunosuppressive medications?			
What time should your transplant labs be drawn?			
Why is it important to get labs?			
4. Health	Ready	Approaching	Not Ready
Does having a transplant/being on dialysis affect your ability to:			
Female – become pregnant			
Male – get someone pregnant			
Do you feel comfortable talking to your doctor by yourself?			
Why is exercise and good nutrition important?			
Why is it important to control your blood pressure?			
What are important reasons for you to call your nurse or doctor?For example, fever, refills, blood pressure, medication issues			
How can using drugs, alcohol, or smoking affect your health?			
Why is it important to receive your dialysis treatments prescribed by your physician or nurse?			
Why is it important to meet your fluid goal or restriction?			
Do you perform your medical procedures yourself?For example, catheterizations, bladder irrigations, or Epogen shots			
5. Self-management skills	Ready	Approaching	Not Ready
Do you remember to take your medications on your own?			
Do you call in your prescription refills yourself?			
Do you review your own lab results with your doctor or nurse?			
Do you know how to schedule an appointment?			
Do you plan your transportation to clinic?			
Do you carry your insurance card with you?			
Do you know who to call if you have questions or concerns? How do you find this number?			

Table 5.3 (continued)

Patient name:	Date:		
6. Insurance	Ready	Approaching	Not Ready
Do you know the name of your insurance?			
Do you understand you may have to pay a fee for clinic visits, labs, and medications?			
7. Ongoing support	Ready	Approaching	Not Ready
Who is your primary care doctor?			
Who is your support system that will help you manage your care (e.g., family, friends, clergy, or community members)?			
What concerns or questions do you have about transition?			

with regional adult care providers to assist with program design and objectives. It is essential to the success of transfers of care for pediatric and adult programs to maintain common goals and expectations. One way to ensure the teams are in sync is to participate in or develop city-wide or regional transition and transfer of care workshops. A workshop in this format allows pediatric and adult programs to develop solutions as a team that ultimately benefit the patients who are transferring from one program to another.

Quality Improvement and Safety

Quality improvement in the dialysis unit is vital to ensuring optimal patient outcomes. Ideally, units should have a dedicated quality improvement coordinator to identify and facilitate quality improvement projects and activities. Units regulated by CMS have pre-defined minimum standards for quality improvement monitoring which can be found on the Measures Assessment Tool (MAT) published by CMS (https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/MMS/Quality-Measure-and-Quality-Improvement-). Units not regulated by CMS may also find the MAT a helpful resource for defining quality metrics and goals [23].

While the MAT is a starting place for identifying quality initiatives, pediatric dialysis units should seek to identify additional ways to improve the care being provided. Facility leaders and staff can consult benchmarking resources from the International Pediatric PD Network (IPPN) or North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) databases to assist with project and metric identification.

Additionally, many healthcare facilities are shifting to a LEAN mentality to identify and surface quality or safety problems. LEAN organizations encourage front-line staff to voice concerns and to be an active participant in the problem-solving process to ultimately provide better and safer patient care. Examples of LEAN problem-solving tools that can easily be integrated into the dialysis unit quality and safety program are the use of STP (situation, target, and proposal) boards, daily safety and readiness huddles, and standard work documents.

Oversight and Ongoing Operations

In addition to quality and safety reviews, dialysis units are required by CMS to show evidence of communication and oversight within the parent organization, whether that be an independent dialysis company or as a component of a hospital system. The overarching purpose of this requirement is to ensure the organizational leadership is informed and aware of the challenges and successes impacting the patients and staff in dialysis units and a forum for bidirectional communica-

tion exists. Members of a dialysis unit oversight committee should include leadership from all areas and service lines in the organization that have a stake in dialysis unit operations. This can include organizational nursing leadership, the medical director of the dialysis program, and leadership representatives from biomedical engineering, intensive care and medical/surgical units associated with the program, quality and safety departments, as well as unit-based leadership. The oversight committee serves as an avenue for open communication.

While communication at the oversight level is extremely important, it is impossible to overemphasize the importance of open, honest, and frequent communication between the nursing and medical leadership. This communication and the development of a collegial relationship between medical and nursing leaders sets the tone for the culture and atmosphere of the dialysis unit. As mentioned earlier, staff satisfaction is associated with better patient outcomes, and a significant factor in staff satisfaction is relationship- based including the RN-MD relationship. The leaders of the program have a responsibility to shape and protect the relationship between team members. This can be accomplished by regular communication that leads to the surfacing of problems and the facilitation of problem-solving.

One such way communication and problem-solving can occur is through strategic planning for the future of the program. Each organization likely has enterprise-wide strategic goals that can and should be honed in on at the unit level. The dialysis program should embrace the goals and develop a way to incorporate goal achievement into daily practice. Common goals among organizations may include metrics around access to care, financial stewardship, or patient satisfaction. Programs should engage front-line staff and leadership as well as quality and safety personnel to develop action plans and common unit-level goals. This requires an ongoing commitment to the fostering of relationships as well as to a team mentality.

Conclusion

The organization and management of a dialysis unit presents unique challenges and opportunities for leaders. The balance between regulatory, organizational, and interpersonal goals is delicate and is unique to pediatric dialysis programs. The principles and practices described in this chapter can provide a solid foundation for the organization and management of a pediatric dialysis unit; however, executing a unit organization and management plan with finesse is the key to success.

References

1. Hahtela N, Mccormack B, Doran D, Paavilainen E, Slater P, Helminen M, Suominen T. Workplace culture and patient outcomes. Nurs Manage. 2017;48(12):36–44. https://doi.org/10.1097/01.numa.0000526910.24168.ee.
2. Manley K, Sanders K, Cardiff S, Webster J. Effective workplace culture: the attributes, enabling factors and consequences of a new concept. Int Pract Dev J. 2011. Retrieved December 01, 2018, from https://www.fons.org/Resources/Documents/Journal/Vol1No2/IPDJ_0102_01.pdf.
3. Galletta M, Portoghese I, Carta MG, Daloja E, Campagna M. The effect of nurse-physician collaboration on job satisfaction, team commitment, and turnover intention in nurses. Res Nurs Health. 2016;39(5):375–85. https://doi.org/10.1002/nur.21733.
4. Boev C, Xia Y. Nurse-physician collaboration and hospital-acquired infections in critical care. Crit Care Nurse. 2015;35(2):66–72. https://doi.org/10.4037/ccn2015809.
5. Quality, Safety & Oversight – Guidance to Laws & Regulations for Dialysis. (2017, October 25). Retrieved from https://www.cms.gov/Medicare/Provider-Enrollment-and-certification/guidanceforlawsandregulations/dialysis.html
6. Woo J, Lin Y. Kids' perceptions toward children's ward healing environments: a case study of Taiwan University Children's Hospital. J Healthc Eng. 2016;2016:1–10. https://doi.org/10.1155/2016/8184653.
7. Quality, Safety & Oversight – Guidance to Laws & Regulations for Dialysis. (2017, October 25). Retrieved from https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/GuidanceforLawsAndRegulations/Downloads/esrdp-gmguidance.pdf

8. Gomez NJ. Nephrology nursing scope and standards of practice. Pitman: American Nephrology Nurses Association; 2017.
9. Schroyer CC, Zellers R, Abraham S. Increasing registered nurse retention using mentors in critical care services. Health Care Manag. 2016;35(3):251–65. https://doi.org/10.1097/hcm.0000000000000118.
10. Hayes B, Bonner A, Douglas C. Haemodialysis work environment contributors to job satisfaction and stress: a sequential mixed methods study. BMC Nurs. 2015;14(1):58. https://doi.org/10.1186/s12912-015-0110-x.
11. Nei D, Snyder LA, Litwiller BJ. Promoting retention of nurses. Health Care Manag Rev. 2015;40(3):237–53. https://doi.org/10.1097/hmr.0000000000000025.
12. Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
13. Figueiredo AE, Bernardini J, Bowes E, Hiramatsu M, Price V, Su C, Brunier G. A syllabus for teaching peritoneal dialysis to patients and caregivers. Perit Dial Int. 2016;36(6):592–605. https://doi.org/10.3747/pdi.2015.00277.
14. RN Work Project. Robert Wood Johnson Foundation. www.rnworkproject.org
15. Brega AG, Freedman MA, Leblanc WG, Barnard J, Mabachi NM, Cifuentes M, West DR. Using the health literacy universal precautions toolkit to improve the quality of patient materials. J Health Commun. 2015;20(Suppl 2):69–76. https://doi.org/10.1080/10810730.2015.1081997.
16. Agency for Healthcare Research and Quality. AHRQ Health Literacy Universal Precautions Toolkit. https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/index.html
17. Centers for Disease Control. Simply put: a guide for creating easy to understand materials. https://www.cdc.gov/healthliteracy/pdf/simply_put.pdf
18. Vollers D, Hill E, Roberts C, Dambaugh L, Brenner ZR. AACNs healthy work environment standards and an empowering nurse advancement system. Crit Care Nurse. 2009;29(6):20–7. https://doi.org/10.4037/ccn2009263.
19. Renal Association Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis Clinical Practice Guidelines 5th Edition 2009–2012. (2010). doi:https://doi.org/10.1159/isbn.978-3-8055-9724-1
20. Modi AC, Pai AL, Hommel KA, Hood KK, Cortina S, Hilliard ME, Drotar D. Pediatric self-management: a framework for research, practice, and policy. Pediatrics. 2012;129(2)
21. Goldstein SL, Gerson AC, Furth S. Health-related quality of life for children with chronic kidney disease. Adv Chronic Kidney Dis. 2007;14(4):364–9. https://doi.org/10.1053/j.ackd.2007.07.006.
22. Kennedy S, Richards C. Camps and their benefit to pediatric nephrology patients. Nephrol Nurs J. 2016;43(1):27–9.
23. Measures Assessment Tool (MAT) for Dialysis. Version 2.4. Retrieved from http://www.esrdnetwork.org/sites/default/files/MAT%20tool%20Updated%202015.pdf
24. Warady BA, Neu A, Schaefer F. Optimal care of the infant, child, and adolescent on dialysis: 2014 update. Am J Kidney Dis. 2014;64(1):128–42.

6 Role of the Advanced Practice Provider in a Pediatric Dialysis Program

Jessica J. Geer and Kathleen F. Mallett

Introduction

There is a growing demand for pediatric nephrology as children with chronic illness are surviving kidney-related complications due to improvement in technology [1]. However, according to a survey completed by the American Academy of Pediatrics on the workplace in pediatric nephrology, there is a potential shortage for pediatric nephrologists in the future. From 2010 to 2014, 43% of fellowship positions were unmatched [2]. At the end of 2013, the average age of pediatric nephrologists in the United States was 57.8 years. Nurse practitioners and physician assistants, both commonly referred to as advanced practice providers (APPs), can be vital members of the multidisciplinary team to help care for children with chronic kidney disease and improve the shortage of pediatric nephrology providers.

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History of the Advanced Practice Provider (APP)

Nurse Practitioner

The first nurse practitioner (NP) program was started at the University of Colorado in 1965 by Dr. Loretta Ford and Dr. Henry Silver in response to the expansion of Medicare and Medicaid coverage to include low-income women, children, elderly, and people with disabilities [3]. The increase in the size of the population needing healthcare services created a shortage of primary care providers, especially in rural areas of the United States. According to the American Association of Nurse Practitioners (AANP), there are currently about 248,000 nurse practitioners in the United States [4]. There are multiple synonymous titles for this role, including advanced practice registered nurse (APRN), advanced registered nurse practitioner (ARNP), and nurse practitioner (NP). For the purposes of this chapter, this role will be referred to as APRN. APRNs are registered nurses (RNs) who have completed a four-year degree in nursing (bachelor of science in nursing or BSN) and then obtain either a graduate or doctorate degree in a population-focused area of study. There are a myriad of program tracks for either degree level including, but not limited to, family practice, pediatrics, acute care, emergency medicine, and psychiatric-mental health [5–7]. Graduate degrees include the master of science in nursing

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(MSN) and post-master's certificate. Doctorate degrees include the doctor of nursing practice (DNP) and doctor of philosophy (Ph.D.). A MSN must be completed prior to obtaining a doctoral degree. Some programs offer a dual degree BSN-DNP option, where in a MSN is obtained as part of the terminal DNP degree. Post-DNP certificates are also available for those who wish to pursue further expansion of their scope of practice. Single-track programs prepare the APRN for national certification and to provide comprehensive care for a population-focused area, whereas dual track programs prepare the APRN to become nationally certified and to practice in either two population-focused areas, or one population-focused area in both primary and acute care. For single-track programs, a minimum of 500 direct patient care clinical hours is required for the MSN. However, for APRNs studying to care for patients across the lifespan (i.e., family practice), or in dual track programs, it is expected that this minimum requirement would be exceeded [8]. For those pursuing the emerging DNP degree, a minimum of 1000 post-baccalaureate practice hours along with a final doctoral project (such as original research, journal publication, or quality improvement projects) are required through the program of study [9]. According to the 2015 American Association of Nurse Practitioners (AANP) Scope of Practice for Nurse Practitioners position statement [10], this additional training allows the APRN to practice in ambulatory, acute, and long-term care as a primary and/or specialty care provider. APRNs assess, diagnose, treat, and manage acute episodic and chronic illnesses. They order, conduct, supervise, and interpret diagnostic and laboratory tests, prescribe pharmacological agents and non-pharmacologic therapies, and teach and counsel patients. Additionally, the APRN typically obtains certification in the patient population in which their practice is focused, depending on state regulations. In terms of pediatric dialysis settings, the APRN may have specific certification in family practice, pediatrics, or clinical nurse specialist areas. Additional specialty certification may be obtained in nephrology to demonstrate clinical expertise, but nephrology certification is not a requirement for licensure or employment at this time.

Licensure and scope of practice as an APRN is determined individually by each state's Board of Nursing through the state rules/regulations and nurse practice acts (NPA). Certification is maintained by either retesting and passing the test specific for original certification or obtaining continuing nursing education (CNE). Most states do require initial certification as part of the licensing process. Each state's Board of Nursing also regulates the level of physician involvement in patient care (for instance, interval follow-up and chart review), the number of APRNs with whom each physician can collaborate, distance between the collaborating provider and the APRN, or if the APRN can admit patients to the hospital [11]. In 2010, the Institute of Medicine (now called the National Academy of Medicine) published a report on "The Future of Nursing," recommending APRNs be allowed to practice at the fullest extent of their education and training in order to increase access to healthcare for all [12]. To address the wide variation among states in the rules and regulations governing ARRN practice, the National Council of the State Boards of Nursing (NCSBN) and the National Academy of Medicine (NAM) have launched a collaborative effort termed the APRN Campaign for Consensus. The goal of the campaign is to align APRN licensing and regulation across the participating states to allow APRNs to practice to the full extent of their training and licensure [13]. Currently, there are three levels of APRN practice: (1) full practice authority; (2) reduced practice; (3) restricted practice. Given the ever-changing policies and requirements, it is prudent to know your state's specific requirements for licensure and scope of practice for the APRN.

Some expectations and responsibilities of the APRN are participation in development and assessment of medication protocols, and to assess, diagnose, theorize, and analyze complex clinical and nonclinical problems. See Table 6.1 for competencies for the APRN in nephrology according to the American Nephrology Nurses Association (ANNA) Position Statement [14].

Table 6.1 Examples of competencies for the APRN in nephrology

1. Independently assess, conceptualize, diagnose, and coordinate care for complex health problems
2. Provide expert nursing care to individuals with varying degrees of kidney impairment
3. Assist patients and families with modality choices
4. Prescribe, administer, and evaluate pharmacologic and non-pharmacologic therapeutic treatment regimens
5. Focus on care that promotes health and prevents kidney disease
6. Manage acute and chronic kidney disease in a variety of healthcare settings

American Nephrology Nurses Association [14]

Physician Assistant

Similar to the APRN, the role of the physician assistant (PA) was born out of necessity in the mid-1960s due to an impending primary care shortage and implementation of Medicaid and Medicare. The first physician assistant program was started in 1965 by Dr. Eugene A. Stead Jr. at Duke University. It began with four Navy Hospital Corpsmen who had received extensive medical training in the military. This role was initially geared toward the returning serviceman who could be fast-tracked on their training [15]. Five years later, Dr. Silver also developed the child health associate's program, a PA program with an emphasis on pediatrics.

The PA requires a graduate degree called the masters of health science (MHS). While a non-healthcare bachelor's degree is acceptable, all applicants to a PA program must meet program pre-requisites that include college-level classes in chemistry, anatomy/physiology, biology, and microbiology along with a minimum of 2000 hours of healthcare experience. This is often obtained through employment as an emergency medical technician (EMT), paramedic, lab assistant, medical assistant, emergency room technician, certified nurse assistant (CNA), or other healthcare fields. Acceptable healthcare hours may be program specific [16]. Most PA programs take approximately 2 years to complete and include classroom instruction along with 2000 clinical hours in a variety of settings that is not limited to family practice, internal medicine, pediatrics, general surgery, OB/GYN, emergency rooms and psychiatry. Physician Assistants must pass a national certification known as the Physician Assistant National Certification Exam (PANCE) which is required by all states for initial licensure. Whereas APRNs are regulated by each state's Board of Nursing, PAs are regulated by state medical boards; these boards do not always have PAs as members to represent the profession. Currently, PAs must have a practice agreement with a specific physician, although there is a policy change occurring within the American Association of Physician Assistants (AAPA) referred to as Optimal Team Practice [17]. The goal is to remove the burden of having a specific physician with whom the PA has a legal agreement. Practice-level decisions about collaboration are emphasized, allowing more flexibility to collaborate in medical teams and avoiding administrative infractions that are unrelated to patient care and outcomes [18].

Licensure is also individualized by state or jurisdiction including the District of Columbia. Initial licensure always includes passing the PANCE, but renewal of the PA license requires either Continuing Medical Education (CME), retesting and passing the PANCE, or a combination of the two. Scope of practice for the PA is regulated at the core by the state regulatory body. It is also determined by the physician's scope and practice setting in which they work. Additional optional certification called a Certificate of Added Qualifications (CAQ) may be obtained to illustrate further competence and commitment within a specialty such as nephrology. Just as with the APRN, it is prudent to be knowledgeable of each state's regulations regarding the practice requirements of the PA.

Orientation for the APP

Dialysis units with a pediatric designation make up <0.1% of all dialysis units [19]. Consequently, the role of an APP in this setting is varied based on the needs of the institution. Some APPs are responsible for both outpatient and inpatient

management, while others may work in only one of these settings; the same may be true for dialysis or transplant. Each program is unique, and experience levels of APPs will differ even within the specialty. In turn, orientation for an APP will depend on previous experience and can be tailored accordingly. Although some APPs may have experience in other areas, it is common for an APP to be brand new to dialysis with no prior experience in nephrology. There are currently no standardized curriculum or fellowship programs for APPs interested in further training in nephrology. Therefore, orientation for nephrology APPs, whether it be in the acute care setting, dialysis, or transplant programs, is primarily developed by the specific department. The APP should be motivated to create his or her own orientation pathway and to initiate learning experiences. Through an extensive orientation, APPs can learn the complex medical management of patients with end stage kidney disease. At most institutions, a typical hospital orientation is 3 months, but learning and obtaining competency in pediatric ESKD care can take 1–2 years depending on the experience of the APP. However, care of the nephrology patient is complex, so learning is life-long. Little is known regarding specific orientation practices in pediatric nephrology for APPs, so forming relationships with peers and other providers with experience in this setting is crucial. Practically speaking, incorporating the necessary education into the daily job duties can be a major challenge. Scheduling and keeping dedicated time for education will require support from division leadership.

First, it is important for the APP to learn the physiology and pathophysiology of renal disease to better understand treatment options. Membership in national organizations may also be useful in identifying relevant topics and continuing education opportunities to include in the orientation process. Additionally, attending national conferences on nephrology and dialysis is vital in the learning process. At conferences, the new APP will be able to network with others around the country, hear descriptions of roles and day-to-day responsibilities, and learn important concepts for practice. Other recommended learning activities can be found in Table 6.2.

Table 6.2 Recommendations for orientation activities for the APP

Read nephrology journal articles and textbooks	Attend nephrology lectures and other didactic opportunities
Round on nephrology patients (inpatient and outpatient)	Become a member in national organizations (ex: American Nephrology Nurses Association (ANNA), National Kidney Foundation (NKF)
Attend national conferences in nephrology and dialysis	Network with other APPs around the country
Shadow dialysis nurses and technicians	Attend home training sessions and home visits

For dialysis, APPs should spend time learning all dialysis modalities, including the operation of dialysis equipment and management of all access types. Spending time with front line dialysis nurses to learn the nuances of treatments is essential. It is often helpful for the APP to attend home dialysis training sessions with the home training nurse and the patient's caregiver in order to better understand issues that can occur during treatment that the APP will be expected to manage. Dialysis nurses and technicians offer a wealth of knowledge of patient care at the bedside. The APP should orient with the dialysis unit educator and nursing manager to learn about the unit and the important regulatory standards that govern its operations.

Since there are fewer APPs in pediatric dialysis, it may be helpful to shadow an adult dialysis APP to learn workflow and responsibilities in a given unit. The APP should understand management of common complications that arise during dialysis treatments such as blood pressure management, fever, access malfunction, and other issues discussed in this textbook. Working closely with a vascular surgeon is helpful in learning the management of arteriovenous fistulas and grafts. It is also helpful to collaborate with pediatric surgery or interventional radiology to understand

the placement of hemodialysis central venous lines and peritoneal dialysis catheters.

In addition, it is important for the dialysis APP to understand renal transplantation. For most pediatric patients, dialysis is considered a bridge to transplant. The APP should understand the medical and psychosocial requirements for transplantation; coordinating care of the dialysis patient with the transplant team is another important APP role. If possible, the APP should observe a kidney transplant during orientation so questions can be answered when they arise from the patient and family.

The APP in the Dialysis Unit

Once licensed and certified, the APRN or PA can manage children on dialysis. Children on chronic dialysis have unique needs requiring ongoing coordination of care. There can be multiple comorbid conditions managed by other specialists leading to numerous healthcare providers, medications, and testing. The ideal multidisciplinary team consists of the nephrologist, APP, case manager, dialysis nurse, pharmacist, dietitian, social worker, psychologist, child life specialist, surgeon, vascular access coordinator, quality improvement coordinator, and pre-transplant nurse coordinator. In the chronic outpatient dialysis setting, APPs are becoming increasingly vital members of the interdisciplinary team, functioning as clinician, educator, case manager, quality improvement leader, and consultant. APPs are considered the bridge between the front line nursing, patients and families, ancillary staff, and nephrologists. Parents often look to APPs because they are the constant members of the provider team seeing their child routinely during most dialysis treatments. Directing and managing care according to evidence-based guidelines and hospital policy is crucial to ensuring optimal care and outcomes for the patient who requires dialysis.

There is an overlap of clinical management issues for both the hemodialysis and peritoneal dialysis patient including anemia, mineral-bone disease, cardiovascular disease, growth and development, infection prevention, and dialysis access. The APP is well-equipped to manage these issues. Additionally, there are secondary management opportunities that the APP can lead including medication reconciliation and end-stage renal disease education.

Role of the APP in Hemodialysis

Rounding

APPs generally round during each dialysis shift, reviewing inter-dialytic weight gains, blood pressure trends, lab results, and any new acute issues that have developed since the last treatment. APPs help guide dialysis nurses and technicians on fluid removal goals. Most APPs are responsible for writing the dialysis weekly note, documenting any acute issues that arose, and participating in the multidisciplinary visit that occurs monthly.

Vascular Access

The role of the APP in the hemodialysis unit involves many aspects including vascular access and troubleshooting. APPs work closely with the unit vascular access coordinator, or in many cases, serve as the vascular access coordinator. For hemodialysis catheters, APPs are responsible for working with the dialysis nurses in monitoring the need for thrombolytic agents such as tissue plasminogen activator (tPA). If a catheter is found to be malfunctioning, the APP must coordinate care for replacement of the line, deciding on urgency of replacement, need for hospital admission, management of fluid and electrolytes prior to surgery, and coordinating dialysis once the catheter is replaced. An example of an APP-led quality initiative is the creation of an algorithm to standardize packing hemodialysis catheters with tPA.

In addition, the APP is another member of the team who can provide education on long-term access for patients and their families. The APP coordinates the referral to the vascular surgeon and ensures vessel mapping is completed prior to arterial-venous fistula (AVF) creation. Post op, the APP assesses the AVF during each dialysis

session to monitor for infection, incision healing, and maturation of the AVF. Once the fistula is ready to be used, the APP helps provide education and support, along with dialysis nurses and child life specialists, with the goal of a successful first attempt at accessing the fistula.

Prior to every treatment, the dialysis RN is required to assess the AVF. If there is an abnormality noted on exam, this gets reported to the APP who also does a physical exam. If there is concern for infection, the APP can order cultures and prescribe appropriate antibiotics.

Routine monitoring of the AVF with ultrasound dilution (Transonic®) exams may uncover a drop in estimated blood flow through the fistula. This would warrant further investigation, and the APP can coordinate a fistulagram and angioplasty if indicated. The APP is often the person who is very familiar with a patient's access and is a vital member of the access support team.

Lab Review

Once stable on chronic hemodialysis, patients usually receive less frequent laboratory monitoring, typically once monthly. The APP can be responsible for reviewing labs and making medication changes as needed with support by the primary nephrologist.

APPs can play an important role in anemia management and renal osteodystrophy control in children with CKD. APPs might develop evidence-based guidelines for erythropoetin adjustments and iron supplementation to manage renal anemia or algorithms for medication changes to manage bone mineral metabolism.

Role of the APP in Peritoneal Dialysis

Initiating Peritoneal Dialysis

The APP is an integral component of the successful management of the pediatric peritoneal dialysis (PD) patient. Providing evidence-based care is multi-faceted and offers several opportunities for the APRN or PA to improve outcomes in this population. For a new PD patient, the APP often coordinates care across a wide spectrum, including monitoring the procedure for PD catheter placement, reviewing microbiology results, prescribing appropriate prophylactic medications, managing initial treatments, ensuring proper post-op care, monitoring for complications and assisting with the discharge process. In order for the family to be successful for home PD therapy, the APP must work alongside the healthcare team to evaluate caregiver readiness and ability to safely provide this complex medical treatment at home.

Managing Outpatient Peritoneal Dialysis

For the patient who receives PD at home, the APP is responsible for reviewing treatment data, making necessary adjustments to the PD prescription to optimize clearance, updating the medication list for accuracy, ensuring medications for possible contamination or peritonitis are ordered and reviewing complicated cases with the nephrologist. Additionally, the APP may be responsible for monthly ESKD clinic visits which is an opportune time to review and reinforce education regarding proper catheter care, treatment techniques, and dialysis adequacy.

Managing Complications of Peritoneal Dialysis

The most common complications of PD are infectious and fall into two categories: exit-site/tunnel infections and peritonitis [20]. The APP can be counted on to provide preliminary care for the patient who may be experiencing an exit-site/tunnel infection or peritonitis episode. Knowledge of evidence-based guidelines such as the International Society of Peritoneal Dialysis Consensus Guidelines for the Prevention and Treatment of Catheter-Related Infections and Peritonitis in Pediatric Patients Receiving Peritoneal Dialysis: 2012 Update [21] is essential in providing the best care and outcomes for the pediatric PD patient who may have an exit-site/tunnel infection or suspected peritonitis. As previously mentioned, the APP is often the first-line provider to be notified of concerns for potential infection and is able to initiate work-up and treatment.

Exit-site/tunnel infections are known to increase the risk of peritonitis and catheter failure

[22]. The initial evaluation of a suspected exit-site/tunnel infection can be done in person or via a cell-phone picture sent to staff by the caregivers. Many of the patients at the authors' centers who are receiving PD live several hours away from our hospital. Questionable infection at the PD catheter exit-site is quantified using a scoring system as outlined in the ISPD Guidelines. Having the ability to initiate evaluation with a picture can help expedite scoring and direct treatment until face-to-face assessment can take place. See the chapter on infectious complications in peritoneal dialysis (Chap. 16) for more information regarding management.

Patients who receive PD at home must have trained caregivers who have demonstrated competency in reconstituting antibiotics for instillation into PD fluid in the event of touch contamination or signs and symptoms of peritonitis. The caregiver is then expected to notify the dialysis staff per defined parameters from training. When the APP is notified, he or she is then responsible for coordinating further evaluation, including a formal assessment (in clinic or the Emergency Department), ordering the cell count and culture and/or exit site cultures, interpreting results, initiating treatment, and coordinating admission (if indicated based on results). Documenting and discussing the findings and treatment plan with the nephrologist and other members of the healthcare team is also the responsibility of the APP to ensure thorough communication and care coordination.

Role of the APP in Critical Care Nephrology

The role of the APP in critical care nephrology has many similarities to the chronic setting. The APP in the acute care setting participates in consults, daily care coordination, patient management, and quality improvement as described in previous sections. Depending on the institution, the acute care APP is often trained on all acute procedures including therapeutic plasma exchange, acute peritoneal dialysis, acute hemodialysis, continuous renal replacement therapy (CRRT), and extracorporeal liver support (ELS). As in the chronic setting, the APP is a member of the interdisciplinary inpatient team, which includes the nephrology attending physician and/or fellow, and nursing staff.

Acute Procedures

The APP can obtain procedural consents and complete appropriate orders. If managing the patient, the APP is usually present for the initiation of all new procedures including CRRT and ELS to help manage complications and is usually present at the bedside until all prescribed renal replacement therapy (RRT) settings are achieved and the patient is hemodynamically stable. For critically ill patients that are managed by the APP, there are daily comprehensive evaluations of the patient including review of patient fluid balance, laboratory findings, medications, nutrition, and patient condition.

In addition, there are occasionally patients with acute kidney injury (AKI) that transition to intermittent hemodialysis while remaining inpatient for a prolonged period of time without recovering renal function. These patients are treated similarly to chronic dialysis patients who are managed in the acute setting. The APP is helpful in coordinating care and managing associated chronic conditions. For example, ensuring chronic labs (Kt/V, PTH, iron stores, etc.) are checked monthly while in the hospital until the patient is stable enough for discharge to the outpatient chronic dialysis unit.

Billing Practices for the APP

According to Centers for Medicare and Medicaid services (CMS) regulations, the monthly capitation payment (MCP) must be furnished face-to-face by a physician, clinical nurse specialist, nurse practitioner, or physician assistant. For center-based patients, payment is based on the number of face-to-face visits each month with one visit being the lowest payment amount and four or more visits the highest payment amount. The physician or APP who provides the complete assessment and establishes the patient's

plan of care should submit the bill for the monthly service [23]. For home-based patients, documentation should support at least one face-to-face encounter per month by the physician or APP.

Of note, decisions made regarding APP reimbursement for Medicaid services are made at the state rather than the federal level, so rates vary state by state. It is important for the APP to be aware of billing practices individual to their location.

The Role of the APP in Transitions of Care

Living with a chronic illness such as chronic kidney disease adversely affects the quality of life of the pediatric patient, especially in those diagnosed at a later age [24]. Feelings of vulnerability, anxiety, and identity crisis can disrupt the life of the pediatric patient. Caregivers may also experience uncertainty, fear, and difficulties managing the patient's health issues [25]. As previously stated, the APP is often the most consistent provider for this population and has a unique role in providing reassurance and continuity of care for the patient and family during these vulnerable times. Three major periods of transition may be identified after a patient is diagnosed with CKD: (1) transition from CKD-ESKD, (2) transition to transplant, and (3) transition from pediatric to adult care. All of these transition periods can prove difficult to navigate for the patient and family, presenting a crucial opportunity for the APP to alleviate the aforementioned struggles. Excellent communication skills that include understanding the principles of motivational interviewing, health literacy, and shared-decision making are paramount for the success of each transition period.

At the basic level, "…health literacy describes the patient's ability to access, understand, interpret, and use health-related information to improve health" [26]. The Institute of Medicine recognizes health literacy as an important component of high-quality health care [27]. Many institutions are recognizing the importance of tailoring treatment for the patient and family utilizing the shared decision-making approach [28]. Healthcare providers should understand the relationship between health literacy and shared decision-making, recognizing that adequate health literacy is vital for participation in the shared decision-making process. It is crucial for the APP to understand that half of all parents have difficulty reading and understanding patient education materials, and many struggle to comprehend medical advice that is critical to the care of their child [29]. Additionally, there is a paucity of research with implicit findings on the effect of low parental health literacy in the ESKD population.

CKD-ESKD

Advanced practice providers are essential team members who can fill a knowledge gap for families that are transitioning from CKD-ESKD. This transition is often a period of uncertainty and apprehension for the patient and their caregiver(s). The APP is in a unique position to champion health literacy efforts and shared decision-making policies for their unit. It is not uncommon to see fluctuations in labs and patient well-being as he or she teeters on the verge of ESKD status. Including the patient and caregivers in health literate conversations early on in their CKD journey is one way to enhance shared decision-making and positively affect adherence, outcomes, and patient satisfaction [26]. In addition, as GFR declines, the burden of self-care and shared decision-making increases, but the ability to understand, apply, and take part in these activities may decrease secondary to the effects of declining renal function [28]. A recent study by Rak et al. [30] found that low word reading literacy skills (<7th grade) contributed to higher numbers of ER visits in the adolescent CKD or ESKD population.

In some programs, the CKD and ESKD teams function separately, while others demonstrate overlap between the teams. This may cause con-

fusion for not only the teams involved, but also the patient and caregiver who may not understand which team is refilling meds, reviewing labs, or whom to call if new issues arise. Transferring care from the CKD team to the ESKD team should ideally be well defined with roles and timelines mutually agreed upon between the teams; the APP is in an ideal position to facilitate this communication effectively.

A meeting to discuss treatment options for ESKD including hemodialysis, peritoneal dialysis, and kidney transplant is required not only from a regulatory perspective, but also to allow the family to make an informed decision. This could also serve as an introduction for the patient and family to the ESKD team and facilitate the transfer of care from CKD to ESKD. The APP can lead a multi-disciplinary team to develop a structured health-literate presentation regarding treatment options for ESKD. This approach also facilitates the shared decision-making process that is proving to be vitally important for patient outcomes [31]. The APP must also work closely with the dialysis staff to coordinate access placement for the chosen dialysis modality in addition to formulating the initial dialysis prescription.

Dialysis to Transplant

Kidney transplant is widely recognized as the treatment with the best outcomes for the patient with ESKD [32]. As mentioned previously, APRNs and PAs may wear many different hats depending on the needs of their program. The role of liaison between the dialysis and transplant teams is crucial to help facilitate readiness for transplant. This may include ensuring vaccinations and required workup such as imaging are ordered and completed, as well as alerting the transplant team of severe illness or situations which would require a patient to become inactive on the wait list. In many programs the APP is the consistent provider for the dialysis patient and proves to be a vital member of the team to advocate for or alert the transplant selection team to situations that would indicate a patient is not ready to be placed on the waitlist.

Pediatric to Adult Care

The transition to adult care requires advanced planning and preparation from the multidisciplinary team. This should incorporate a collaboration between the healthcare team along with the patient and caregiver to teach self-care. Helping the adolescent/young adult (AYA) gain autonomy and responsibility for her or his own care is necessary prior to transitioning to adult care, but this can be a stressful time for the patient and caregiver, creating feelings of anxiety and depression. The recommended age to begin the transition process is 12–14 years of age; however, many factors play a role in education readiness including emotional, psychological, and physiological maturity. As previously stated, the decline in GFR may affect the ability of the patient to achieve adequate health literacy.

The caregiver's level of health literacy should also be taken into account, recognizing that educational level does not always correlate with how health literate a caregiver is [24]. Care should be tailored accordingly, and the APP is in an excellent position to help develop or improve existing materials to not only ensure they are designed to promote health literacy, but also are individualized for each patient. The AYA is at greatest risk for non-adherence/attendance at clinic visits and preventable hospitalizations in the first 3–4 years after transition to adult care. Transition champions from both the pediatric and adult sides facilitate a smoother transition for the adolescent/young-adult [25], and this is an excellent role for the APP in dialysis.

The Role of the APP in Improving Patient Outcomes

Assessing and improving the quality of care provided to patients with end-stage renal disease is an important responsibility for the entire dialysis

team, including the APP. As part of quality improvement, evidence-based processes of care are monitored and evaluated. A systematic approach for improvement is implemented and results are discussed routinely [33]. APPs are often involved in quality improvement projects in the dialysis unit. Since outcomes are tracked on a monthly basis, problems can be easily identified. For example, if a unit is not meeting their goal for anemia management, the APP can collaborate with the medical director, nursing leadership, pharmacist, and other members of the interdisciplinary team to review the current practice and decide on interventions to be implemented. After each intervention, results are tracked and discussed on a regular basis.

In addition to quality improvement projects, the APP can impact the overall quality of care delivered. There are few studies in the adult literature examining the role of the APP in the dialysis unit and the impact on quality of care. In one study, a joint model of care delivery utilizing an advanced practice nurse with a nephrologist was compared to a nephrologist alone. Team satisfaction and perceptions of care delivery were higher in the advanced practice nurse/nephrologist model. In addition, more frequent adjustments to dry weights, labs, and medications were made, leading to a conclusion that this model may be more efficient for the chronic dialysis patient [34].

Conclusion

Care of the pediatric patient with ESKD is multifaceted and requires management from an interdisciplinary team of which advanced practice providers have proven themselves to be a vital member. The APP is often considered the front-line healthcare provider, offering continuity of care and follow-up of complex medical issues. Nephrology practices that include APPs as part of their ESKD healthcare team often appreciate improved outcomes and satisfaction from patients, other dialysis team members, and caregivers secondary to the experiences and leadership that he or she provides. The APP can thrive in an environment that is supportive of his or her learning needs, with structured orientation that allows for customization and flexibility. APPs are capable of not only working with physicians and staff to provide the best evidence-based care, but are also capable of leading QI projects that will improve practices and standards of care at their institution as well as nationally.

References

1. Althouse LA, Stockman JA 3rd. Pediatric workforce: a look at pediatric nephrology data from the American Board of Pediatrics. J Pediatr. 2006;148(5):575–6.
2. Primack WA, et al. The US pediatric nephrology workforce: a report commissioned by the American Academy of Pediatrics. Am J Kidney Dis. 2015;66(1):33–9.
3. Dellabella, H. 50 years of the nurse practitioner profession. 2015 [1/3/19]; Available from: https://www.clinicaladvisor.com/web-exclusives/50-years-of-the-nurse-practitioner-profession/article/453044/
4. American Association of Nurse Practitioners. NP facts. 2018 August 20, 2018 [1/3/19]; Available from: https://storage.aanp.org/www/documents/research/npfacts.pdf
5. Pediatric nursing certification board. CPNP-PC vs PPCNP-BC: Make an Informed Choice With This Chart. 2019 Available from: https://www.pncb.org/compare-pnp-certification
6. American academy of nurse practitioners certification board. Certifications. 2019; Available from: https://www.aanpcert.org/certifications
7. American Nurses Credentialing Center. Our Certifications. 2019; Available from: https://www.nursingworld.org/our-certifications/
8. National Task Force on Quality Nurse Practitioner Education. Criteria for Evaluation of Nurse Practitioner Programs. 2012 [cited 4th ed]; Available from: https://www.aacnnursing.org/Portals/42/CCNE/PDF/evalcriteria2012.pdf
9. American Association of Colleges of Nursing. The essentials of doctoral education for advanced nursing practice. 2006; Available from: https://www.aacnnursing.org/Portals/42/Publications/DNPEssentials.pdf.
10. American Association of Nurse Practitioners. Scope of practice for nurse practitioners. 2015 [1/3/19]; Available from: https://storage.aanp.org/www/documents/advocacy/position-papers/scopeofpractice.pdf
11. Advisory Board. A guide to understanding state restrictions on NP practice 2019; Available from: https://www.advisory.com/research/medical-group-strategy-council/resources/2013/understanding-state-restrictions-on-np-practice
12. Institute of Medicine Committee on the Robert Wood Johnson Foundation Initiative on the Future

of Nursing, a.t.I.o.M., in *The Future of Nursing: Leading Change, Advancing Health*. 2011, National Academies Press (US) Copyright 2011 by the National Academy of Sciences. All rights reserved.: Washington (DC).
13. National Council of State Boards of Nursing. *APRN Consensus Model*. 2019 [10/15/18]; Available from: https://www.ncsbn.org/aprn-consensus.htm
14. American Nephrology Nurses Association. Position Statement: Advanced Practice in Nephrology Nursing. 1997 2017 [1/3/19]; Available from: https://www.annanurse.org/download/reference/health/position/advancedPractice.pdf
15. Physician Assistant History Society, PA Timeline. 2017.
16. American Academy of PAs. What is a PA?. 2019; Available from: https://www.aapa.org/what-is-a-pa/
17. American Academy of PAs. What is a PA? Frequently asked questions. 2018 [cited 2018]; Available from: https://www.aapa.org/wp-content/uploads/2018/06/Frequently_Asked_Questions_4.3_FINAL.pdf
18. American Academy of PAs. Frequenty Asked Questions: Optimal Team Practice 2018 [1/3/19]; Available from: https://www.aapa.org/wp-content/uploads/2018/01/Core-FAQ.pdf
19. Chand DH, et al. Dialysis in children and adolescents: the pediatric nephrology perspective. Am J Kidney Dis. 2017;69(2):278–86.
20. Chua AN, Warady BA. Care of the pediatric patient on chronic dialysis. Adv Chronic Kidney Dis. 2017;24(6):388–97.
21. Warady BA, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
22. Swartz SJ, et al. Exit site and tunnel infections in children on chronic peritoneal dialysis: findings from the Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative. Pediatr Nephrol. 2018;33(6):1029–35.
23. Centers for Medicare & Medicaid Services, Clarification of payment for ESRD-related services under the monthly capitation payment, Department of Health & Human Services, Editor. 2011.
24. Gerson AC, et al. Health-related quality of life of children with mild to moderate chronic kidney disease. Pediatrics. 2010;125(2):e349–57.
25. Tong A, et al. Experiences and perspectives of adolescents and young adults with advanced CKD. Am J Kidney Dis. 2013;61(3):375–84.
26. Taylor DM, et al. Limited health literacy in advanced kidney disease. Kidney Int. 2016;90(3):685–95.
27. Keim-Malpass J, Letzkus LC, Kennedy C. Parent/caregiver health literacy among children with special health care needs: a systematic review of the literature. BMC Pediatr. 2015;15:92.
28. Taylor DM, et al. A systematic review of the prevalence and associations of limited health literacy in CKD. Clin J Am Soc Nephrol. 2017;12(7):1070–84.
29. Cheng TL, Dreyer BP, Jenkins RR. Introduction: child health disparities and health literacy. Pediatrics. 2009;124(Suppl 3):S161–2.
30. Rak EC, et al. Caregiver word reading literacy and health outcomes among children treated in a pediatric nephrology practice. Clin Kidney J. 2016;9(3):510–5.
31. Gutman T, et al. Child and parental perspectives on communication and decision making in pediatric CKD: a focus group study. Am J Kidney Dis. 2018;72(4):547–59.
32. Hebert SA, et al. Special considerations in pediatric kidney transplantation. Adv Chronic Kidney Dis. 2017;24(6):398–404.
33. McClellan WM, Goldman RS. Continuous quality improvement in dialysis units: basic tools. Adv Ren Replace Ther. 2001;8(2):95–103.
34. Harwood L, et al. The advanced practice nurse-nephrologist care model: effect on patient outcomes and hemodialysis unit team satisfaction. Hemodial Int. 2004;8(3):273–82.

7 Quality Improvement Strategies and Outcomes in Pediatric Dialysis

Helen Currier, Pamela S. Heise, and Leyat Tal

Introduction

In 1999, when the Institute of Medicine (IOM) report from the USA revealed the high incidence of preventable medical errors, it shook not only the healthcare system but also the public's faith in the system [1, 2]. More recently, preventable medical errors are considered the third-leading cause of death in the USA [3]. The IOM defines high-quality care as care that is safe, effective, efficient, equitable, timely, and patient-centered [1]. Establishing a culture of transparency and safety allows for all members of the healthcare system to speak up if there is an area that is not meeting the quality standards. Once an area of improvement is identified and there is an acknowledgment of a gap between knowledge and clinical practice, only then can we deliver better quality of care to our patients.

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Clinical Practice Guidelines and Clinical Performance Measures

Quality metrics in chronic kidney disease (CKD) programs are driven by clinical practice guidelines (CPG) and clinical performance measures (CPM). "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Rather than dictating a *one-size-fits-all* approach to patient care, clinical practice guidelines offer an evaluation of the quality of the relevant scientific literature and an assessment of the likely benefits and harms of a particular treatment. This information enables healthcare providers to proceed accordingly, selecting the best care for a unique patient based on his or her preferences" [4]. CPMs provide a method to measure quality quantitatively through data collection and evaluation [5].

There are two well-established CPGs in dialysis: the Kidney Disease Outcomes Quality Initiative (KDOQI), which provides guidelines and commentaries produced by the National Kidney Foundation and published in the American Journal of Kidney Diseases (AJKD), and the Kidney Disease: Improving Global Outcomes (KDIGO), which is a self-managed charity incorporated in Belgium. In 1960, the International Society of Nephrology (ISN) Clinical Practice Guidelines Committee was

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established, to oversee the increasing number of guidelines being issued. The ISN is a nonprofit organization "dedicated to advancing worldwide kidney health [6]." ISN Practice Committee members do not develop guidelines, they evaluate, form recommendations, encourage development, and endorse guidelines; however, they support dissemination of KDIGO guidelines through the ISN journal, *Kidney International*, and contribute to the KDIGO advisory board [6].

Although the dialysis CPGs are widely based on adult research and evidence, pediatric recommendations have been established in most guidelines (Table 7.1). For example, KDOQI updated its guidelines to include a CPG for Nutrition in Children with chronic kidney disease (CKD), which addresses the nutritional needs of infants, children, and adolescents with CKD stages 2–5, end-stage kidney disease (ESKD) on dialysis, or a kidney transplant [7].

Outpatient chronic dialysis in the USA has moved from a *fee-for-service* to a *pay-per-performance* (also known as "value-based purchasing") system. These systems provide incentives that are tied to improved outcomes, so the need to provide and measure quality of care is critical in this industry. Although acute dialysis programs are currently not held to the same requirements, establishing measurable quality metrics is necessary to improving care across the spectrum of acute kidney injury (AKI) and associated acute therapies. It is not uncommon for pediatric nephrology practitioners to care for dialysis patients in both outpatient and acute settings. This can be challenging for a pediatric dialysis program with limited resources. Oftentimes, metrics for measuring and reporting meaningful care have been adopted from the adult dialysis population without being validated for pediatric-specific outcomes. "The pediatric ESRD patient is a member of a unique subpopulation of ESRD patients. The cause of ESRD in the pediatric patient differs markedly from the adult patient; treatment modalities in the pediatric ESRD patient differ substantially from the adult patient; and outcomes such as growth, development, and school attendance are also unique to the pediatric ESRD patient" [7]. According to the Agency for Healthcare Research and Quality (AHRQ), there are four distinguishing differences of child healthcare, often referred to as the "four Ds" [8, 9]:

Table 7.1 Dialysis clinical practice guidelines

KDOQI	KDIGO
Acute kidney injury (AKI)	Acute kidney injury (AKI)
Anemia	Anemia in CKD
Bone metabolism	Blood pressure in CKD
Cardiovascular disease	CKD evaluation and management
Chronic kidney disease, classification	CKD-mineral and bone disorder (CKD-MBD)[a] diabetes and CKD
Diabetes	Glomerulonephritis (GN)
Glomerulonephritis	Hepatitis C in CKD
Hemodialysis adequacy	Lipids in CKD
Hepatitis C	Living kidney donor
Nutrition in CKD	Transplant candidate
Peritoneal dialysis adequacy	Transplant recipient
Transplant	
Vascular access	

Developmental Status Change	Children pass through developmental stages quickly, and measurement approaches must be appropriate to each stage.
Differential Epidemiology	Children have fewer chronic physical ailments than adults, making it harder to reliably measure performance related to the care of chronic conditions among children.
Dependence	Children depend on adults for access to healthcare.
Demographic Patterns	Children are the most diverse section of our society (13), and many live in poverty and single-family homes.

The Children's Hospital Association (CHA) recognizes the need for identifying pediatric-specific measures. In March 2019, they released "Demonstrating Value in Pediatrics: A Measure Menu, Workbook and Guidance for Value-based Care, Payment and Reporting Programs." It is a resource to guide practitioners in the development of a quality-based program for pedi-

atric populations. The CHA added a fifth "D: Detecting Differences" to address the challenges healthcare measures encounter, trying to differentiate among levels of quality [10].

Oversight of Centers for Medicaid and Medicare (CMS) and State Regulations

In the USA, the Centers for Medicare & Medicaid Services (CMS) regulate end-stage renal disease (ESRD) facilities. All ESRD facilities must adhere to the Conditions for Coverage (CfC) for ESRD facilities. These CfCs establish minimum standards that dialysis facilities must meet to be certified. The rule (or law) focuses on the patients and the results of care provided to the patients, establishes performance expectations for facilities, encourages patients to participate in their plan of care and treatment, and preserves strong process measures when necessary to promote meaningful patient safety, well-being, and continuous quality improvement (QI) [11]. The CfCs for ESRD facilities outline minimum health and safety standard requirements.

Quality Assessment and Performance Improvement Program

The updated 2008 CfC for ESRD mandates that all dialysis facilities be required to "develop, implement, maintain, and evaluate as effective, a data-driven, interdisciplinary Quality Assessment and Performance Improvement (QAPI) program [11]." Led by the medical director, the QAPI committee must also, at a minimum, include a physician (may be the medical director), a registered nurse, a masters-prepared social worker, and a registered dietitian. According to the "five Ds," children's healthcare has distinguishing differences from adult healthcare; therefore, the pediatric care team includes other disciplines such as advanced practice provider (i.e., pediatric nurse practitioner (PNP)), creative arts therapist(s) (i.e., music therapist), quality of life program coordinator, *pediatric* dietitian, child life specialist, school liaison, transplant coordinator, pharmacist, business manager, and/or quality manager. These individuals should also be reflected on the QAPI interdisciplinary team (IDT). For integrated pediatric and adult care facilities, team members may have cross-functional responsibilities between pediatrics and adults.

The goal of a chronic dialysis QAPI program is to develop methods to "measure, analyze and track quality indicators or other aspects of performance that the facility adopts that reflect processes of care and facility operations. These performance components must influence or relate to the desired outcomes or be the outcome themselves" [12]. Expected outcomes based on standards (e.g., Association for the Advancement of Medical Instrumentation (AAMI) for water quality and KDOQI for clinical outcomes) and CMS CPMs for the QAPI can be found in the CfC (effective October 14, 2008) V626 494.110 Condition: Quality Assessment and Performance Improvement and are summarized in the Measures Assessment Tool (MAT).

Networks

In 1978, the US Congress expanded the ESRD program to include the ESRD Network Program with the goal for quality oversight. Regulation requires this program to organize all Medicare-approved ESRD facilities into designated geographic areas referred to as Networks. The ESRD Network Organizations acts as the administrative governing body to the Network and liaison to the federal government. To help achieve coordinated delivery of ESRD services, representatives of hospitals and health facilities serving dialysis and transplant patients in each area of the country (USA) are linked with patients, physicians, nurses, social workers, dietitians, and technicians into Network Councils. There are 18 Network Organizations across the USA and territories (CMS). CMS expects the Networks to "develop a relationship with the dialysis professionals, providers, and patients and create a collaborative environment to improve patient care"

[9]. CMS contracts with the Networks to evaluate the needs of dialysis patients and ESRD facilities for the purpose of developing quality improvement activities (QIA). The QIAs are designed to increase kidney transplantation, increase the number of patients dialyzing at home, decrease bloodstream infections, decrease hospitalizations, address pain and depression, and increase the number of dialysis patients returning to work. Each Network determines which facility participates in each activity, based upon facility-specific data. Data collection for the pediatric population began in 2002, with an increased focus on developing QIAs for children.

In 2008, the *5-Diamond Patient Safety Program* was developed by the ESRD Networks, as an innovative training and recognition program, to assist dialysis providers in increasing awareness and building a culture of safety among patients and staff [13]. The program was designed to focus on specific areas in need of improvement and consistency. In 2019, the program was expanded to include pediatric-specific content for all modules. These are the modules with a quality and safety focus:

Patient safety principles	Missed treatments
Constant site cannulation	Patients-provider conflict (Grievances)
Emergency preparedness	Sharps safety
Hand hygiene	Slips, trips, and falls
Influenza vaccination	Vascular access monitoring
Medication reconciliation	COVID-19

The ESRD Quality Incentive Program of the USA

In 2014, the pediatric population was added to the scope of the ESRD Quality Incentive Program (QIP). QIP is the first value-based purchasing (VBP) program, where providers are paid based on the quality of care they provide to Medicare beneficiaries [14]. Performance on predetermined clinical performance measures is directly correlated to payment received. If facilities do not meet the specific standards, the ESRD QIP score will reduce Medicare payment up to two percent to that facility. The reduction applies to all services performed for one full year, known as the Payment Year (PY). Comparison of two periods determines this percentage:

1. The Comparison Period – This serves as the basis for evaluation. Data on the designated metrics is collected for 1 year.
2. The Performance Period – Data on the same metrics is collected the year following the Comparison Period and evaluated against the Comparison Period.

CMS uses a specific methodology to calculate a facility's Total Performance Score (TPS) (Fig. 7.1). Based on this algorithm, if the Performance Period does not exceed the Comparison Period or threshold established by CMS, facilities will experience a reduction in Medicare payment. TPSs are publicly reported online on the Dialysis Facility Compare website, and facilities are required to post a Performance Score Certificate, which includes the TPS and specific outcome of each quality measure.

The QIP program is ever evolving. For Payment Year (PY) 2019, the ESRD QIP, included eight clinical performance measures and six reporting measures to assess dialysis facility performance for care provided during the calendar year (CY) 2017 (with one exception, as noted in Table 7.2). Facility performance on these measures impacted payments made in CY 2019. Exclusions exist for some measures at the facility and patient level. Facilities with fewer than 11 eligible patients are excluded from most measures, and several measures exclude patients younger than 18 years. CMS may adjust, modify, or create measures annually for the QIP based on status of current measures. This program has been modeled through 2022.

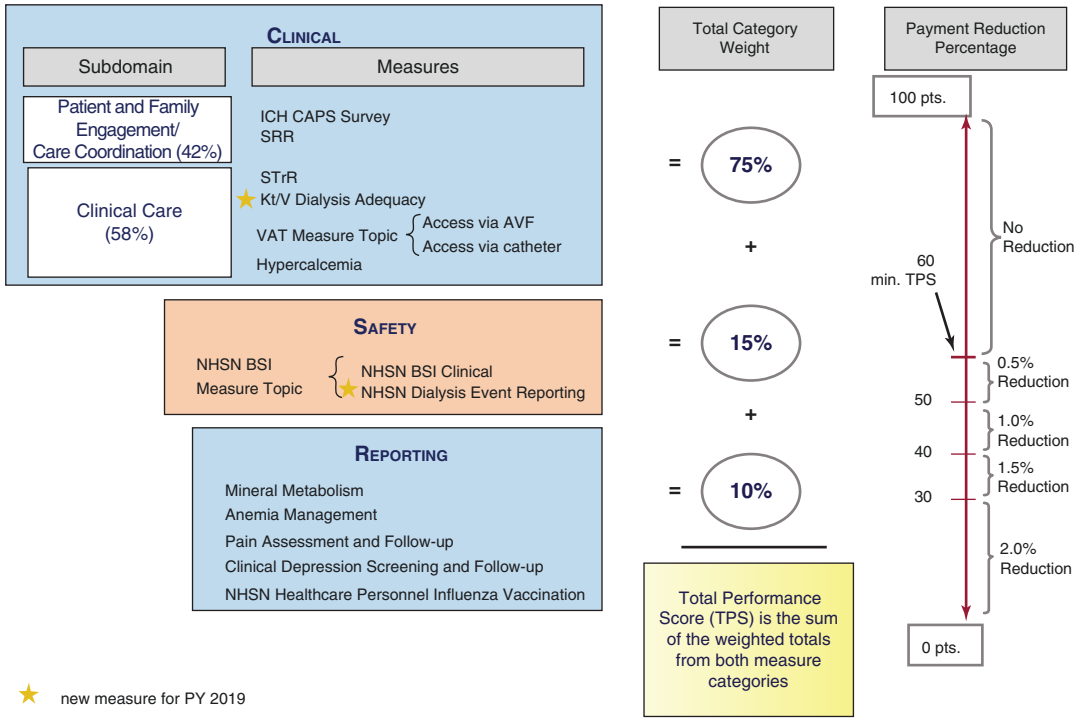

Fig. 7.1 Total performance score methodology

Table 7.2 QIP PY2019 clinical, safety, and reporting measures

Clinical measures	
[a]ICH CAHPs surveyPatient and family engagement/care coordination	Percentage of patient responses to multiple survey measures to assess their dialysis providers, the quality of dialysis care they receive, and information sharing about their disease – survey is administered twice a year
Standardized readmission ratio (SRR)	Ratio of the number of observed unplanned 30-day hospital readmissions to the number of expected unplanned 30-day hospital readmissions
Kt/V dialysis adequacy (comprehensive)	Percentage of all patient months for patients whose delivered dose of dialysis (either hemodialysis or peritoneal dialysis) met the specified threshold
[a]Vascular access type (VAT) measure topic (2 measures)	Fistula: percentage of patient-months on hemodialysis during the last hemodialysis treatment of the month using an autogenous arteriovenous (AV) fistula with 2 needles Catheter: percentage of patient-months for patients on hemodialysis during the last hemodialysis treatment of the month with a catheter continuously for 90 days or longer prior to the last hemodialysis session
[a]Hypercalcemia	Proportion of all adult patient-months with 3-month rolling average of total uncorrected serum or plasma calcium greater than 10.2 mg/dL
Safety measures	
NHSN bloodstream infection in hemodialysis patients	Standardized infection ratio (SIR) among patients receiving hemodialysis at outpatient hemodialysis centers
NHSN Dialysis Event reporting	Number of months for which facility reports NHSN Dialysis Event data

(continued)

Table 7.2 (continued)

Reporting measures	
Mineral metabolism	Number of months for which facility reports serum or plasma phosphorus values for each Medicare patient
Pain assessment and follow-up	Facility reports in CROWNWeb 1 of 6 conditions for each qualifying patient once before September 1, 2017, and once before March 1, 2018
Anemia management	Number of months for which facility reports ESA dosage (as applicable) and hemoglobin/hematocrit for each Medicare patient at least once per month during the performance period
Clinical depression screening and follow-up	Facility reports in CROWNWeb 1 of 6 conditions for each qualifying patient once before March 1, 2018
NHSN healthcare personnel influenza vaccination reporting measure	Facility submits Healthcare Personnel Influenza Vaccination Summary Report to NHSN in accordance with specifications of the Healthcare Personnel Safety Component Protocol by May 15, 2017 (Note: this measure doesn't measure facility performance during 2017, but rather the "flu season" of October 1, 2016, to March 31, 2017)

[a]Pediatric population exempt from PY2019

Consolidated Renal Operations in a Web-Enabled Network (CROWNWeb)

CROWNWeb is a secure, web-based system that captures clinical and administrative data from Medicare-certified dialysis facilities across the USA and its territories. The CROWNWeb system provides a single, central database, used by all ESRD Facilities, ESRD Networks, and CMS, as a repository for 100% of clinical data to support various program goals, such as the National Quality Incentive Program, Public Reporting, and 5 Star. CROWNWeb data is important in the calculation of facility-specific quality scores and percentage payment reductions to implement the ESRD QIP.

The National Renal Administrator's Association (NRAA) offers the use of the NRAA Health Information Exchange (HIE) to any NRAA member or nonmember organization for electronic data submission of CROWNWeb quality data. To use the HIE, an organization must contract with the NRAA. Submitting patient and clinical data to CROWNWeb through the NRAA HIE is cost-effective and efficient. Without a HIE interface to an electronic medical record, one must enter CROWNWeb data manually.

National Healthcare Safety Network (NHSN)

The NHSN is the Centers for Disease Control and Prevention (CDC)'s healthcare-associated infection tracking system. Tracking outpatient dialysis infections in QAPI is essential as infectious complications are a leading cause for death in pediatric dialysis patients [15]. In addition, NHSN reporting and infection rates are new QIP measures in PY2019 and directly affects Medicare reimbursement. The events reported to the dialysis division of NHSN include intravenous antibiotic starts, positive blood cultures, pus redness, or increased swelling at the vascular access site.

Dialysis Facility Report (DFR)

The DFR is created by CMS to provide dialysis facilities, consumers, the public, CMS and its affiliates with valuable information on patient characteristics, treatment patterns, hospitalization, mortality, and transplantation patterns in Medicare certified dialysis facilities. The DFR is provided as a resource for characterizing selected aspects of clinical experience at a facility relative

to other caregivers in a state, ESRD Network, and across the USA. Since these data can be useful in QI and assurance activities, each state's surveying agency may utilize the DFR, as a resource during the survey and certification process.

Dialysis Facility Compare

Dialysis Facility Compare (DFC) is a rating system sponsored by Medicare and provides information for patients/families on more than 7000 dialysis facilities. The rating is based on data that comes from four key sources: Medicare claims, data dialysis centers report to Medicare (CROWNWeb), data dialysis centers report to the CDC via NHSN, and an In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems Survey (ICH CAHPS) – a survey of patients' experiences. The program rates facilities' CPMs and awards up to five stars (children are currently exempt from the five-star program) for quality measures.

Please see the website for more details: https://www.medicare.gov/dialysisfacilitycompare/#data/about-data

Developing a Quality Assessment Performance Improvement (QAPI) Program

The goal of the QAPI program is to ensure ongoing quality assessment and performance improvement of quality metrics. Selection of quality and compliance metrics should include process and outcome measures based on published metrics and/or internally identified areas of risk or outcomes. Metrics should reflect the measures that are reported in QIP; clinical goals can be determined by using guidance from KDOQI and KDIGO, evidence-based practices, national averages, and/or benchmarking. It is the job of the QAPI team to identify and trend these quality metrics. As outliers are identified, a *root cause analysis* (RCA) can help identify the problem, identify potential barriers, and create a plan for improvement. A RCA is a tool used to analyze near misses and adverse events using a systematic process [16]. Successful RCAs include the interdisciplinary team and focus on uncovering problems without focusing on individual mistakes.

In order to monitor metrics, it is helpful to create a dashboard or heat map. Table 7.3 includes an example of quality and compliance indicators and facility developed goals. The affiliated ESRD Network and National Renal Administrator Association both can service as a resource in tool development. The ESRD Network of Texas posted a QAPI guide and QAPI dashboard for both hemodialysis (HD) and peritoneal dialysis (PD) programs that is available for download from their website https://www.esrdnetwork.org/professionals/quality-improvement/qapi-tools-and-resources.

Electronic medical records (EMR) provide an easy method to capture data. If resources are available, reports can be generated from the EMR to provide data for QAPI metrics.

Challenges for the Small Pediatric Program

Developing a QAPI program presents unique challenges to the small pediatric facility. Smaller programs have fewer staff and often rely on part-time nurses, registered dieticians, and social workers to fill many different roles. The pediatric nurse is likely to have responsibility across the different modalities (i.e., HD, PD, transplant) and CKD care. Data entry and retrieval for programs without EMR require manual retrieval of data points. It is still recommended that a dashboard be used; however, it may require ingenuity to develop tools meeting CMS requirements for quality initiatives in all dialysis programs.

Quality Improvement Design

The first step in quality improvement (QI) is assembling a team. As care is not implemented in silos, it is also unreasonable to think that one

Table 7.3 Example of sections that may be included in a QAPI dashboard (heat map)

Hospitalizations				
	Facility goal	QIP threshold – benchmark	January	February
# HD Pts hospitalized				
# HD hospitalization days (QIP is expressed as a ratio)		1.248–0.670		
# PD Pts hospitalized				
# PD hospitalization days (QIP is expressed as a ratio)		1.248–0.670		
# HHD Pts hospitalized				
# HHD hospitalization days (QIP is expressed as a ratio)				
Total # Pts hospitalized				
Total # hospitalization days				
# Pt readmitted <30 days (QIP is expressed as a ratio)		1.268–0.629		
# unstable patients				
Adequacy				
HD Kt/V monthly	Facility goal	QIP threshold – benchmark	January	February
HD URR overall (% of Pts who treat 3×/week w/ values ≥65)	95%			
HD Kt/V single pool (% of Pts who treat 3×/week w/values ≥1.2)	100%	93.1%–99.15%		
HD Kt/V standardized (>3 day Wk Tx)(% of Pts who treat > 3×/week w/values ≥2.2)	100%			
HHD Kt/V (% of pt ≥2.0)	100%			
Number of HD/HHD patients with missing Kt/V value for month	0			
PD Kt/V monthly	Facility goal	QIP threshold – benchmark	January	February
0–17 age group PD Kt/V monthly (% of Pts with values ≥1.8)	100%	93.1%–99.15%		
18 & up age group PD Kt/V monthly (% of Pts with values ≥1.7)	100%	93.1%–99.15%		
Number of PD patients without a Kt/V value for month	0			
Home Kt/V quarterly	Facility goal	QIP threshold – benchmark	January	February
0–17 age group PD Kt/V quarterly	100%	93.1%–99.15%		
18 & up age group PD Kt/V quarterly	100%	93.1%–99.15%		
Anemia				
	Facility goal	CMS goal	January	February
HD anemia overall (Hgb 10–12 g/dL)	75%			
HD anemia >90 days (Hgb 10–12 g/dL)	75%			
HD anemia overall (Hgb <10 g/dL)	15%			
PD anemia overall (Hgb 10–12 g/dL)	75%			
PD anemia >90 days (Hgb 10–12 g/dL)	75%			
PD anemia (Hgb <10 g/dL)	15%			
% HHD anemia overall (10–12 g/dL)	75%			

Table 7.3 (continued)

HD Tsat overall	70%			
PD Tsat overall	70%			
HHD Tsat overall	70%			
HD ferritin ≥100	70%			
Blood transfusions	0			
Mineral bone disease				
Albumin overall	Facility goal	CMS goal	January	February
HD albumin (% patients w/values over ≥3.8)	80%			
PD albumin (% patients w/values over ≥3.6)	75%			
HHD albumin (% patients w/values over ≥3.8)	80%			
Phos, Ca, K+, fluid overall	Facility goal	QIP threshold – benchmark	January	February
Phosphorous – total % in target	55%			
% HD Phos	55%			
% PD Phos	55%			
% HHD Phos	55%			
Calcium HD (% patients with values 8.4–10.2)	75%			
Calcium PD (% patients with values 8.4–10.2)	75%			
Calcium HHD (% patients with values 8.4–10.2)	75%			
Hypercalcemia 18 + (% patients with 3 month rolling average >10.2) (all dialysis pt)		1.77%–0%		
HD potassium (% patients with values 3.5–6.5)	95%			
PD potassium (% patients with values 3.5–6.5)	95%			
HHD potassium (% patients with values 3.5–6.5)	95%			
Interdialytic fluid gain (pre-HD <5% target Wt)	80%			
% of 3-day Wk Pts with average UFR <13 ml/kg/hr	100%			
% of 4-day Wk Pts with average UFR <13 ml/kg/hr				
HD iPTH overall	Facility goal	CMS goal	January	February
% HD iPTH ≤100	<30%			
% HD iPTH 100–300	>50%			
% HD iPTH >500	<20%			
PD iPTH overall	Facility goal	CMS goal	January	February
% PD iPTH ≤100	<30%			
% PD iPTH 100–300	>=50%			
% PD iPTH >500	<20%			
HHD iPTH overall	Facility goal	CMS goal	January	February
% HHD iPTH ≤100	<30%			
% HHD iPTH 100–300	>50%			
% HHD iPTH >500	<20%			
Vascular access				
Vascular access	Facility goal	QIP threshold – benchmark	January	February
AVF prevalence total HD/HHD census	66%			
AVF prevalence >20 kg				

(continued)

Table 7.3 (continued)

AVF prevalence of eligible patients >20 kg, not transitioning to PD, appropriate vessels, no transplant in the next year, developmentally appropriate	66%			
AVG prevalence total HD/HHD census				
Catheter prevalence >90 days		18.57%–5.07%		
AVF prevalence in HD Pts >18 yrs		52.52%–76.16%		
Cath prevalence in HD Pts. >18 yrs for >90 days		18.57%–5.07%		
# Chronic HD catheter inserted				
# Chronic HD catheter reinserted				
# AVF created				
# Chronic PD catheter inserted				
# Chronic PD catheter reinserted				
Infections				
Infections	Facility goal	NHSN/SCOPE goals	January	February
# Total vascular access infection	0	0		
# CLABSI	0	0		
# Exit-site/tunnel infections (HD)	0	0		
NHSN Dialysis Event Report CLABSI per 100 patient months	1.46	1.46		
# Peritonitis infections	0	0		
# Tunnel infections (PD)	0	0		
# Exit-site infections (PD)	0	0		
Peritonitis rate-facility-data-rolling 12-month cumulative annualized (infections/patient year)	0.32			
Exit-site infection rate-facility-data-rolling 12-month cumulative annualized	0.11			
Immunizations				
	Facility goal	CMS goal	January	February
% TB, quan, or X-ray	100%	100%		
% Hep B series (% eligible patients)	100%	100%		
% Hep B immune (exclude nonresponders)	100%	100%		
% Influenza (% eligible patients)	100%	100%		
% Pneumococcal 23 (% eligible patients)	100%	100%		
Infection control observations				
		Facility goal	CMS goal	January	February
Hand hygiene bundle compliance		95%			
SCOPE central line bundle observation compliance		90%			
Transplant				
	Facility goal	CMS goal	January	February
# ESRD Pts on transplant waitlist				
% of HD Pts on waitlist	50%	8.12%–33.90%		
% of PD Pts on waitlist	50%	8.12%–33.90%		
Total % of ESRD Pts on waitlist	50%	8.12%–33.90%		

Table 7.3 (continued)

Education				
	Facility goal	CMS goal	January	February
Patient education	100%	100%		
Emergency preparedness	100%	100%		
Depression screening				
	Facility goal	CMS goal	January	February
Total eligible patients due (>12 yrs old)				
Total patients negative screen				
Total patient positive screen				
% completion of eligible patients to date	100%			
Events summary				
	Facility goal	CMS goal	January	February
Environment				
Fall				
ID consent				
Lab specimen/test				
Line/tube				
Medication/fluid event				
Safety/security/conduct				
Skin/tissue				
Vascular access device				
Total # incidents				
Plan of care compliance				
	Facility goal	CMS goal	January	February
Initial – # due				
Initial – # completed				
90 days – # due				
90 days – # completed				
Annual – # due				
Annual – # completed				
Change of modality – # due				
Change of modality – # completed				
Unstable pt # due				
Unstable pt # completed				
AKI # due				
AKI completed				
% POC completion	100%			
Biomed summary				
	Facility goal	CMS goal	January	February
Total number of HD machines (includes chronic & acute)				
Number of machines scheduled for PM				
PM percentage completed				
Number of machine breakdowns				
Breakdown percentage				
Number of machines with multiple breakdowns				
Number of machines out >72 hours				
AAMI water analysis	100%			

person can implement QI changes effectively on their own. Successful QI teams have a diverse group of members with different perspectives on patient care and the involved processes for care delivery. Depending on the metric, members can include hospital administrators, clinical and business managers, pharmacists, nurses, mental health professionals, technicians, physicians, patients, caregivers, and executive sponsor(s). Executive sponsors help the team overcome any institutional barriers [17]. According to the Institute for Healthcare Improvement (IHI), in order to achieve success, a QI team should have the following members:

1. Clinical leader – This member understands the implications of change to other parts of the system and has the authority to test and implement changes recommended by the team [18].
2. Technical expertise – This member understands the scope and depth of the QI problem and has the improvement method skills to guide the team. In a technical area, such as dialysis, it is even more critical to include subject matter experts (SMEs). In the subspecialty of pediatric nephrology, SME participation is essential.
3. Day-to-day leader – This member overseas the day-to-day tasks of the QI project.
4. Project (executive) sponsor – This member is a leader within the organization who can provide resources and help overcome barriers.

The different members (or stakeholders) will have varying roles and levels of engagement with the QI project. In order to better understand the different stakeholders in a project, a power versus interest grid can help guide the QI team leaders in selection of the appropriate stakeholders, i.e., which ones are needed for institutional buy-in and which ones are needed for identifying areas for process improvement [18, 19] Fig. 7.2. Stakeholders include both supportive of change and resistors, as tackling concerns earlier on will help identify additional barriers and subsequently make changes more successful.

This hypothetical clinical scenario will illustrate key concepts and tools used in QI.

Anemia Management in ESRD

Anemia management requires diligent monitoring of iron status and hematocrit to ensure that erythropoietin-stimulating agents (ESA) are used effectively and appropriately, with the goal to achieve desired hemoglobin and limit negative outcomes. Programmatic goals are set utilizing a combination of clinical practice guidelines (i.e., KDIGO) and aggregate patient data. In addition, available benchmarking and externally reported outcomes (i.e., regionally and/or nationally) can be helpful. In this scenario, the dialysis program reviewed prior achievement of goals and had met a benchmark goal of 65% of hemodialysis patients, whose hemoglobin was within a target range of 10–12 g/dL. Based on this achievement, the new benchmark goal for the current year was

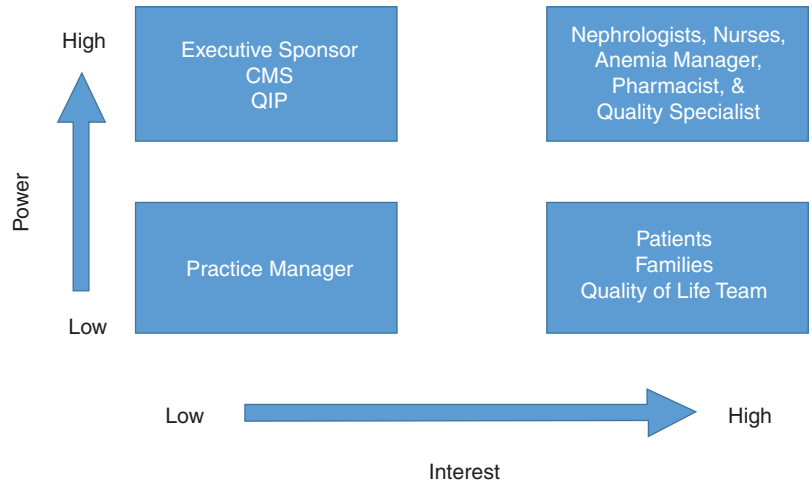

Fig. 7.2 Power versus interest grid, anemia stakeholder

increased to 75%. Three months into the new reporting year, the QAPI team however observes that they are below the new goal. A team is assembled for further assessment. This subgroup of the QAPI team included the pediatric nephrologists (inclusive of medical director), advanced practice providers, dialysis nurses (with a potential anemia manager champion), pharmacist, dialysis program quality, and/or regulatory specialists as available. The power-interest grid was used to clarify stakeholder engagement (Fig. 7.2).

What Is the Problem?

Once a team is in place, the next step is to assess and outline what are the possible factors that could be contributing to the quality metric not meeting its benchmark. It is important to spend time discussing every step of the process with all QI team members involved to be able to identify areas for improvement. There are many tools available that can be used to identify factors to guide improvement efforts [20, 21]. Below are some of the more common tools used:

- Cause and effect (fishbone or Ishikawa diagram) – This diagram helps the team organize possible causes contributing to the quality problem into categories that can then help guide the next steps in improvement. The fishbone diagram is constructed like the skeleton of a fish, where the problem is at the far right of the diagram (at the head). Each category is a diagonal line that is drawn off the central line (spine). The way the categories are labeled may vary based on the specific problem that is being examined (Fig. 7.3). A commonly seen example of a set of fishbone diagram categories would include the following: people/patients, process, environment, materials, methods, and equipment [21].
- Process mapping – In order to diagnose the problem, the team must first learn how the current process works. Process mapping is extremely helpful in providing a visual "bird's-eye view" of the entire process, especially when there are different pathways or steps within the process [19, 21].
- Pareto chart – This bar graph allows the team to organize the causes from the fish-

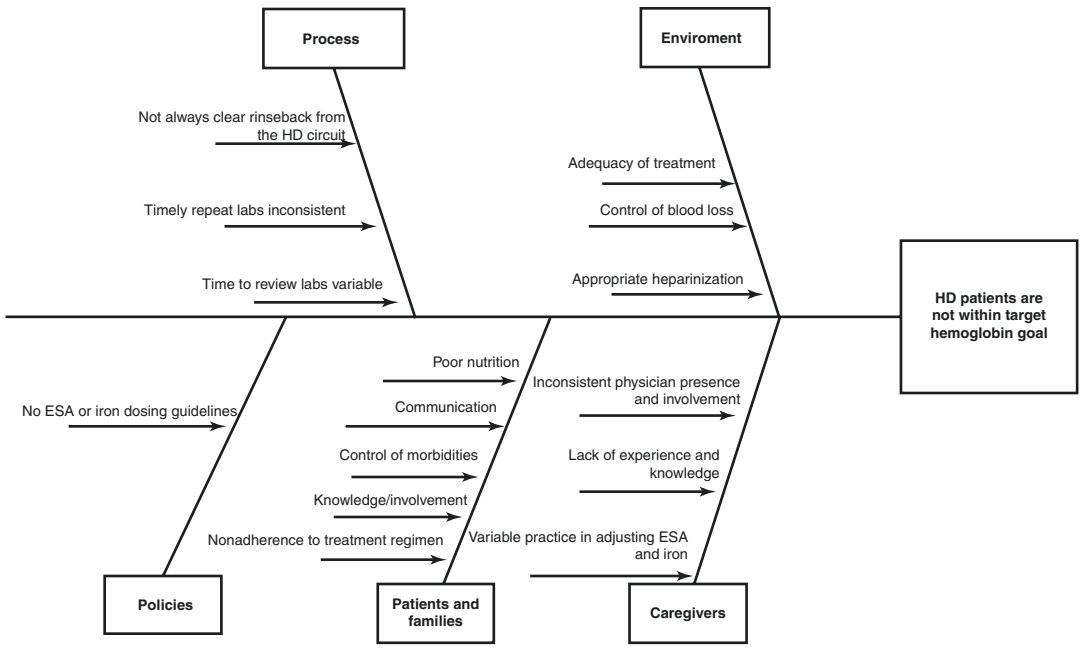

Fig. 7.3 Fishbone diagram

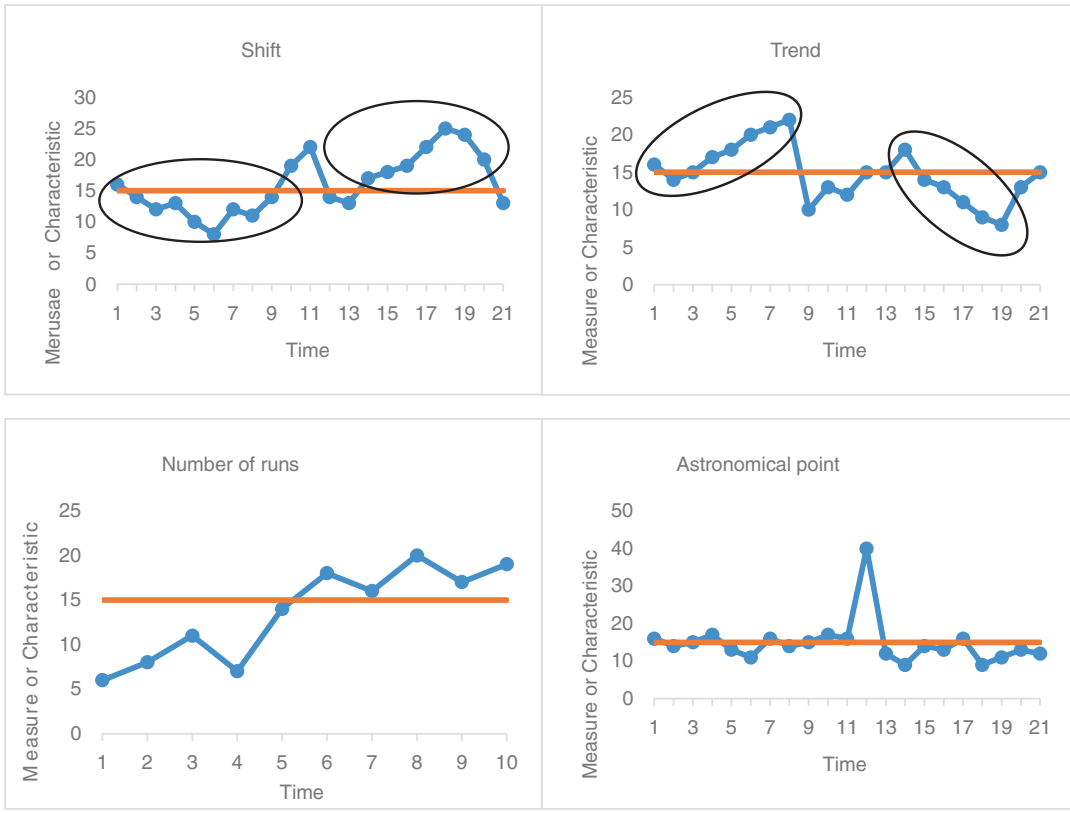

Fig. 7.4 A pareto chart

bone diagram to determine which causes would potentially provide the largest impact and is a manifestation of the 80–20 rule (80% of the problem is caused by 20% of the causes) [21]. The different causes are lined up on the x-axis, by decreasing order of frequency; some suggest at least 30 or more causes can be documented and prove helpful [20]. This visual depiction can help guide the improvement team on which of the causes to address first that will provide the largest impact (Fig. 7.4).

Quality Improvement Methodology

There are multiple QI methodologies that can be used when starting a project. Examples include Six Sigma, Lean, and the Model for Improvement [18]. Often the methodology chosen is determined by the team's experience. This example will focus on the Model for Improvement, which is based on the following three questions [21]:

1. What are we trying to accomplish?
2. How will we know that a change will lead to improvement?
3. What changes can we make that will result in improvement?

These questions advance improvement through the process of the Plan-Do-Study-Act (PDSA) cycle. Addressing these questions ensures that everyone on the team has an understanding of the situation, the plan for intervention, and the roles of all the members of the team [22].

What Are We Trying to Accomplish?

First, develop an aim statement that establishes the magnitude of change to be achieved. Writing a clear, concise, and results-oriented aim state-

ment ensures that everyone on the team understands the goals of the QI project, focuses efforts on activities that are meaningful to the project, and avoids team members investigating less relevant aspects of the problem [20]. Creating a S.M.A.R.T. aim can help avoid any ambiguity in the group [23]:

- S – Specific: What will the goal accomplish? How and why will it be accomplished? Who are the target population?
- M – Measurable: What will improvement look like? How will you measure whether or not the goal has been achieved?
- A – Achievable: Is this an attainable goal? Do you have the necessary knowledge, skills, abilities, and resources to accomplish the goal within the allotted timeframe?
- R – Relevant: Is it meaningful? Does it relate to broader program or organizational goals?
- T – Time-bound: What is the established completion date and is that date feasible?

For example, the aim statement for the anemia management QI project described above would be as follows: to improve the percentage of patients with ESRD on hemodialysis (HD) >90 days whose hemoglobin is within the defined target range 10–12 g/dL by 15% by May 2020.

How Will We Know a Change Is an Improvement?

In order to determine whether an intervention that has been implemented has actually led to an improvement, the team will need to have a balanced set of measurements [24]. These measures can be divided into outcome measures, process measures, and balancing measures [19, 20, 25] (Table 7.4).

Setting global measures can act as a reminder of the overall goal of the QI project and what the team is ultimately trying to achieve. Cycle measures can vary from PDSA cycle to PDSA cycle, depending on what was learned in the previous cycle and what new intervention is being tested [20].

Table 7.4 Measure definitions

Outcome measure	How does the system affect your patient?
Process measure	Is the system/intervention performing as planned?
Balancing measure	Are there unintended consequences?

What Changes Can We Make That Will Result in Improvement?

Once the problem and measures are defined, the next step is to plan for change and test for improvement. The Model for Improvement framework of Plan-Do-Study-Act (PDSA) cycle is a process where teams can test a change, gather data, and, based on the results, determine the next PDSA cycle, leading to a series of PDSA cycles until the final aim is reached (Fig. 7.5). Unlike research, testing change on a small scale allows the team to test multiple interventions without disrupting the system as a whole and makes it less likely to create resistance to the final change.

Plan

During the plan stage, the team needs to set the goals and objectives for the PDSA cycle. Determine what your outcome, process, and balancing measures are for this PDSA cycle and over what time period its success will be assessed. These measures may be different from the global measures. Describe in detail how the test will be carried out, and determine who is going to be responsible for each task, including the plan for data collection. Here, predictions on what is expected to happen when the test is implemented should be stated. Predictions are helpful to compare to actual practice as a way to examine why a change did or did not make the anticipated improvement [25]. The PDSA worksheet (Fig. 7.6), by the Institute for Healthcare Improvement, is a helpful guide on how to methodologically approach a PDSA cycle.

After extensive review to understand why dialysis dependent patients were not meeting

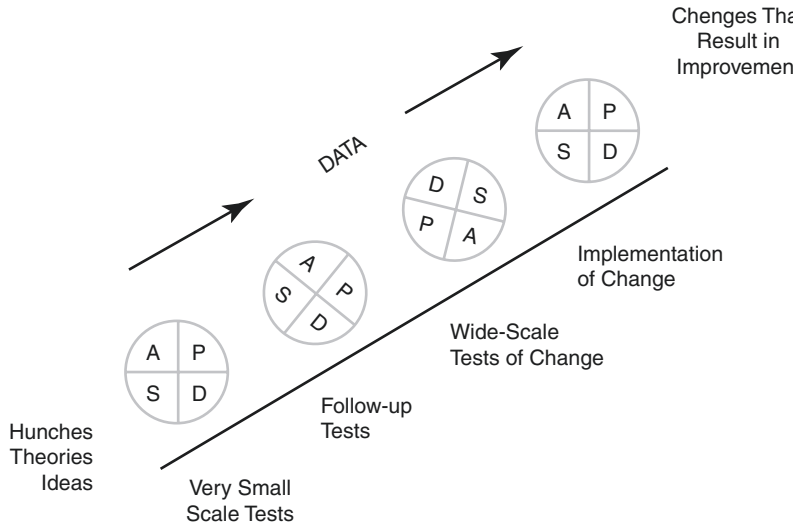

Fig. 7.5 Plan-Do-Study-Act (PDSA) cycle

the target hemoglobin goal, the team identified that provider variability as it relates to dose adjustment of ESA was one of the top areas for improvement. To minimize variability, an anemia management protocol was developed, and one dialysis nurse was designated as the anemia manager to adjust all ESA and iron dosing. The outcome measure is the number of HD patients whose Hgb was in target range between 10 and 12 g/dL. The process measure is the number of HD patients whose ESA and iron were adjusted by the anemia manager according to the anemia management protocol, and the balancing measure is whether or not ESA and/or iron dose adjustments were delayed if the anemia manager was not available.

Do

The "Do" stage is where the intervention that was described in the planning stage is implemented into the clinical setting [19, 20, 25]. Data are collected on the predefined measures.

Study

The study stage looks at how the results from the intervention compare with the initial predictions. Since multiple cycles can be done in a short amount of time, the data can be analyzed over time [19, 25]. A simple, yet powerful, way to determine whether or not the implementation is resulting in change is to use a run chart (also termed time series chart) [20]. A run chart is a visual display of data plotted over time. It illustrates whether a change has led to an improvement, and whether the change shows non-random variations or patterns [20, 25]. The use of a run chart in improvement work includes [20, 26]:

- Displaying data to make process performance visible
- Determine whether a change tested resulted in improvement
- Determine whether gains made through improvement are being sustained over time

To construct a run chart, the horizontal axis is usually a unit of time, and the vertical axis is the quality measure being studied. In order to interpret a run chart, the median will need to be calculated and drawn as the centerline. Using the following probability-based rules allows for objective analysis of the run chart to determine whether the improvement happened by chance or not [26].

- Shift
  - Shift is when six or more data points fall above or below the median line. If the data point falls on the median line, then it does not count.

Fig. 7.6 PDSA worksheet

Template: PDSA Worksheet

Objective:

1. Plan: Plan the test, including a plan for collecting data.

Questions and predictions:

-
-

Who, what, where, when:

Plan for collecting data

2. DO: Run the test on a small scale.

Describe what happened. What data did you collect? What observations did you make?

3. Study: Analyze the results and compare them to your predictions.

Summarize and reflect on what you leared:

4. Act: Based on what you leared from the test, make a plan for your next step.

Determine what modifications you should make – adapt, adopt, or abandon:

- Trend
  - If five or more data points are going in the same direction (all up or all down). If two data points are the same, only one is counted.
- Runs
  - A run is a series of data points on one side of the median. If the process is occurring in a random pattern, the data points should go above and below the median with regularity. If the process is occurring in a non-random pattern, then the run chart will show "too few" or "too many" runs. The way to determine how many runs there are is to count the number of times the line connecting the data points crosses the median and add one. To determine if there are "too few" or "too many" runs, one can reference the published charts based on a <5% probability of being due to chance [20, 27].
- Astronomical point
  - An astronomical point is one that is obviously different from the rest of the data points on the graph. Anyone looking at the chart would agree that the data point is blatantly different from the others, and work towards trying to figure out what occurred differently.

Act

In this stage, the team builds on the knowledge that was learned from the previous cycle in order to plan out the next PDSA cycle. Consider the following questions [20]:

- Do you keep the intervention? Is it ready to be implemented on a larger scale?
- Do you modify the intervention?
- Do you abandon the intervention?

Answering these questions will help the team determine the next PDSA cycle.

Sustainability

Once improvement is implemented, practices need to be instituted to maintain sustainability and ensure that the system does not regress back to its prior state. How does the system hold on to the improvement gained in the face of staff and organizational turnover [28]? Discussing the barriers that could affect an improvement's sustainability in the planning stages of the QI project will make it more likely to succeed. There are several sustainability models that can help identify potential causes that can increase or decrease the chances of the project's success [28]. Some approaches that can help make improvements more permanent within the organization include standardization (creating policies or best practices), documentation, establishing permanent measures to follow, training both current and new staff, and ensuring that the resources needed to move from small-scale testing to a change in the organization are available [21].

Conclusion

Quality assessment and improvement is meant to be dynamic. To define a problem or opportunity, collecting and evaluating aggregate data is essential. A collaborative QAPI program helps create a standard methodology to evaluate and improve care for children with ESRD. [29]. Key factors for success include prioritizing performance improvement goals, developing methods to measure and manage the whole system performance, committing to transparency, allowing change, and sharing outcomes and improvement with the facility, interdisciplinary care team, patients, and their families.

References

1. Institute of Medicine Committee on Quality of Health Care in America, in Crossing the Quality Chasm: A New Health System for the 21st Century. 2001. Washington, DC: National Academies Press.

2. Institute of Medicine, Crossing the quality chasm: a new health system for the 21st century. 2001. Washington, DC: National Academy Press.
3. Makary MA, Daniel M. Medical error-the third leading cause of death in the US. BMJ. 2016;353:i2139.
4. Institute of Medicine. Clinical practice guidelines we can trust. 2011 [cited 2020 29 Jan]; Available from: https://www.nap.edu/resource/13058/Clinical-Practice-Guidelines-2011-Report-Brief.pdf
5. Agency for Healthcare Research and Quality. Module 7. Measuring and benchmarking clinical performance. 2013; Available from: https://www.ahrq.gov/ncepcr/tools/pf-handbook/mod7.html
6. International Society of Nephrology. About ISN. 2020; Available from: https://www.theisn.org/about-isn/about-isn
7. Andreoli SP, et al. American Society of Pediatric Nephrology position paper on linking reimbursement to quality of care. J Am Soc Nephrol. 2005;16(8):2263–9.
8. Schoenbaum, S.C., & Sundwall, D.N., & United States. Agency for Health Care Policy and Research. Office of the Forum for Qualtiy and Effectiveness in Health Care,, Using clinical practice guidelines to evaluate quality of care. 1995, Rockville, MD: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Health Care Policty and Research.
9. Centers for medicare & Medicaid Services. ESRD network organizations. 2017; Available from: https://www.cms.gov/Medicare/End-Stage-Renal-Disease/ESRDNetworkOrganizations/index.html
10. Association, C.s.H., Demonstrating value in pediatrics a measure menu, workbook and guidance for value-based care, payment and reporting. 2019.
11. Medicare program; conditions for coverage for end-stage renal disease facilities-third party payment. 2016; Available from: https://www.federalregister.gov/documents/2016/12/14/2016-30016/medicare-program-conditions-for-coverage-for-end-stage-renal-disease-facilities-third-party-payment
12. The Renal Network. Quality Assessment and Performance Improvement (QAPI). 2011-2018; Available from: http://therenalnetwork.org/quality-improvement/qapi/
13. 5-Diamond patient safety program. Available from: https://www.5diamondpatientsafety.org/Home.aspx
14. Services, C.f.M.M. ESRD quality incentive program. Available from: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ESRDQIP
15. Warady BA, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
16. Quality, A.f.H.R.a., Rethinking root cause analysis.
17. Institute for Healthcare Improvement. Science of improvement: forming the team. 2020 [cited 2019 14 November]; Available from: http://www.ihi.org/resources/Pages/HowtoImprove/ScienceofImprovementFormingtheTeam.aspx
18. Silver SA, et al. How to begin a quality improvement project. Clin J Am Soc Nephrol. 2016;11(5):893–900.
19. Gaudreault-Tremblay MM, et al. Quality improvement in pediatric nephrology-a practical guide. Pediatr Nephrol. 2020;35(2):199–211.
20. Provost LP, Murray SK. The health care data guide: learning from data for improvement. San Francisco: Jossey-Bass; 2011.
21. Langley GJ, Moen RD, Nolan KM, Nolan TW, Norman CL, Provost LP. The improvement guide. 2nd ed. San Francisco: Jossey-Bass; 2009.
22. Weller J, Boyd M, Cumin D. Teams, tribes and patient safety: overcoming barriers to effective teamwork in healthcare. Postgrad Med J. 2014;90(1061):149–54.
23. Doran GT. There's a S.M.A.R.T. way to write management's goals and objectives. Manag Rev. 1981;70(11)
24. Institute for Healthcare Improvement. Science of improvement: establishing measures. 2020 [cited 2020 2 Feb]; Available from: http://www.ihi.org/resources/Pages/HowtoImprove/ScienceofImprovementEstablishingMeasures.aspx
25. McQuillan RF, et al. How to measure and interpret quality improvement data. Clin J Am Soc Nephrol. 2016;11(5):908–14.
26. Perla RJ, Provost LP, Murray SK. The run chart: a simple analytical tool for learning from variation in healthcare processes. BMJ Qual Saf. 2011;20(1):46–51.
27. Swed FS, Eisenhart C. Tables for testing randomness of grouping in a sequence of alternatives. Ann Math Stat. 1943;14(1):66–87.
28. Silver SA, et al. How to sustain change and support continuous quality improvement. Clin J Am Soc Nephrol. 2016;11(5):916–24.
29. Currier H, Miller DH. Clinical application: improving quality for children with kidney disease: Unique dimensions. In: Axley B, Robbins KC, editors. Applying continuous quality improvement in clinical practice. Pitman: American Nephrology Nurses' Association; 2009.

8 Antibiotic Stewardship in the Pediatric Dialysis Unit

Jason G. Newland and Alicia M. Neu

Introduction

Antimicrobials have been essential medications in improving patient care. These therapeutic agents have allowed us not only to treat common bacterial infections such as pneumonia but also to perform important surgical procedures (e.g., kidney transplants, Cesarean sections, etc.) safely and prevent life-threatening infections (e.g., *Pneumocystis jirovecii*). However, the use and especially the overuse of antibiotics result in the development of antibiotic resistance [1–3]. While antibiotics have only been in existence since the early 1900s, we are already observing bacteria (e.g., *Enterobacter* sp.) that can be resistant to all known and approved antibiotic agents.

Clinically, antibiotic-resistant bacterial infections result in worse patient outcomes. Patients infected with antibiotic-resistant bacterial infections have a greater risk of morbidity and mortality. The Centers for Disease Control and Prevention (CDC) estimates that approximately two million Americans are infected with antibiotic-resistant bacteria annually and up to 150,000 Americans die annually from an antibiotic-resistant infection [4, 5]. Data suggests antibiotic-resistant infections will kill approximately ten million people worldwide annually by 2050 if nothing is done to address this worldwide crisis. The potential economic impact will be an estimated $100 trillion US dollar loss [6].

Antibiotic-Resistant Bacterial Infections in Children

Multidrug-resistant bacterial infections do occur and have been increasing in children. In 1998, Herold and colleagues demonstrated that methicillin-resistant *Staphylococcus aureus* (MRSA) was rapidly increasing in children with no exposure to healthcare, the main risk factor for MRSA previously [7]. Furthermore, over the first decade of the twenty-first century, a dramatic increase in MRSA-related invasive infections (e.g., osteomyelitis, complicated pneumonia, complicated skin and soft tissue) was observed [8]. The rate of colonization of MRSA has been observed to be as high as 9% in children [9, 10]. In a group of adults on hemodialysis, 49% were colonized with *S. aureus*, of which 10% were MRSA [11]. Since data have demonstrated nasal colonization with *S. aureus* is a risk factor for peritonitis in peritoneal dialysis patients, this increase in resistance has changed the type of antibiotic prophylaxis required for procedures

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including placement of peritoneal and hemodialysis catheters and antibiotic treatments used when an infection occurs [12, 13].

The isolation of multidrug-resistant Gram-negative bacteria has also been increasing. Data from a series of publications from Latania Logan and colleagues has demonstrated that bacteria in the *Enterobacteriaceae* family have been on the rise. Bacteria such as *E. coli*, *Klebsiella* sp., and *Enterobacter* sp. are demonstrating a dramatic increase in resistance to important antibiotics such as ceftriaxone and carbapenems [14, 15]. Additionally, resistance among *Pseudomonas aeruginosa* and *Acinetobacter* species is also increasing in children [16, 17]. The most common healthcare location to observe these highly resistant Gram-negative bacteria is in the intensive care unit.

Common Pathogens in Pediatric Dialysis Patients

Among infections in pediatric peritoneal dialysis patients, the most common bacteria include Gram-positive (38%), Gram-negative (20%), and polymicrobial (10%) [18]. For pediatric hemodialysis, Gram-positive pathogens are identified in 67% of cases followed by Gram-negative (14%) and polymicrobial (19%). Coagulase-negative *Staphylococcus* is the most common infecting bacterial pathogen in these patients [19]. Data on the rate at which multidrug-resistant infections are identified in pediatric dialysis patients is a research gap, though it is likely not trivial based on overall trends in bacterial resistance.

Negative Consequences of Antibiotic Use

Antibiotic-associated adverse drug event (ADE) is another harm experienced by patients. Antibiotics are the most common drug affiliated with visits to the emergency department for ADEs. In children, almost 70,000 ED visits are made annually for antibiotic-associated ADEs with 40% occurring in children 2 years or younger. The most common antibiotics identified in these children are amoxicillin in children 2 years and younger and sulfamethoxazole-trimethoprim (SMX-TMP) in children 10–19 years of age [20]. The national rates of serious ADEs requiring hospitalization due to SMX-TMP that can be life-threatening have tripled [21].

In addition to ADEs, *Clostridioides difficile* infection (CDI) is another adverse consequence of antibiotic use. In children, CDI is increasing in both inpatient and outpatient settings. Children who develop CDI while hospitalized are at significant increased risk of mortality, a longer length of hospitalization, and increased hospital cost [22, 23]. In adults with end-stage renal disease, CDI is also associated with increased risk of death, longer hospital stays, and increased costs [24].

Finally, the use of antibiotics results in the change of intestinal flora. Pathogens that can become predominant in the intestine after the treatment with antibiotics are fungal species. Fungal peritonitis in children on peritoneal dialysis has significant consequences including death, removal of the catheter, and transitioning to hemodialysis. Cases of peritoneal dialysis-associated fungal peritonitis in children have been associated with the most costly hospitalizations [25]. Risk for fungal peritonitis in both children and adults has been linked to recent antibiotic therapy [26, 27]. The risk and potential consequences of fungal peritonitis are so high that the guidelines for the prevention and treatment of peritoneal dialysis-related peritonitis recommend the use of prophylactic nystatin or fluconazole when antibiotics are prescribed for a patient receiving peritoneal dialysis [28].

Antibiotic Use in Children

Antibiotics are commonly prescribed to children in all healthcare settings. Among hospitalized children, approximately 60% will receive at least one dose of an antibiotic during their hospital stay [29]. Recent data demonstrate that 15% of antibi-

otic use in hospitalized children is inappropriate. One of the most common reasons is prolonged surgical antibiotic prophylaxis and prescribing a more broad-spectrum antibiotic when culture and susceptibility data demonstrate that a narrower antibiotic is sufficient. Inpatient data regarding total antibiotic use and the appropriateness of this use in pediatric dialysis patients is limited [30].

In the outpatient setting, approximately 49 million antibiotic courses are administered to children annually. Almost 70% of these antibiotic prescriptions treat respiratory tract infections such as otitis media, group A streptococcus pharyngitis, and sinusitis. Approximately 50% receive a broad-spectrum antibiotic (e.g., azithromycin), when a narrow-spectrum agent (e.g., amoxicillin) is recommended [31]. Additional work by Kronman and colleagues suggests over one million excess antibiotic prescriptions are prescribed annually for children with a respiratory tract infection. While this data does not specifically assess how many patients on dialysis receive inappropriate antibiotics in the outpatient setting, it is likely this does occur [32].

Antibiotic Use in Dialysis Patients

Approximately one in three adults undergoing chronic hemodialysis at an outpatient facility (32.9 doses/100 patient-months) receives a parenteral antibiotic dose in a 12-month period. The most common antimicrobials administered are vancomycin (22.3 doses/100 patient-months) and cefazolin (5.1 doses/100 patient-months). Approximately 30% of these doses are inappropriate. The most common inappropriate reason was treatment of a presumed infection that did not meet pre-specified infection criteria, such as vancomycin for a single positive blood culture with coagulase-negative *Staphylococcus* [33].

As previously stated, data are limited on the amount of antibiotics used in pediatric dialysis patients and the rate of their inappropriate use. Likely, children requiring either peritoneal or hemodialysis receive frequent doses of antibiotics. These doses are presumably for suspected dialysis-related infections (i.e., peritonitis, bloodstream infections, etc.). Children do have more access-related infections than adults requiring the use of antibiotics [34–38]. However, since children frequently receive antibiotics for common respiratory tract infections, many pediatric dialysis patients may be receiving a significant amount of antibiotics that often are inappropriate. More data are needed to assess the extent of all antibiotic use in pediatric dialysis patients.

Antimicrobial Stewardship

Antimicrobial stewardship is defined as "optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on subsequent resistance" [39]. In addition, antimicrobial stewardship includes providing antimicrobials at the correct time. For example, when a peritoneal dialysis catheter is placed, a beta-lactam antibiotic should be administered up to 1 hour prior to incision [28].

The CDC has provided guidance on the core elements for establishing both inpatient and outpatient antimicrobial stewardship programs (ASPs) [40]. The key elements that pertain to performing antimicrobial stewardship in pediatric dialysis include leadership support, antimicrobial stewardship education for all personnel and caregivers, data tracking and reporting, and implementation of antimicrobial stewardship strategies. In the development of any program, support must be obtained from administrative leaders including chief executive officers/presidents of hospitals, nephrology division chief and/or dialysis physician lead, and nurse managers. All staff and caregivers should be educated on the importance of the appropriate use of antibiotics and the potential negative consequences (e.g., antibiotic resistance, adverse drug reactions, *C. difficile* infections) of continued inappropriate antibiotic use.

In order to improve antibiotic use, data demonstrating the excess and inappropriate use is

needed. The common antibiotic use measure recommended by the CDC to monitor inpatient antibiotic utilization is days of therapy (DOT) per 1000 patient days [41]. Days of therapy accounts for the number of antibiotics prescribed and their duration. For example, a patient prescribed two antibiotics for 5 days would have received 10 DOT. In the outpatient setting, the percentage of patients receiving an antibiotic for specific conditions (e.g., bronchitis, pharyngitis) has been used [42]. In the limited studies of antibiotic use in dialysis patients, antibiotic doses per 100 patient-months have been utilized [33]. These metrics are quantity-based and do not assess appropriateness. Currently, ASPs rarely follow appropriateness of antibiotic use due to the difficulty in obtaining the necessary data to make this determination and the disagreement among healthcare providers on what constitutes appropriate use. Further research is needed to develop the best methods to assess the appropriateness of antibiotics in all patient populations.

In addition to these process measures, patient-specific outcome measures should be followed. The rate of antibiotic resistance among common pathogens (e.g., *E. coli*, *S. aureus*) can be followed [43]. Other potential harms that may occur from excess antibiotic use include *C. difficile* infections and antibiotic-related adverse drug reactions [44, 45]. Finally, antimicrobial costs have been utilized to demonstrate the effectiveness of ASPs [46].

Antimicrobial Stewardship Strategies

Antimicrobial stewardship interventions must be implemented to improve the use of antibiotics in dialysis patients. Numerous strategies are recommended by the CDC and have been shown to be effective in improving antibiotics for hospitalized children and those cared for in the outpatient setting [47–50]. Studies have also been performed in adult patients in outpatient hemodialysis units that have been successful in improving antibiotic use [51, 52].

Inpatient

The core strategies recommended by the Infectious Diseases Society of America (IDSA) for inpatient antimicrobial stewardship include prospective audit with feedback and prior approval. Prospective audit with feedback (PAF) is the most common strategy utilized by pediatric ASPs and is performed by allowing the provider to order the antimicrobial, and then the ASP reviews the use of the antibiotic and then provides recommendations and feedback when needed [42]. A version of this strategy is termed "Handshake Stewardship" where the ASP team makes an active effort to meet in-person with each medical team to provide both recommendations on current antibiotic use and to be available for questions from the providers [48]. Key recommendations that often occur in PAF are discontinuing unnecessary antibiotics and deescalating from broad-spectrum antibiotics to more focused, narrow antibiotics. Prior approval with formulary restriction is the second core strategy which requires the clinician to gain approval from the ASP before the antibiotic is administered. Additionally, this strategy limits antibiotics of the same class being utilized at an institution. Both strategies have been effective, and most pediatric ASPs utilize a combination of these strategies for the different antimicrobials on the hospital formulary [53].

Evidenced-based guidelines have been an effective strategy in improving the use of antibiotics in children. After the publication of the IDSA and Pediatric Infectious Disease Society (PIDS) community-acquired pneumonia guideline, a significant improvement in the use of ampicillin for uncomplicated pneumonia across the USA has been observed [54, 55]. In pediatric peritoneal dialysis, the ISPD guideline provides the recommended empiric therapy for peritoneal dialysis-associated peritonitis to be cefepime plus or minus vancomycin depending on the local methicillin-resistant *S. aureus* rate. Additionally, the guideline provides recommended antimicrobial agents and durations of therapy based upon specific pathogens [28]. Hospitals and dialysis centers should develop facility-specific empiric

and definitive treatment recommendations based upon their local culture and susceptibility data.

Additional strategies for inpatient ASPs recommended by the IDSA guideline, the National Quality Foundation Antimicrobial Stewardship Playbook, and the American Academy of Pediatrics and PIDS ASP toolkit include required indications on all antibiotic orders, intravenous to oral conversion of highly bioavailable antibiotics, and elimination of duplicate therapy for Gram-negative and anaerobic infections [42, 56, 57]. Additionally, the antibiotic timeout is intended for the frontline clinician to stop and assess the reason and need for the antibiotic. This "timeout" is recommended to occur after a patient has received antibiotics for 48 hours. Finally, ASPs can ensure dosing strategies are correct, especially in patients with renal function abnormalities.

Outpatient

The most successful outpatient antimicrobial stewardship strategies have utilized behavioral economics. Gerber and colleagues utilized education with and without peer comparison to improve the appropriate use of narrow-spectrum antibiotics in the treatment of common bacterial acute respiratory tract infections (otitis media, sinusitis, group A streptococcus pharyngitis). The clinicians who were provided a report card illustrating their antibiotic use versus their peers had a significantly lower use of antibiotics than those who did not receive the report card. However, after the report card was discontinued, the improvement in antibiotic use returned to the same level of those providers who received education alone [47, 58].

Another behavioral economic technique, the nudge, has been utilized in improving antibiotic use for acute respiratory tract infections in adult primary care practices. In a group practice, providers were randomized to either have a poster with their picture, signature, and brief message on the appropriate use of antibiotics versus no posters. Providers who had a poster in their exam room decreased their inappropriate antibiotic percentage 20% more than those without a poster [59].

Finally, Meeker and colleagues performed a large outpatient antimicrobial stewardship study among outpatient providers comparing the following three strategies: accountable justification, suggestive alternative, and peer comparison. In this study, 47 clinics were randomized to receive 0, 1, 2, or all 3 of these strategies to improve their antibiotic prescribing in acute respiratory tract infections. Clinics randomized to accountable justification required written justification for why they were using an antibiotic when an antibiotic was not indicated. If a justification was not provided, the following was placed in the medical record, "no justification given." For suggestive alternative, a pop-up window appeared after the diagnosis was entered in the electronic health record stating antibiotics were not indicated and suggesting other treatment options such as over-the-counter medications. Finally, providers in clinics that were randomized to peer comparison received a monthly email describing their antibiotic use. The top 10% of lowest inappropriate antibiotic prescribers received an email stating they were a "Top Performer." The additional 90% received an email stating they were "Not a Top Performer." The results of this study demonstrated that accountable justification and peer comparison were the most effective strategies. However, after removing the behavioral intervention, inappropriate antibiotic prescribing increased, and only the peer comparison group remained significantly decreased versus controls [60].

Dialysis Specific

Antimicrobial stewardship programs have been effective in adult dialysis units. In a recent study, the impact of implementing ASPs in six adult dialysis centers was evaluated. The ASPs within these centers contained four key components (Fig. 8.1): leadership support, education, collaboration with the other sites through monthly calls, and the use of a positive deviance process. This process does the following: (1) describes the problem and goals, (2) identifies the personnel

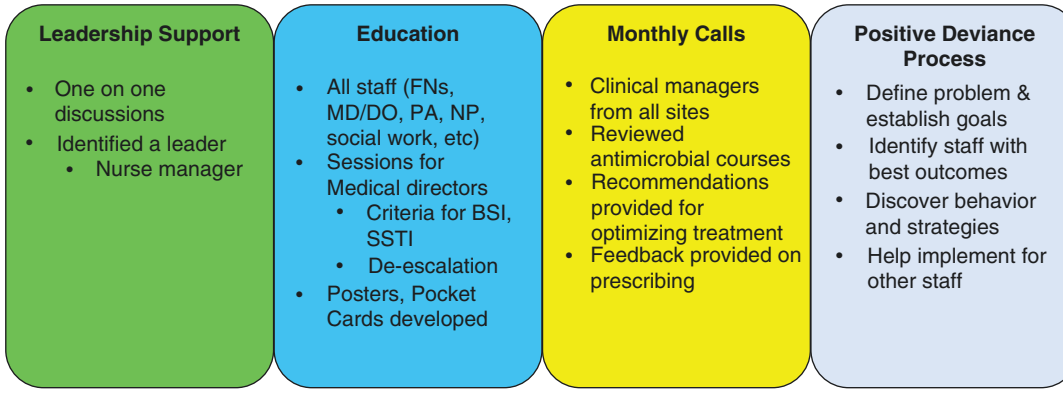

Fig. 8.1 Structure for performing antimicrobial stewardship in dialysis units

best achieving these goals (positive deviants), (3) understands the behaviors the positive deviants are performing, and (4) implements these behaviors across all staff and/or clinical sites. This study observed an average 6% monthly decline in antibiotic doses per 100 patient-months. Furthermore, a 55% overall reduction of antibiotic doses per 100 patient-months occurred from the beginning to the end of the intervention [51].

Diagnostics

Identifying the specific bacterial pathogen causing an infection in a patient receiving dialysis is paramount in performing effective antimicrobial stewardship. Data have demonstrated that the rate of culture-negative peritoneal dialysis-associated peritonitis can be as high as 30% [28]. Without pathogen identification and antibiotic susceptibilities, unnecessary broad-spectrum antibiotics with prolonged durations will occur. Therefore, specific strategies are essential to maximize the ability to identify bacterial pathogens in patients receiving hemodialysis and peritoneal dialysis.

Hemodialysis

In patients receiving hemodialysis, non-specific signs and symptoms could signify a catheter-related bloodstream infection (CRBSI). For this reason, if antibiotics are to be empirically started for non-specific symptoms, then blood cultures must be obtained. One study demonstrated that a majority of CRBSIs had already received antimicrobials prior to obtaining a blood culture, which can significantly decrease the positivity rate of these important cultures [61]. Blood cultures should still be obtained if a patient has already received antibiotics when suspicion for CRBSI is present.

After obtaining blood cultures, the most important factor in recovering bacteria in adults and children is the volume of blood collected [62]. Studies have shown, even in children, that blood culture positivity rate is significantly improved when the appropriate amount of blood is obtained [63]. For adults, 20–30 ml is recommended for each blood culture set. In children, the blood volume collected can be based on weight by kilogram or age of the child (Table 8.1). Due to the

Table 8.1 Recommended blood volumes to obtain for blood cultures based on weight

Weight of patient	Recommended volume of blood culture (ml)[a]	% of total blood volume[a]
≤1 kg	2	4
1.1–2 kg	4	4
2.1–12.7 kg	6	3
12.8–36.3 kg	20	2.5
>36.3 kg	40–60	1.8–2.7

[a]Assumes two sets of blood cultures are obtained
This table is adapted from Miller et al. [62]

logistical difficulty in using weight, some institutions have recommended that for every 1 year of life, 1 milliliter of blood should be obtained. The minimum blood volume obtained is 1 ml for preterm and term infants. Every institution that obtains blood cultures should have standard processes and recommendations on blood culture volumes and a method to evaluate the reliability of this collection.

Another important factor in maximizing the sensitivity of blood cultures is the number of sets obtained. When a blood culture is obtained, ideally the blood volume is placed into an aerobic and anaerobic bottle, one set. Additionally, two sets of blood cultures should be obtained from different sites (e.g., hemodialysis catheter hub, hemodialysis circuit, peripheral) [64, 65]. Not only does this help in better identifying pathogens, but it also allows clinicians to better determine if a bacterium identified from a blood culture is possibly a contaminant. Data have demonstrated that blood culture contamination is higher when obtained from catheter hubs versus peripheral cultures [62]. However, in patients on chronic dialysis, peripheral venipuncture is often avoided to preserve vessels for future access. For this reason, guidelines have recommended in hemodialysis patients with suspected CRBSI that two sets of blood cultures may be obtained from the hemodialysis circuit and the catheter hub. If dialysis is ongoing and obtaining blood cultures is not feasible or desirable from the catheter hub, then two sets of blood cultures collected from the hemodialysis circuit, separated in time (minutes), may be a practical approach, although no data are available assessing the sensitivity and specificity of this approach [64, 65].

Peritoneal Dialysis

As previously mentioned, culture-negative peritoneal cultures occur in almost one-third of peritoneal dialysis-associated peritonitis. As in hemodialysis, peritoneal cultures should be obtained prior to the start of antibiotics, and a large volume of peritoneal fluid is recommended. After obtaining up to 50 ml of peritoneal fluid, the fluid may either be centrifuged or 20–30 ml placed into three or four blood culture bottles. If the fluid is centrifuged, the sediment is resuspended with approximately 10 ml of saline, and then this fluid is plated on solid microbiology media that identify aerobic and anaerobic bacteria. Importantly, the fluid should be processed within 6 hours of being collected. In some instances, families in rural communities will need to collect the fluid on their own and then bring it to a facility that has the microbiology capabilities needed to perform the required cultures [28].

Infection Prevention

Essential to reducing the use of antibiotics is preventing infections. In hemodialysis and peritoneal dialysis, extra attention is needed to prevent healthcare-associated infections due to the increased risk of infection associated with the presence of a foreign body. The development of required procedures for both the placement and maintenance of hemodialysis and peritoneal catheters has led to significant reductions in bloodstream infections, exit site infections, and peritonitis [34, 66].

The CDC has developed a guideline on the prevention of catheter-related bloodstream infections with key areas to address (Table 8.2). While

Table 8.2 Key areas for the prevention of intravascular catheter infections

Education, staffing, and training	Antibiotic lock prophylaxis
Selection of catheter and site	Replacement of catheters
Hand hygiene and aseptic technique	Replacement of administration sets
Maximal sterile barrier precautions	Patient cleansing
Skin preparation	Systemic antibiotic prophylaxis
Catheter site dressing regimens	Performance improvement
Catheter securement devices	Anticoagulants
Antimicrobial and antiseptic impregnated catheters	Needleless intravascular catheter systems

this guideline addresses prevention of all catheter-related bloodstream infection, it lists important procedures specific to dialysis patients and hemodialysis catheters. For example, povidone iodine antiseptic ointment or bacitracin/gramicidin/polymyxin B ointment is recommended at the exit site after insertion of the catheter and after each dialysis session [67].

A comprehensive peritoneal dialysis infection prevention bundle specifically for children has been developed and shown to significantly reduce peritoneal dialysis-associated peritonitis by over 30%. Important to this prevention bundle was the development of a performance improvement collaborative, SCOPE (Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease), that provided the infrastructure for dialysis facilities to collaborate and learn together the best methods for implementation of the prevention bundle elements [34, 68]. Similar to hemodialysis catheters, prevention strategies are targeted to both the insertion of the peritoneal catheter and the ongoing maintenance of assuring that the catheter does not become infected. Three bundles were developed which included (1) peritoneal dialysis catheter insertion bundle, (2) peritoneal dialysis catheter/exit site follow-up care bundle, and (3) peritoneal dialysis patient and caregiver training bundle. The specific elements in each bundle can be found in Chap. 16.

Vaccination

Vaccination is a key component in efforts to reduce the use of antibiotics by preventing unnecessary infections. Children with chronic kidney disease are at increased risk of infection due to their impaired immune system. While concerns have existed about a child's response to vaccines while on dialysis, data suggest that their immune response to many vaccines is not significantly different from children with normal renal function. Children on dialysis should follow the recommended schedule published annually by the CDC's Advisory Committee on Immunization Practices (ACIP). Children receiving corticosteroids at a daily dose greater than 2 mg/kg or 20 mg for more than 14 days should not receive the measles, mumps, rubella, and varicella zoster vaccines, as they are comprised of attenuated live viruses.

In addition to the routine schedule, dialysis patients are at increased risk of severe disease due to influenza and *Streptococcus pneumoniae.* Annually, all children on dialysis should receive the inactivated influenza vaccine. For children less than 8 years of age who have not received the vaccine, two doses are required in the first year separated by 1 month. For *S. pneumoniae*, children should receive the ACIP-required 13-valent conjugate vaccine plus the 23-valent polysaccharide vaccine once they are 2 years of age or older. For older children or teenager who received the 7-valent conjugate, a single dose of the 13-valent vaccine should be given, followed 4 weeks later by the 23-valent vaccine. The 23-valent polysaccharide vaccine should be administered 5 years after the original dose [69].

Summary

The increasing incidence of antibiotic-resistant bacterial infections threatens the ability of clinicians to be able to provide important care such as dialysis to our pediatric patients. Children requiring dialysis are at increased risk of these types of infections. Antimicrobial stewardship is imperative in this population to aid in limiting the potential antibiotic-resistant infections as well as adverse drug events that can be associated with the use of antibiotics (e.g., CDI). Numerous strategies have been effective in improving antibiotic use in both the inpatient and outpatient setting including prospective audit with feedback and peer comparison. Furthermore, the most effective antimicrobial stewardship relies on diagnosing the infection by obtaining the correct cultures, with the correct blood or peritoneal fluid volumes prior to the use of antibiotics. Finally, the best way to decrease antimicrobial use and perform the best stewardship is to prevent infections through the use of evidenced-based care bundles and vaccination.

References

1. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. Emerg Infect Dis. 2004;10(3):514–7.
2. Megged O. Extended-spectrum beta-lactamase-producing bacteria causing community-acquired urinary tract infections in children. Pediatr Nephrol. 2014;29(9):1583–7.
3. Donskey CJ. Antibiotic regimens and intestinal colonization with antibiotic-resistant gram-negative bacilli. Clin Infect Dis. 2006;43 Suppl 2:S62–9.
4. Burnham JP, Olsen MA, Kollef MH. Re-estimating annual deaths due to multidrug-resistant organism infections. Infect Control Hosp Epidemiol. 2019;40(1):112–3.
5. CDC. Antibiotic resistance threats in the United States, 2013, Center for Disease Control and Prevention, Editor. 2013, U.S. Department of Health and Human Services: Atlanta, GA.
6. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations 2014 [cited 2018 April 15]; Available from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf. .
7. Herold BC, et al. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA. 1998;279(8):593–8.
8. Herigon JC, et al. Antibiotic management of Staphylococcus aureus infections in US children's hospitals, 1999–2008. Pediatrics. 2010;125(6):e1294–300.
9. Creech CB 2nd, et al. Increasing rates of nasal carriage of methicillin-resistant Staphylococcus aureus in healthy children. Pediatr Infect Dis J. 2005;24(7):617–21.
10. Fritz SA, et al. Prevalence of and risk factors for community-acquired methicillin-resistant and methicillin-sensitive staphylococcus aureus colonization in children seen in a practice-based research network. Pediatrics. 2008;121(6):1090–8.
11. Price A, et al. Methicillin-resistant Staphylococcus aureus and methicillin-susceptible Staphylococcus aureus screening in a cohort of haemodialysis patients: carriage, demographics and outcomes. J Hosp Infect. 2015;90(1):22–7.
12. Blowey DL, Warady BA, McFarland KS. The treatment of Staphylococcus aureus nasal carriage in pediatric peritoneal dialysis patients. Adv Perit Dial. 1994;10:297–9.
13. Szeto CC, et al. ISPD catheter-related infection recommendations: 2017 update. Perit Dial Int. 2017;37(2):141–54.
14. Logan LK, et al. Extended-spectrum beta-lactamase-producing and third-generation cephalosporin-resistant enterobacteriaceae in children: trends in the United States, 1999–2011. J Pediatric Infect Dis Soc. 2014;3(4):320–8.
15. Logan LK, et al. Carbapenem-resistant enterobacteriaceae in children, United States, 1999–2012. Emerg Infect Dis. 2015;21(11):2014–21.
16. Logan LK, et al. Multidrug- and carbapenem-resistant Pseudomonas aeruginosa in children, United States, 1999–2012. J Pediatric Infect Dis Soc. 2017;6(4):352–9.
17. Logan LK, et al. Acinetobacter baumannii resistance trends in children in the United States, 1999–2012. J Pediatric Infect Dis Soc. 2019;8(2):136–42.
18. Sethna CB, et al. Risk factors for and outcomes of catheter-associated peritonitis in children: the SCOPE collaborative. Clin J Am Soc Nephrol. 2016;11(9):1590–6.
19. Onder AM, et al. Predictors and outcome of catheter-related bacteremia in children on chronic hemodialysis. Pediatr Nephrol. 2006;21(10):1452–8.
20. Lovegrove MC, et al. US emergency department visits for adverse drug events from antibiotics in children, 2011–2015. J Pediatric Infect Dis Soc. 2019;8(5):384–91.
21. Goldman JL, et al. Trends in adverse reactions to trimethoprim-sulfamethoxazole. Pediatrics. 2013;131(1):e103–8.
22. Kim J, et al. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001–2006. Pediatrics. 2008;122(6):1266–70.
23. Sammons JS, et al. Clostridium difficile infection is associated with increased risk of death and prolonged hospitalization in children. Clin Infect Dis. 2013;57(1):1–8.
24. Pant C, et al. Clostridium difficile infection is associated with poor outcomes in end-stage renal disease. J Investig Med. 2012;60(2):529–32.
25. Redpath Mahon AC, et al. Factors associated with high-cost hospitalization for peritonitis in children receiving chronic peritoneal dialysis in the United States. Pediatr Nephrol. 2019;34(6):1049–55.
26. Raaijmakers R, et al. Fungal peritonitis in children on peritoneal dialysis. Pediatr Nephrol. 2007;22(2):288–93.
27. Warady BA, Bashir M, Donaldson LA. Fungal peritonitis in children receiving peritoneal dialysis: a report of the NAPRTCS. Kidney Int. 2000;58(1):384–9.
28. Warady BA, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32 Suppl 2:S32–86.
29. Gerber JS, et al. Variability in antibiotic use at children's hospitals. Pediatrics. 2010;126(6):1067–73.
30. Lee BR, et al. The burden of inappropriate antibiotic surgical prophylaxis in pediatric patients: a national point prevalence study. in Pediatric Academic Society; 2018. Toronto, Canada.

31. Hersh AL, et al. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics. 2011;128(6):1053–61.
32. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. Pediatrics. 2014;134(4):e956–65.
33. Snyder GM, et al. Antimicrobial use in outpatient hemodialysis units. Infect Control Hosp Epidemiol. 2013;34(4):349–57.
34. Neu AM, et al. Implementation of standardized follow-up care significantly reduces peritonitis in children on chronic peritoneal dialysis. Kidney Int. 2016;89(6):1346–54.
35. Sharma A, et al. Survival and complications of cuffed catheters in children on chronic hemodialysis. Pediatr Nephrol. 1999;13(3):245–8.
36. Stefanidis CJ. Prevention of catheter-related bacteremia in children on hemodialysis: time for action. Pediatr Nephrol. 2009;24(11):2087–95.
37. Sucupira C, et al. Surveillance system of hemodialysis-associated infections in a pediatric unit. Infect Control Hosp Epidemiol. 2012;33(5):521–3.
38. Wang K, et al. Cuffed-tunneled hemodialysis catheter survival and complications in pediatric patients: a single-center data analysis in China. Int J Clin Exp Med. 2015;8(6):9765–71.
39. Gerding DN. The search for good antimicrobial stewardship. Jt Comm J Qual Improv. 2001;27(8):403–4.
40. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services; 2014.
41. CDC. National Healthcare Safety Network (NHSN) Patient Safety Component Manual; 2018. Atlanta, GA.
42. Barlam TF, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51–77.
43. Hecker MT, et al. Impact of syndrome-specific antimicrobial stewardship interventions on use of and resistance to fluoroquinolones: an interrupted time series analysis. Am J Infect Control. 2019;
44. Sammons JS, Toltzis P, Zaoutis TE. Clostridium difficile infection in children. JAMA Pediatr. 2013;167(6):567–73.
45. Tamma PD, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017;177(9):1308–15.
46. Parker SK, et al. Anti-infective acquisition costs for a stewardship program: getting to the bottom line. Clin Infect Dis. 2017;65(10):1632–7.
47. Gerber JS, et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA. 2013;309(22):2345–52.
48. Hurst AL, et al. Handshake stewardship: a highly effective rounding-based antimicrobial optimization service. Pediatr Infect Dis J. 2016;35(10):1104–10.
49. Metjian TA, et al. Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital. Pediatr Infect Dis J. 2008;27(2):106–11.
50. Newland JG, et al. Impact of a prospective-audit-with-feedback antimicrobial stewardship program at a children's hospital. J Pediatric Infect Dis Soc. 2012;1(3):179–86.
51. D'Agata EMC, et al. The positive effects of an antimicrobial stewardship program targeting outpatient hemodialysis facilities. Infect Control Hosp Epidemiol. 2018;39(12):1400–5.
52. D'Agata EMC, et al. Clinical and economic benefits of antimicrobial stewardship programs in hemodialysis facilities: a decision analytic model. Clin J Am Soc Nephrol. 2018;13(9):1389–97.
53. McPherson C, et al. Characteristics of pediatric antimicrobial stewardship programs: current status of the Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) Collaborative. Antibiotics (Basel). 2018:**7**(1).
54. Neuman MI, et al. Influence of hospital guidelines on management of children hospitalized with pneumonia. Pediatrics. 2012;130(5):e823–30.
55. Newman RE, et al. Impact of a guideline on management of children hospitalized with community-acquired pneumonia. Pediatrics. 2012;129(3):e597–604.
56. Hamdy RF, et al. Pediatric ASP toolkit; 2019.
57. Partners NQ. National quality partners playbook: antibiotic stewardship in acute care; 2016.
58. Gerber JS, et al. Durability of benefits of an outpatient antimicrobial stewardship intervention after discontinuation of audit and feedback. JAMA. 2014;312(23):2569–70.
59. Meeker D, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. JAMA Intern Med. 2014;174(3):425–31.
60. Meeker D, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. JAMA. 2016;315(6):562–70.
61. Tokars JI, et al. A prospective study of vascular access infections at seven outpatient hemodialysis centers. Am J Kidney Dis. 2001;37(6):1232–40.
62. Miller JM, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67(6):813–6.
63. Connell TG, et al. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics. 2007;119(5):891–6.

64. Kallen AJ. Identifying and classifying bloodstream infections among hemodialysis patients. Semin Dial. 2013;26(4):407–15.
65. Mermel LA, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
66. Yi SH, et al. Sustained infection reduction in outpatient hemodialysis centers participating in a collaborative bloodstream infection prevention effort. Infect Control Hosp Epidemiol. 2016;37(7):863–6.
67. O'Grady NP, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162–93.
68. Neu AM, et al. Design of the standardizing care to improve outcomes in pediatric end stage renal disease collaborative. Pediatr Nephrol. 2014;29(9):1477–84.
69. Esposito S, et al. Vaccine administration in children with chronic kidney disease. Vaccine. 2014;32(49):6601–6.

Part II

Considerations Around the Initiation of Dialysis

9 The Decision to Initiate Dialysis in Children and Adolescents

Rima S. Zahr, Larry A. Greenbaum, and Franz Schaefer

Introduction

The initiation of chronic dialysis in a child is a dramatic event for the patient and family. There are absolute indications for initiating dialysis in some patients (e.g., bilateral nephrectomy, uremic pericarditis). In other patients, the reasons behind the timing of dialysis initiation are less clear. The pediatric nephrologist integrates a great deal of information—laboratory data, clinical impressions, and psychosocial issues—in order to reach a decision regarding the timing of dialysis initiation. An assessment of kidney function is usually a critical part of this process. There is considerable debate regarding the merits of "early" initiation of dialysis in adults. The data needed to address this issue in children is sparse, and the debate is complicated in children by issues such as growth, psychosocial factors, an impending kidney transplant, and the need for a lifetime of renal replacement therapy.

Methodology for Measuring Kidney Function

Assessment of a patient's kidney function, usually defined as the patient's glomerular filtration rate (GFR), is useful for determining when to initiate dialysis. This purposely ignores other aspects of kidney function, such as erythropoietin production and synthesis of calcitriol, because dialysis does not replace these functions. However, GFR may be transiently affected by a variety of factors other than the intrinsic kidney disease. For example, intravascular volume depletion, nonsteroidal anti-inflammatory drugs, and antihypertensive therapy, especially angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), may decrease GFR. In such instances, a fall in GFR should be interpreted cautiously. A potentially reversible process warrants a repeat measurement of kidney function after eliminating the possible underlying cause of the decrease in the GFR.

The gold standard for measuring GFR is inulin clearance, but this technique is usually only available in a research setting. Alternative exogenous substances for measuring GFR include chromium 51-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol, and iothalamate [1, 2].

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There is evidence for a good correlation between inulin clearance and some of these alternatives [3], although the accuracy may decrease in the setting of a low GFR [4, 5] and in patients with edema [6]. These techniques are expensive and require multiple blood draws over 3 to 4 hours, making them impractical for frequent monitoring. Single-sample methods, while more convenient, are especially problematic when the GFR is low [7].

Creatinine clearance (CrCl) is a widely used approach for estimating GFR. Like inulin, creatinine is freely filtered at the glomerulus, but unlike inulin, there is secretion of creatinine by the proximal tubule. This causes the CrCl to overestimate GFR. The effect of creatinine secretion is small at a normal GFR, causing a 5–10% overestimation of GFR. The relative impact of creatinine secretion increases as GFR decreases, leading to a more significant overestimation of GFR. In one study of adults with a mean GFR of 22 ml/min, the CrCl was close to double the inulin clearance [8]. Further, a variety of factors influence creatinine secretion. Creatinine secretion is lower in patients with polycystic kidney disease and higher in patients with glomerular disease [9]. Some medications, such as cimetidine, trimethoprim, and some fibrates, decrease creatinine secretion. Advanced liver disease may increase creatinine secretion. Finally, a valid calculation of CrCl requires an accurately timed urine collection. All of these factors limit the accuracy of CrCl, especially at the low levels of GFR when decisions regarding dialysis initiation are necessary.

Despite its limitations, CrCl is an easy and inexpensive surrogate for GFR. CrCl is calculated via the following equation:

$$\mathrm{CrCl} = \frac{U_{\mathrm{vol}} \times U_{\mathrm{Cr}} \times 1.73}{\mathrm{min} \times S_{\mathrm{Cr}} \times \mathrm{BSA}} \qquad (9.1)$$

where CrCl is the creatinine clearance (ml/min/1.73 m^2); U_{vol}, urine volume (mL); U_{Cr}, urine creatinine concentration (mg/dL); Min, collection period in minutes (1440 for 24 hours); S_{Cr}, serum creatinine (mg/dL); and BSA, body surface area in m^2.

A CrCl requires a timed urine collection, usually 12 or 24 hours, necessitating bladder catheterization in the absence of urinary continence. This is a significant impediment to repeat measurements in young children.

At low levels of GFR, the percentage of filtered urea that is reabsorbed is approximately equal to the percentage of filtered creatinine that is secreted. Therefore, the mean of CrCl and urea clearance is another way of estimating GFR; it is quite accurate at low levels of GFR in adults [10, 11].

In children, an estimated GFR (eGFR) may be calculated from the serum creatinine using an equation that uses patient height and a constant of 0.413 irrespective of age and gender [12]. The equation is referred to as the "CKiD creatinine equation" or the "modified Schwartz equation."

$$\mathrm{eGFR} = \frac{\mathrm{Height}\left(\mathrm{cm}\right) \times 0.413}{\mathrm{Scr}} \qquad (9.2)$$

This equation and subsequent referenced equations in this chapter are based on measuring creatinine using the enzymatic method traceable to isotope dilution mass spectrometry (IDMS traceable). A different constant was used for estimating GFR with an equation using the Jaffe method for determination of creatinine [13]. Hence, it is critical to be aware of the laboratory methodology that is being utilized when applying these formulas.

The accuracy of these formulas has been questioned by a number of studies [14, 15]. The formulas appear especially problematic in malnourished children and at the low levels of kidney function where decisions regarding dialysis initiation need to be made [15]. There are multiple factors that decrease the accuracy of formulas that depend on the serum creatinine concentration to estimate GFR. The serum creatinine concentration depends on the balance between creatinine generation and excretion. Creatinine is largely derived from breakdown of muscle creatine. Thus, creatinine generation is proportional to muscle mass, which varies greatly in children and is mostly related to size, but also varies due to gender, age, and individual differences. In adults, there are racial differences in creatinine generation [16].

Children with uremia may lose muscle mass due to malnutrition, possibly reducing the rise in

serum creatinine concentration. Spinal cord injury and amputation are other potential causes of a misleadingly low serum creatinine. During cooking, creatine in meat is converted to creatinine. Therefore, serum creatinine is partially influenced by the amount of dietary meat, which often decreases in kidney insufficiency due to phosphorus restriction and anorexia. Extrarenal creatinine excretion increases in patients with chronic kidney disease (CKD) [17]. Moreover, tubular creatinine secretion increases as the GFR decreases [8]. Extrarenal excretion and tubular secretion blunt the increase in serum creatinine concentration that should occur as GFR decreases. As stressed above, medications and the specific disease causing CKD can affect creatinine secretion as well [9].

The serum protein cystatin C, an endogenous protein produced by all nucleated cells, is an alternative to creatinine for estimating GFR [18] and is preferred in children with decreased GFR [15, 19] and obese children [20]. There are also equations that use a combination of cystatin C and creatinine to determine eGFR [12, 18, 21]. A more complex formula, derived from the CKiD study, utilizes creatinine, cystatin C, blood urea nitrogen (BUN), height, and sex for estimating GFR [22].

For adult patients, the CKD-EPI creatinine equation [23] has generally replaced older equations such as the Cockcroft-Gault [24] and the Modification of Diet in Renal Disease (MDRD) equation [25]. There are also CKD-EPI equations that utilize cystatin C alone or cystatin C and serum creatinine [26].

In young adults, there are clearly limitations of the creatinine-derived equations. For an 18-year-old, the CKD-EPI creatinine equation provides a higher eGFR than the CKiD creatinine equation [27, 28]. Neither equation is accurate in young adults when compared to iohexol GFR [28]. The CKD-EPI equations using either cystatin C alone or cystatin C with creatinine are the best options, though an average of the CKD-EPI creatinine equation and the CKiD creatinine equation is also a reasonable option [28].

Predialysis Patient Monitoring and Preparation for Dialysis

Systematic patient monitoring is necessary in children with CKD to minimize complications such as malnutrition, hypertension, renal osteodystrophy, and poor growth. In addition, regular monitoring identifies children who have relative or absolute indications for starting dialysis. Anticipation of the need for dialysis permits nonemergent placement of a peritoneal dialysis catheter, creation of a vascular access for hemodialysis, or performance of a preemptive kidney transplant. Table 9.1 outlines the necessary components for monitoring children with an eGFR < 30 ml/min/1.73 m^2.

In addition to medical monitoring, it is important that children and families are psychologically prepared for dialysis. This includes reviewing treatment options and exploring accommodations that will be needed at home and for the child's education.

Indications for Initiating Dialysis

Absolute Indications for Initiating Dialysis

A variety of signs and symptoms are absolute indications for dialysis initiation. These are manifestations of kidney failure that cause significant morbidity and mortality. There is usually a dra-

Table 9.1 Evaluation schedule for children with stage IV–V chronic kidney disease

Timing	Evaluation
At least every 3 months	Length/height, weight gain, head circumference in infants, blood pressure, acid-base status, electrolytes, creatinine, BUN, CBC, albumin, PTH, estimation of GFR
Every 6–12 months	Echocardiography, ABPM, neurodevelopmental assessment in infants

Abbreviations: *BUN* blood urea nitrogen, *CBC* complete blood count, *PTH* parathyroid hormone, *ABPM* ambulatory blood pressure monitoring

matic or marked improvement with the initiation of dialysis. An alternative explanation for the clinical finding should be considered, especially if the GFR is unexpectedly high or if dialysis does not result in improvement.

Neurologic consequences of uremia that are absolute indications for dialysis include encephalopathy, confusion, asterixis, seizures, myoclonus, and wrist or foot drop. Children should begin dialysis if there is hypertension that does not respond to antihypertensive therapy or pulmonary edema due to volume overload unresponsive to diuretics. Other absolute indications for starting dialysis are pericarditis, bleeding diathesis, and refractory nausea and emesis, especially if associated with weight loss.

Bilateral nephrectomy, as may be necessary in some children with congenital nephrotic syndrome or autosomal recessive polycystic kidney disease, is an absolute indication for dialysis.

Beyond anuria, there is debate regarding whether there is a level of GFR that is an absolute indication for dialysis. There are recommendations that the presence of malnutrition is an indication for dialysis initiation. Again, there is no consensus regarding the measurement of malnutrition, the degree of malnutrition that must be present, or the role of alternative strategies to alleviate malnutrition prior to the institution of dialysis.

Relative Indications for Initiating Dialysis

Uremic Symptoms

While severe uremic symptoms are absolute indications for dialysis, less dramatic symptoms are relative indications. These include fatigue and weakness, cognitive dysfunction, decreased school performance, pruritus, depression, nausea, emesis, anorexia, restless leg syndrome, and poor sleep patterns. The persistence and severity of these symptoms are important criteria. This is especially true when evaluating gastrointestinal symptoms. Intractable emesis is an absolute indication for dialysis, while occasional emesis, especially if there are no signs of malnutrition, may not require dialysis initiation.

Many of the symptoms that can be associated with uremia have alternative explanations. Medications may cause fatigue, depression, or nausea. Anemia, a correctable problem, may contribute to fatigue. Depression and poor school performance may be related to psychosocial issues. Comorbid conditions may also cause significant symptoms. Conversely, many patients with uremic symptoms may minimize or deny symptoms in an effort to avoid dialysis or because they perceive these symptoms, which may have developed quite gradually, as normal.

Hyperkalemia

Hyperkalemia is a potentially life-threatening complication of CKD [29, 30]. As GFR decreases, the remaining nephrons compensate by increasing potassium excretion, but there is a linear relationship between GFR and the ability to excrete a potassium load [31]. Hyperkalemia usually does not become problematic until the GFR is less than 10–20 ml/min/1.73m^2, unless the potassium intake is excessive or excretion is reduced [31]. Hyperkalemia develops at a higher GFR in adults and children with hyporeninemic hypoaldosteronism, which may also cause a type IV renal tubular acidosis [31]. Similarly, other patients have a decreased tubular responsiveness to aldosterone, and this pseudohypoaldosteronism may cause hyperkalemia at higher levels of GFR [31]. These patients may also have type IV renal tubular acidosis. Medications, especially ACE inhibitors, calcineurin inhibitors, and potassium-sparing diuretics, are another important cause of reduced urinary potassium excretion.

Treatment of hyperkalemia in association with CKD relies on decreasing dietary potassium intake and increasing potassium excretion. In older children, avoidance of foods with high potassium content can have a dramatic effect on potassium intake. Whereas in older children who are receiving liquid formula supplementation it is possible to select a formula with a low potassium content, the potassium content of infant formula does not vary greatly, limiting the effectiveness of formula selection. It should be noted, however,

that soy-based and elemental formulas are especially high in potassium. Human milk has a lower potassium content than most formulas, while cow's milk has about twice the potassium content of most infant formulas. A reduction in the potassium delivery from infant formula is possible by fortifying the formula with sugar (e.g., Polycose) and/or fat. With a higher caloric content, less formula, and hence less potassium, is needed to provide adequate calories. Alternatively, Renastart™, a formula with a very low potassium concentration, is used as a dietary supplement or is combined with another formula; it is not meant to be given as the sole source of nutrition [32].

Increasing potassium excretion can help ameliorate the hyperkalemia of CKD. Loop diuretics increase urinary potassium excretion. Discontinuation of medications that decrease urinary potassium excretion, such as ACE inhibitors, ARBs, nonsteroidal anti-inflammatory drugs, or potassium-sparing diuretics, can have a significant effect on the serum potassium level [33, 34]. Although not usually a significant mechanism of potassium excretion, stool potassium losses become more important as kidney function declines [35]. Constipation should be treated since it may decrease stool potassium losses [36]. Sodium polystyrene sulfonate (Kayexalate®), an exchange resin, binds potassium in the gastrointestinal tract, significantly increasing stool potassium losses. Pretreatment of formula with sodium polystyrene sulfonate is effective, but may cause constipation and problems with other electrolytes, including hypernatremia due to increased formula sodium content [37–39]. Newer oral potassium exchange resins include patiromer [40] and sodium zirconium cyclosilicate [41, 42]. There is some experience pre-treating formula with patiromer [43].

Because of the effectiveness of dietary and medical interventions, the initiation of chronic dialysis is seldom necessary solely to manage hyperkalemia. Nevertheless, repeated episodes of severe hyperkalemia may be considered an absolute indication for dialysis. Poor adherence to dietary restriction or medications usually contributes to refractory hyperkalemia. Hemodialysis and peritoneal dialysis are quite effective at correcting hyperkalemia, although dietary restriction, and occasionally medical management, is usually still necessary.

Hyperphosphatemia

A decrease in filtered phosphate parallels the decrease in GFR characteristic of CKD. With mild to moderate kidney insufficiency, an increase in the fractional excretion of phosphate by the remaining nephrons initially compensates for the loss of functioning nephrons, permitting the serum phosphorus to remain normal [44]. As the GFR falls, compensation is inadequate, and hyperphosphatemia ensues, typically at CKD stage III [45, 46]. Hyperphosphatemia causes secondary hyperparathyroidism by suppressing 1,25-dihydroxyvitamin D production and calcium levels and through direct stimulation of PTH secretion [47]. Correction of hyperphosphatemia is essential for controlling secondary hyperparathyroidism. In addition, hyperphosphatemia may elevate the serum calcium-phosphorus product and contribute to vascular calcifications [48, 49]. In adult patients with CKD, serum phosphate levels predict mortality and progression of CKD [49–51], while fibroblast growth factor 23 (FGF23) levels, which increase in response to hyperphosphatemia, are a predictor of CKD progression in children [52].

The successful management of hyperphosphatemia in CKD depends on a reduction in phosphate intake by a combination of dietary phosphate restriction and the use of phosphate binders [53]. Early in kidney failure, before hyperphosphatemia develops, a reduction in phosphate intake helps to control secondary hyperparathyroidism [47]. As kidney function declines, dietary restriction alone, because of nutritional constraints and limitations of food palatability, is often inadequate to control hyperphosphatemia, necessitating the use of phosphate binders. Calcium carbonate and calcium acetate are effective phosphate binders in children with CKD, although excessive use may cause hypercalcemia and contribute to systemic calcifications [54]. Sevelamer, a calcium-free phosphate-binding agent, has been effectively utilized to control hyperphosphatemia in children

[55]. Additional calcium-free phosphate binders include lanthanum carbonate, sucroferric oxyhydroxide, and ferric citrate [56–59].

A majority of the available phosphate binders must be administered in large doses (several grams per day) to be effective; unfortunately, the need to swallow large numbers of large-sized tablets or capsules limits the acceptability of medical therapy in children. Hence, poor adherence to dietary and medical therapy is the most important obstacle to the successful control of hyperphosphatemia.

While dialysis therapy removes phosphate, it is almost never adequate to control hyperphosphatemia by itself. There is a continued need for dietary restriction and phosphate binders. The initiation of dialysis because of refractory hyperphosphatemia is seldom effective at controlling hyperphosphatemia since the underlying problem, non-adherence to therapy, is still present. Hence, isolated hyperphosphatemia is seldom the only indication for dialysis, unless there is a belief that the combination of dialytic phosphate removal and improved adherence, perhaps due to the more regimented medical care required by dialysis, will facilitate control of hyperphosphatemia. The presence of refractory hyperparathyroidism further lowers the threshold for dialysis initiation.

Malnutrition

Uremia causes symptoms such as emesis and anorexia that may prevent adequate caloric intake. In adults and children, dietary protein and energy intake declines as the GFR decreases [60–64]. In children, this may adversely affect growth [65]. Infants during the first 6 months of life, when growth is rapid, are particularly vulnerable to the negative effects of poor nutrition.

Studies in adult patients show an association between malnutrition when starting dialysis and decreased patient survival [62, 63, 66–75]. Nutritional parameters improve in adult patients after the initiation of dialysis [60, 63, 76–81]. When looking at body fat as an index of nutritional status, poor nutritional status at the start of dialysis was associated with a greater increase in body fat [78]. In other studies, there was a positive correlation between the nutritional status at the start of dialysis and the follow-up nutritional status, suggesting that dialysis may not completely compensate for poor nutrition at dialysis initiation [77, 79].

The improved survival with an increased dialysis dose, the mortality risk associated with malnutrition, and the improvement in nutritional status associated with dialysis are the basis for recommendations to initiate dialysis therapy when a patient has advanced CKD and malnutrition [82–84]. Yet, there are no prospective studies demonstrating that the early initiation of dialysis improves outcome. Aggressive nutritional supplementation, possibly using an enteral feeding gastrostomy tube, may reverse malnutrition in some children without the need for dialysis [85, 86].

There is no one ideal marker of malnutrition. Signs of poor nutrition in children with CKD may include inadequate weight gain, poor linear growth, and loss of muscle mass. If malnutrition is not improved via conservative interventions, then the child with advanced CKD should begin dialysis.

Growth Failure

Growth retardation is a common complication of CKD in children [87]. The causes of "uremic" growth failure include malnutrition (most markedly in infants), electrolyte and fluid losses (in children with hypo-/dysplastic kidney disorders), metabolic acidosis, osteodystrophy, and, most importantly beyond infancy, impaired function of the somatotropic hormone axis. Electrolyte and bicarbonate losses can usually be managed conservatively, with favorable effects on growth rates. Forced feeding usually improves the nutritional status, but linear growth may not respond to nutritional recovery once growth failure is established [88]. In children with stable predialytic CKD, recombinant growth hormone therapy is indicated. The efficacy of this therapy strongly depends on residual kidney function, mandating a timely start of treatment [89, 90]. Unresponsiveness to recombinant growth hor-

mone may be considered as an argument to start dialysis, although improved growth rates are not consistently observed after initiation of standard peritoneal or hemodialysis [91]. However, a subsequent study demonstrated that short daily hemodiafiltration improved responsiveness to growth hormone, leading to remarkable, complete catch-up growth [92]. Hence, the availability of an intense hemodialysis program may be an argument to start dialysis in a child with growth hormone-resistant growth failure.

Timing of Elective Dialysis Initiation

The level of kidney function that is an absolute indication for initiating dialysis in children is uncertain. The adult literature is fraught with conflicting conclusions and opinions [93–95]. The debate is complicated by uncertainty regarding the best methodology for evaluating residual kidney function (see Section "Predialysis Patient Monitoring and Preparation for Dialysis"). The IDEAL study directly addressed this question in adults [96]. Patients were randomized to dialysis initiation at an eGFR of 10–15 ml/min/1.73 m^2 (early-start) or at an eGFR of 5–7 ml per minute (late-start). The late-start group began dialysis close to 6 months later than the early-start group, but there was no difference in mortality or other adverse events between the two groups. Hence, planned, early initiation of dialysis was not associated with a clinical benefit [96].

In children, there are limited published studies. In a study of children in the United States Renal Data System (USRDS), higher eGFR at dialysis initiation was associated with a higher mortality, especially among patients who initiated hemodialysis [97]. In another study of children in the USRDS, mortality also increased as eGFR at dialysis initiation increased, especially among patients 6 years and older [98]. In a European study, there was no difference in mortality based on level of eGFR at dialysis initiation [99]. There are no randomized studies in children.

Estimated GFR at Dialysis Initiation

In adults, prior to the publication of the IDEAL trial, the eGFR at dialysis initiation was gradually increasing in many countries. However, this trend has either stabilized or reversed since the publication of the IDEAL trial [100, 101].

In a large cohort of European pediatric patients, the median eGFR at initiation of renal replacement therapy (RRT) was 10.4 ml/min/1.73 m^2, with the small percentage of patients who received a preemptive transplant having a significantly higher eGFR at the time of transplant (13.5 ml/min/1.73 m^2) [102]. Variables associated with a lower eGFR at onset of RRT included younger age, female gender, and a short interval between the first visit to a pediatric nephrologist and commencement of RRT.

In a study of Canadian children, the median eGFR at dialysis initiation was 8.1 ml/min/1.73 m^2 [103]. Canadian children with a genetic cause of end-stage kidney disease (ESKD), living further from a treatment facility, and females were more likely to initiate dialysis at a higher eGFR. In a study of children in the USRDS, a higher eGFR at dialysis initiation was more common in whites, females, underweight or obese patients, and patients with glomerulonephritis as the underlying etiology of ESKD [97].

Consensus Statements Regarding Dialysis Initiation

The results of the IDEAL study have influenced guidelines on the timing of dialysis initiation; prior guidelines were more likely to reference a GFR threshold for initiating dialysis. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend dialysis initiation for specific indications, including symptoms or signs of kidney failure, refractory volume overload, hypertension or nutritional deterioration, and cognitive impairment [104]. Per these guidelines, this "often but not invariably" ensues at a GFR between 5 and 10 ml/min/1.73m^2.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend similar clinical criteria to KDIGO for initiating dialysis [105]. The KDOQI guidelines do not provide a GFR criterion, citing the challenges of estimating GFR and the lack of evidence that decision-making based on GFR is beneficial. The European Best Practice Board (EBPB) guidelines on when to start dialysis were specifically updated in response to the IDEAL study [106]. These guidelines recommend consideration of initiation of dialysis when the GFR is <15 ml/min/1.73m^2 *and* there are specific indications, including signs or symptoms of uremia, uncontrolled hypertension or volume overload, or a deterioration in nutritional status. In addition, the EBPB guidelines emphasize that this will occur in the majority of patients at a GFR of 6–9 ml/min/1.73m^2 and that patients with rapid deterioration require close supervision [106].

The Canadian Society of Nephrology guidelines, updated in 2014, recommend an "intent to defer" strategy that involves careful monitoring of patients with a GFR < 15 ml/min/1.73m^2, with dialysis initiation when there are clinical indications. However, unlike other guidelines, it is recommended to initiate dialysis if the eGFR is 6 ml/min/1.73m^2 or less [107].

Arguments for Early ("Timely") Initiation

This was based on the observation that adults who start dialysis with a lower GFR have increased morbidity and mortality [108–110]. This may be secondary to the effects of malnutrition since decreased residual kidney function is associated with poor nutrition and poor nutrition when starting dialysis is associated with increased morbidity and mortality (see Section "Malnutrition"). Moreover, in the 1990s, many adult patients initiated dialysis at a lower GFR than was recommended [111–113]. This led to the argument that more timely initiation of dialysis has the potential to lessen the high mortality in adult dialysis patients.

Since these observations, there has been a trend toward earlier initiation of dialysis in adults [100, 101]. This has been associated with subsequent observations suggesting that early initiation of dialysis may be harmful, with increasing mortality in patients who start early [114, 115]. However, this detrimental effect of early dialysis may be secondary to increased age and comorbidity in the patients who start early [116]. A lower serum creatinine, which results in a higher estimate of GFR, may also be explained by decreased muscle mass and poor nutritional status [117]. Hence, some patients with putative early initiation of dialysis may have a falsely elevated eGFR due to poor nutritional status, a well-defined risk factor for morbidity and mortality. This would create additional bias suggesting that early initiation of dialysis is harmful. Similarly, a falsely low creatinine may also be present in malnourished children or children with comorbidities that may limit muscle mass (e.g., neurologic injury that prevents ambulation), and thus observational studies that analyze eGFR at dialysis initiation in children must be interpreted with caution.

Arguments for Delayed Initiation

While a number of studies have shown a worse outcome in adults who have a lower GFR at dialysis initiation, there are a variety of biases that make interpretation difficult [110]. These include lead-time bias, referral time bias, and patient selection [83]. Lead-time bias refers to the fact that patients who start dialysis at lower GFR are further along in their disease than patients who start at a higher GFR. A fairer comparison is survival from a time when patients had the same GFR. After accounting for lead-time, two studies found no survival benefit for early dialysis initiation [118, 119]. Moreover, and as noted above, early initiation of dialysis may be associated with increased mortality [114, 115]. In adult and pediatric patients, late referral to a nephrologist is a predictor of poor outcomes [120–124]. Such patients are more likely to have a lower GFR at dialysis initiation, again tending to bias the out-

come against late initiation of dialysis. In addition, late referral patients are more likely to have a history of non-compliance with follow-up and more significant comorbid conditions [110].

Early initiation of dialysis exposes the patients to risks of complications from dialysis therapy, including peritonitis, irreversible loss of peritoneal function, access infections, and loss of large blood vessels for vascular access [125]. These issues are especially important in children given the need for a lifetime of ESKD care. In addition, especially in the case of peritoneal dialysis, there is a risk of family and patient "burn-out" as the time on dialysis increases. Hemodialysis may prevent school attendance and certainly requires an extended amount of time at the dialysis unit. Many children feel "washed out" after completing hemodialysis, limiting the ability to complete homework or play with friends. Morning hypotension may prevent school attendance in children receiving peritoneal dialysis.

Residual kidney function is associated with better outcomes in adults receiving dialysis [126, 127], and dialysis accelerates the loss of residual kidney function [128]. This is more significant with hemodialysis than continuous ambulatory peritoneal dialysis, in both adults and children [129–132]. The use of automated PD may [133, 134] or may not provoke a more rapid decline in residual kidney function than classical CAPD [132, 135]. Of particular relevance to children, it appears that short, high-turnover NIPD may exert similarly detrimental effects on residual kidney function as intermittent extracorporeal procedures.

While some children may bypass dialysis and receive a preemptive transplant, this exposes the child to the risks of long-term immunosuppression (infection and malignancy) and the growth-stunting effects of corticosteroids. Moreover, early transplantation should, statistically, lead to earlier graft failure. These factors argue against overly aggressive use of preemptive transplantation.

In some children, dialysis may be delayed because a living-related transplant is imminent. This avoids the morbidity of dialysis initiation. In other cases, psychosocial issues may delay dialysis initiation. In both of these instances, the possible benefits of early initiation are counterbalanced by the other factor.

Choice of Mode of Dialysis

Kidney transplantation is the optimal therapy for children with ESKD [136, 137]. However, transplantation is often not an immediate option because of the lack of a suitable donor. For some patients, psychosocial issues may also need to be addressed before proceeding with transplantation.

The majority of adult patients receive treatment with hemodialysis. In pediatric patients, peritoneal dialysis is the more frequently used modality, though there is a trend for increased use of hemodialysis in the United States [138]. There is debate in the adult literature regarding the optimal form of therapy; however, there are no randomized studies that properly address this issue. Selection bias has made it difficult to perform comparative studies of morbidity and mortality between peritoneal dialysis and hemodialysis in pediatric patients [139].

Peritoneal dialysis may be especially advantageous during the first 2 years of therapy [140, 141]. This may be related to the improved preservation of residual kidney function with peritoneal dialysis [129, 130, 142]. In addition, the inability of peritoneal dialysis to match the weekly urea clearance of hemodialysis may be less of a problem when the patient has residual kidney function, as is common during the first 2 years of therapy [143]. Finally, membrane failure may decrease the benefits of peritoneal dialysis after the first 2 years of dialysis [125]. Prolonged treatment with peritoneal dialysis may lead to membrane failure, which is associated with increased mortality [144, 145]. Moreover, a high transporter state in children on peritoneal dialysis is associated with poor growth [146]. The advantages of peritoneal dialysis during the first 2 years are especially relevant for children since they receive transplants sooner than adult patients due to the availability

Table 9.2 Contraindications to hemodialysis in children

Absolute	Relative
Very small patients Lack of vascular access Contraindications to anticoagulation Cardiovascular instability	Poorly controlled hypertension or hypertensive cardiomyopathy Lack of proximity to a pediatric hemodialysis center

Table 9.3 Contraindications to peritoneal dialysis in children

Absolute	Relative
Omphalocele or gastroschisis Bladder exstrophy Diaphragmatic hernia Peritoneal membrane failure	Impending abdominal surgery Impending living-related transplant Lack of an appropriate caregiver

of living-related donors and their higher priority on the cadaveric transplant list.

The adult literature supports the premise that the preferred mode of dialysis may depend on the patient population [147–149]. In children, peritoneal dialysis has a number of advantages. A home-based therapy is less disruptive with school and social activities. In infants, the performance of hemodialysis is associated with a significant risk for morbidity and mortality, especially if anuria is present [150]. Problems include difficulties with vascular access, refractory anemia, inadequate urea removal, and the risk of hemodynamic instability [150]. In addition, nutrition in infants is dependent on a high fluid intake, making it very difficult for thrice-weekly hemodialysis to provide adequate fluid removal unless the patient has substantial residual kidney function.

The choice of dialysis modality is based on a number of considerations. There are relative and absolute contraindications for both modalities (see Tables 9.2 and 9.3). Psychosocial considerations are quite important given the family commitment needed to make peritoneal dialysis successful. Unless there are contraindications, peritoneal dialysis is the optimal modality for the majority of children, although both the family and the patient must be comfortable with the decision.

References

1. Pottel H. Measuring and estimating glomerular filtration rate in children. Pediatr Nephrol. 2017;32(2):249–63.
2. Schwartz GJ, Furth S, Cole SR, Warady B, Munoz A. Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. Kidney Int. 2006;69(11):2070–7.
3. Soveri I, Berg UB, Björk J, Elinder C-G, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. Am J Kidney Dis. 2014;64(3):411–24.
4. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. Am J Kidney Dis. 1990;16(3):224–35.
5. Morton KA, Pisani DE, Whiting JH Jr, Cheung AK, Arias JM, Valdivia S. Determination of glomerular filtration rate using technetium-99m-DTPA with differing degrees of renal function. J Nucl Med Technol. 1997;25(2):110–4.
6. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? Clin Kidney J. 2016;9(5):682–99.
7. Li Y, Lee HB, Blaufox MD. Single-sample methods to measure GFR with technetium-99m-DTPA. J Nucl Med. 1997;38(8):1290–5.
8. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int. 1985;28(5):830–8.
9. Modification of Diet in Renal Disease Study Group. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996;7(4):556–66.
10. Lubowitz H, Slatopolsky E, Shankel S, Rieselbach RE, Bricker NS. Glomerular filtration rate. Determination in patients with chronic renal disease. JAMA. 1967;199(4):252–6.
11. van Olden RW, Krediet RT, Struijk DG, Arisz L. Measurement of residual renal function in patients treated with continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 1996;7(5):745–50.
12. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4(11):1832–43.
13. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259–63.

14. De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, Kassai B, et al. Schwartz formula: is one k-coefficient adequate for all children? PLoS One. 2012;7(12):e53439–e.
15. Björk J, Nyman U, Berg U, Delanaye P, Dubourg L, Goffin K, et al. Validation of standardized creatinine and cystatin C GFR estimating equations in a large multicentre European cohort of children. Pediatr Nephrol. 2019;34(6):1087–98.
16. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, et al. Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. Am J Kidney Dis. 2001;38(4):744–53.
17. Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. Clin Sci. 1980;58(4):327–35.
18. Andersen TB, Eskild-Jensen A, Frokiaer J, Brochner-Mortensen J. Measuring glomerular filtration rate in children; can cystatin C replace established methods? A review. Pediatr Nephrol. 2009;24(5):929–41.
19. Salvador CL, Tøndel C, Rowe AD, Bjerre A, Brun A, Brackman D, et al. Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. Pediatr Nephrol. 2019;34(2):301–11.
20. Correia-Costa L, Schaefer F, Afonso AC, Bustorff M, Guimaraes JT, Guerra A, et al. Normalization of glomerular filtration rate in obese children. Pediatr Nephrol. 2016;31(8):1321–8.
21. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis. 2006;48(2):221–30.
22. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445–53.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–70.
26. Inker LA, Shaffi K, Levey AS. Estimating glomerular filtration rate using the chronic kidney disease-epidemiology collaboration creatinine equation: better risk predictions. Circ Heart Fail. 2012;5(3):303–6.
27. Selistre L, De Souza V, Cochat P, Antonello ICF, Hadj-Aissa A, Ranchin B, et al. GFR estimation in adolescents and young adults. J Am Soc Nephrol. 2012;23(6):989–96.
28. Ng DK, Schwartz GJ, Schneider MF, Furth SL, Warady BA. Combination of pediatric and adult formulas yield valid glomerular filtration rate estimates in young adults with a history of pediatric chronic kidney disease. Kidney Int. 2018;94(1):170–7.
29. Cowan ACJ, Gharib EG, Weir MA. Advances in the management of hyperkalemia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2017;26(3):235–9.
30. Rodan AR. Potassium: friend or foe? Pediatr Nephrol. 2017;32(7):1109–21.
31. Palmer BF, Clegg DJ. Hyperkalemia across the continuum of kidney function. Clin J Am Soc Nephrol. 2018;13(1):155–7.
32. Keung LG. Renastart use in an infant on peritoneal dialysis. Adv Perit Dial. 2017;33:79–83.
33. Palmer BF. Renal complications associated with use of nonsteroidal anti-inflammatory agents. J Investig Med. 1995;43(6):516–33.
34. Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. Kidney Int. 2000;58(5):2084–92.
35. Hayes CP Jr, McLeod ME, Robinson RR. An extravenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Am Phys. 1967;80:207–16.
36. Allon M. Treatment and prevention of hyperkalemia in end-stage renal disease. Kidney Int. 1993;43(6):1197–209.
37. Shahar-Nissan K, Peled O, Krause I. The ice cream challenge: a favourable extemporaneous Kayexalate formulation improves compliance in paediatric patients. Br J Clin Pharmacol. 2019;85(10):2450–2.
38. Thompson K, Flynn J, Okamura D, Zhou L. Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate(®)) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. J Ren Nutr. 2013;23(5):333–9.
39. Le Palma K, Pavlick ER, Copelovitch L. Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware the high prevalence of electrolyte derangements in clinical practice. Clin Kidney J. 2018;11(2):166–71.
40. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of Patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314(2):151–61.
41. Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. N Engl J Med. 2015;372(16):1577–8.

42. Packham DK, Kosiborod M. Pharmacodynamics and pharmacokinetics of sodium zirconium cyclosilicate [ZS-9] in the treatment of hyperkalemia. Expert Opin Drug Metab Toxicol. 2016;12(5):567–73.
43. Paloian NJ, Bowman B, Bartosh SM. Treatment of infant formula with patiromer dose dependently decreases potassium concentration. Pediatr Nephrol. 2019;34(8):1395–401.
44. Portale AA, Booth BE, Halloran BP, Morris RC Jr. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest. 1984;73(6):1580–9.
45. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31–8.
46. Portale AA, Wolf M, Jüppner H, Messinger S, Kumar J, Wesseling-Perry K, et al. Disordered FGF23 and mineral metabolism in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):344–53.
47. Wesseling-Perry K, Salusky IB. Chronic kidney disease: mineral and bone disorder in children. Semin Nephrol. 2013;33(2):169–79.
48. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, et al. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol. 2009;20(2):381–7.
49. Lezaic V, Tirmenstajn-Jankovic B, Bukvic D, Vujisic B, Perovic M, Novakovic N, et al. Efficacy of hyperphosphatemia control in the progression of chronic renal failure and the prevalence of cardiovascular calcification. Clin Nephrol. 2009;71(1):21–9.
50. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–8.
51. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.
52. Portale AA, Wolf MS, Messinger S, Perwad F, Jüppner H, Warady BA, et al. Fibroblast growth factor 23 and risk of CKD progression in children. Clin J Am Soc Nephrol. 2016;11(11):1989–98.
53. Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2010;25(3):385–94.
54. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
55. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2015(11):CD008327-CD.
56. Hutchison AJ, Wilson RJ, Garafola S, Copley JB. Lanthanum carbonate: safety data after 10 years. Nephrology. 2016;21(12):987–94.
57. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney Int. 2014;86(3):638–47.
58. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol. 2015;26(2):493–503.
59. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014;189(6):727–40.
60. Pollock CA, Ibels LS, Zhu FY, Warnant M, Caterson RJ, Waugh DA, et al. Protein intake in renal disease. J Am Soc Nephrol. 1997;8(5):777–83.
61. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57(4):1688–703.
62. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM. Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol. 1995;6(5):1386–91.
63. McCusker FX, Teehan BP, Thorpe KE, Keshaviah PR, Churchill DN. How much peritoneal dialysis is required for the maintenance of a good nutritional state? Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Kidney Int. 1996;56:S56–61.
64. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR. Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol. 2000;15(3–4):259–65.
65. Sedman A, Friedman A, Boineau F, Strife CF, Fine R. Nutritional management of the child with mild to moderate chronic renal failure. J Pediatr. 1996;129(2):s13–8.
66. U.S. Renal Data Systems (USRDS). Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. Am J Kidney Dis. 1992;20(5 Suppl 2):32–8.
67. Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, et al. Canadian hemodialysis morbidity study. Am J Kidney Dis. 1992;19(3):214–34.
68. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15(5):458–82.
69. Bergstrom J. Nutrition and mortality in hemodialysis. J Am Soc Nephrol. 1995;6(5):1329–41.
70. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, et al. Impact of the initial lev-

els of laboratory variables on survival in chronic dialysis patients. Am J Kidney Dis. 1996;28(4):541–8.
71. Avram MM, Mittman N, Bonomini L, Chattopadhyay J, Fein P. Markers for survival in dialysis: a seven-year prospective study. Am J Kidney Dis. 1995;26(1):209–19.
72. Barrett BJ, Parfrey PS, Morgan J, Barre P, Fine A, Goldstein MB, et al. Prediction of early death in end-stage renal disease patients starting dialysis. Am J Kidney Dis. 1997;29(2):214–22.
73. Kopple JD, Zhu X, Lew NL, Lowrie EG. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int. 1999;56(3):1136–48.
74. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis. 1998;31(6):997–1006.
75. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol. 1996;7(2):198–207.
76. Blake PG, Flowerdew G, Blake RM, Oreopoulos DG. Serum albumin in patients on continuous ambulatory peritoneal dialysis--predictors and correlations with outcomes. J Am Soc Nephrol. 1993;3(8):1501–7.
77. Pupim LB, Kent P, Caglar K, Shyr Y, Hakim RM, Ikizler TA. Improvement in nutritional parameters after initiation of chronic hemodialysis. Am J Kidney Dis. 2002;40(1):143–51.
78. Ishimura E, Okuno S, Kim M, Yamamoto T, Izumotani T, Otoshi T, et al. Increasing body fat mass in the first year of hemodialysis. J Am Soc Nephrol. 2001;12(9):1921–6.
79. Goldwasser P, Kaldas AI, Barth RH. Rise in serum albumin and creatinine in the first half year on hemodialysis. Kidney Int. 1999;56(6):2260–8.
80. Parker TF 3rd, Wingard RL, Husni L, Ikizler TA, Parker RA, Hakim RM. Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients. Kidney Int. 1996;49(2):551–6.
81. Mehrotra R, Berman N, Alistwani A, Kopple JD. Improvement of nutritional status after initiation of maintenance hemodialysis. Am J Kidney Dis. 2002;40(1):133–42.
82. National Kidney Foundation. KDOQI clinical practice guidelines for peritoneal dialysis adequacy: 2006 update. Am J Kidney Dis. 2006;48(suppl 2):S91–S175.
83. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13):S289–91.
84. Kelly J, Stanley M, Harris D. The CARI guidelines. Acceptance into dialysis guidelines. Nephrology. 2005;10(Suppl 4):S46–60.
85. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12(11):2418–26.
86. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25(4):699–704.
87. Greenbaum LA, Warady BA, Furth SL. Current advances in chronic kidney disease in children: growth, cardiovascular, and neurocognitive risk factors. Semin Nephrol. 2009;29(4):425–34.
88. Feneberg R, Bürkel E, Sahm K, Weck K, Mehls O, Schaefer F. Long-term effects of tube feeding on growth and body composition in uremic infants. J Am Soc Nephrol. 2001;12:A2200.
89. Koch VH, Lippe BM, Nelson PA, Boechat MI, Sherman BM, Fine RN. Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. J Pediatr. 1989;115(3):365–71.
90. Schaefer F, Haffner D, Wuhl E, Mehls O. Long-term experience with growth hormone treatment in children with chronic renal failure. Perit Dial Int. 1999;19(Suppl 2):S467–72.
91. Neu AM, Ho PL, McDonald RA, Warady BA. Chronic dialysis in children and adolescents. The 2001 NAPRTCS annual report. Pediatr Nephrol. 2002;17(8):656–63.
92. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25(3):867–73.
93. Janmaat CJ, van Diepen M, Krediet RT, Hemmelder MH, Dekker FW. Effect of glomerular filtration rate at dialysis initiation on survival in patients with advanced chronic kidney disease: what is the effect of lead-time bias? Clin Epidemiol. 2017;9:217–30.
94. Crews DC, Scialla JJ, Boulware LE, Navaneethan SD, Nally JV Jr, Liu X, et al. Comparative effectiveness of early versus conventional timing of dialysis initiation in advanced CKD. Am J Kidney Dis. 2014;63(5):806–15.
95. Rosansky SJ, Eggers P, Jackson K, Glassock R, Clark WF. Early start of hemodialysis may be harmful. Arch Intern Med. 2011;171(5):396–403.
96. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010;363(7):609–19.
97. Winnicki E, Johansen KL, Cabana MD, Warady BA, McCulloch CE, Grimes B, et al. Higher eGFR at dialysis initiation is not associated with a survival benefit in children. J Am Soc Nephrol. 2019;30(8):1505–13.
98. Okuda Y, Soohoo M, Tang Y, Obi Y, Laster M, Rhee CM, et al. Estimated GFR at Dialysis initiation and mortality in children and adolescents. Am J Kidney Dis. 2019;73(6):797–805.
99. Preka E, Bonthuis M, Harambat J, Jager KJ, Groothoff JW, Baiko S, et al. Association between timing of dialysis initiation and clinical outcomes

in the paediatric population: an ESPN/ERA-EDTA registry study. Nephrol Dial Transplant. 2019;34(11):1932–40.
100. Li Y, Jin Y, Kapke A, Pearson J, Saran R, Port FK, et al. Explaining trends and variation in timing of dialysis initiation in the United States. Medicine. 2017;96(20):e6911–e.
101. Ferguson TW, Garg AX, Sood MM, Rigatto C, Chau E, Komenda P, et al. Association between the publication of the initiating dialysis early and late trial and the timing of dialysis initiation in Canada. JAMA Intern Med. 2019;179(7):934–41.
102. van Stralen KJ, Tizard EJ, Jager KJ, Schaefer F, Vondrak K, Groothoff JW, et al. Determinants of eGFR at start of renal replacement therapy in paediatric patients. Nephrol Dial Transplant. 2010;25(10):3325–32.
103. Dart AB, Zappitelli M, Sood MM, Alexander RT, Arora S, Erickson RL, et al. Variation in estimated glomerular filtration rate at dialysis initiation in children. Pediatr Nephrol. 2017;32(2):331–40.
104. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
105. National Kidney Foundation KDOQI Clinical Practice Guideline for Hemodialysis Adequacy. 2015 update. Am J Kidney Dis. 2015;66(5):884–930.
106. Tattersall J, Dekker F, Heimburger O, Jager KJ, Lameire N, Lindley E, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. Nephrol Dial Transplant. 2011;26(7):2082–6.
107. Nesrallah GE, Mustafa RA, Clark WF, Bass A, Barnieh L, Hemmelgarn BR, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. CMAJ. 2014;186(2):112–7.
108. Bonomini V, Feletti C, Scolari MP, Stefoni S. Benefits of early initiation of dialysis. Kidney Int. 1985;17(9):S57–9.
109. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. Am J Nephrol. 1995;15(4):283–9.
110. Churchill DN. An evidence-based approach to earlier initiation of dialysis. Am J Kidney Dis. 1997;30(6):899–906.
111. Van Biesen W, Wiedemann M, Lameire N. End-stage renal disease treatment: a European perspective. J Am Soc Nephrol. 1998;9(12 Suppl):S55–62.
112. Mehrotra R, Lee J, Elivera H, Ahmed Z. Trends in initiation of dialysis in an urban dialysis clinic in the United States: a long way from dialysis outcomes quality initiative guidelines. Adv Perit Dial. 1999;15:138–43.
113. Obrador GT, Arora P, Kausz AT, Ruthazer R, Pereira BJ, Levey AS. Level of renal function at the initiation of dialysis in the U.S. end-stage renal disease population. Kidney Int. 1999;56(6):2227–35.
114. Beddhu S, Samore MH, Roberts MS, Stoddard GJ, Ramkumar N, Pappas LM, et al. Impact of timing of initiation of dialysis on mortality. J Am Soc Nephrol. 2003;14(9):2305–12.
115. Kazmi WH, Gilbertson DT, Obrador GT, Guo H, Pereira BJ, Collins AJ, et al. Effect of comorbidity on the increased mortality associated with early initiation of dialysis. Am J Kidney Dis. 2005;46(5):887–96.
116. Lassalle M, Labeeuw M, Frimat L, Villar E, Joyeux V, Couchoud C, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int. 2010;77(8):700–7.
117. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003;14(9):2366–72.
118. Korevaar JC, Jansen MA, Dekker FW, Jager KJ, Boeschoten EW, Krediet RT, et al. When to initiate dialysis: effect of proposed US guidelines on survival. Lancet. 2001;358(9287):1046–50.
119. Traynor JP, Simpson K, Geddes CC, Deighan CJ, Fox JG. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. J Am Soc Nephrol. 2002;13:2125–32.
120. Chow KM, Szeto CC, Law MC, Kwan BC, Leung CB, Li PK. Impact of early nephrology referral on mortality and hospitalization in peritoneal dialysis patients. Perit Dial Int. 2008;28(4):371–6.
121. Hasegawa T, Bragg-Gresham JL, Yamazaki S, Fukuhara S, Akizawa T, Kleophas W, et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. Clin J Am Soc Nephrol. 2009;4(3):595–602.
122. McClellan WM, Wasse H, McClellan AC, Kipp A, Waller LA, Rocco MV. Treatment center and geographic variability in pre-ESRD care associate with increased mortality. J Am Soc Nephrol. 2009;20(5):1078–85.
123. Lee BJ, Forbes K. The role of specialists in managing the health of populations with chronic illness: the example of chronic kidney disease. BMJ. 2009;339:b2395.
124. Jander A, Nowicki M, Tkaczyk M, Roszkowska-Blaim M, Jarmoliński T, Marczak E, et al. Does a late referral to a nephrologist constitute a problem in children starting renal replacement therapy in Poland?--a nationwide study. Nephrol Dial Transplant. 2006;21(4):957–61.
125. Andreoli SP, Langefeld CD, Stadler S, Smith P, Sears A, West K. Risks of peritoneal membrane failure in children undergoing long-term peritoneal dialysis. Pediatr Nephrol. 1993;7(5):543–7.
126. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative

Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15(4):1061–70.
127. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13(5):1307–20.
128. Rottembourg J. Residual renal function and recovery of renal function in patients treated by CAPD. Kidney Int. 1993;40:S106–10.
129. Lang SM, Bergner A, Topfer M, Schiffl H. Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. Perit Dial Int. 2001;21(1):52–7.
130. Schulman G. The role of hemodialysis and peritoneal dialysis for the early initiation of dialysis. Blood Purif. 2001;19(2):175–8.
131. Feber J, Scharer K, Schaefer F, Mikova M, Janda J. Residual renal function in children on haemodialysis and peritoneal dialysis therapy. Pediatr Nephrol. 1994;8(5):579–83.
132. Fischbach M, Terzic J, Menouer S, Soulami K, Dangelser C, Helmstetter A, et al. Effects of automated peritoneal dialysis on residual daily urinary volume in children. Adv Perit Dial. 2001;17:269–73.
133. Hufnagel G, Michel C, Queffeulou G, Skhiri H, Damieri H, Mignon F. The influence of automated peritoneal dialysis on the decrease in residual renal function. Nephrol Dial Transplant. 1999;14(5):1224–8.
134. Hiroshige K, Yuu K, Soejima M, Takasugi M, Kuroiwa A. Rapid decline of residual renal function in patients on automated peritoneal dialysis. Perit Dial Int. 1996;16(3):307–15.
135. de Fijter CW, ter Wee PM, Donker AJ. The influence of automated peritoneal dialysis on the decrease in residual renal function. Nephrol Dial Transplant. 2000;15(7):1094–6.
136. McDonald SP, Craig JC. Australian, New Zealand Paediatric Nephrology A. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
137. Chesnaye NC, van Stralen KJ, Bonthuis M, Harambat J, Groothoff JW, Jager KJ. Survival in children requiring chronic renal replacement therapy. Pediatr Nephrol. 2018;33(4):585–94.
138. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
139. Litwin M, Grenda R, Prokurat S, Abuauba M, Latoszynska J, Jobs K, et al. Patient survival and causes of death on hemodialysis and peritoneal dialysis--single-center study. Pediatr Nephrol. 2001;16(12):996–1001.
140. Fenton SS, Schaubel DE, Desmeules M, Morrison HI, Mao Y, Copleston P, et al. Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. Am J Kidney Dis. 1997;30(3):334–42.
141. Collins AJ, Hao W, Xia H, Ebben JP, Everson SE, Constantini EG, et al. Mortality risks of peritoneal dialysis and hemodialysis. Am J Kidney Dis. 1999;34(6):1065–74.
142. Coles GA, Williams JD. What is the place of peritoneal dialysis in the integrated treatment of renal failure? Kidney Int. 1998;54(6):2234–40.
143. Alloatti S, Manes M, Paternoster G, Gaiter AM, Molino A, Rosati C. Peritoneal dialysis compared with hemodialysis in the treatment of end-stage renal disease. J Nephrol. 2000;13(5):331–42.
144. Davies SJ, Phillips L, Griffiths AM, Russell LH, Naish PF, Russell GI. What really happens to people on long-term peritoneal dialysis? Kidney Int. 1998;54(6):2207–17.
145. Wang T, Heimburger O, Waniewski J, Bergstrom J, Lindholm B. Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. Nephrol Dial Transplant. 1998;13(5):1242–9.
146. Schaefer F, Klaus G, Mehls O. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. Mid-European Pediatric Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1999;10(8):1786–92.
147. Maiorca R, Vonesh E, Cancarini GC, Cantaluppi A, Manili L, Brunori G, et al. A six-year comparison of patient and technique survivals in CAPD and HD. Kidney Int. 1988;34(4):518–24.
148. Vonesh EF, Moran J. Mortality in end-stage renal disease: a reassessment of differences between patients treated with hemodialysis and peritoneal dialysis. J Am Soc Nephrol. 1999;10(2):354–65.
149. Tanna MM, Vonesh EF, Korbet SM. Patient survival among incident peritoneal dialysis and hemodialysis patients in an urban setting. Am J Kidney Dis. 2000;36(6):1175–82.
150. Al-Hermi BE, Al-Saran K, Secker D, Geary DF. Hemodialysis for end-stage renal disease in children weighing less than 10 kg. Pediatr Nephrol. 1999;13(5):401–3.

Urological Issues in Pediatric Dialysis

10

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Abbreviations

CIC	Clean intermittent catheterization
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
FSGS	Focal segmental glomerulosclerosis
LUT	Lower urinary tract
PBS	Prune belly syndrome
PD	Peritoneal dialysis
PUV	Posterior urethral valves
UTI	Urinary tract infection
VCUG	Voiding cystourethrogram
VUR	Vesicoureteral reflux

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Introduction

The prevalence of end-stage kidney disease (ESKD) in the pediatric population is approximately 50 cases per million, while 4 cases per million receive renal replacement therapy [1]. While the etiology of ESKD remains consistent across time, the prevalence of ESKD has been increasing across all pediatric age groups, particularly among older children [2, 3]. In contrast to adults, where glomerulopathy and vasculopathy are the major causes of kidney disease, at least 40% of the chronic kidney disease (CKD) in children is due to congenital urological abnormalities [4–8]. As a result, the urologist is an essential member in any team managing pediatric CKD. Similarly, all providers of children with CKD benefit from understanding these urological management principles.

This chapter will review the common urological conditions that cause kidney failure in children, the diagnosis and pathophysiology of these conditions, and an overview of the urologic management. As dialysis represents the treatment phase during CKD between the development of ESKD and kidney transplantation, this chapter will discuss issues present prior to the initiation of dialysis and following kidney transplantation. Also, unique implications for pediatric dialysis and kidney transplantation will be addressed, including urology specific pretransplant evaluation and indications for nephrectomy in the CKD patient.

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Urological Causes of Chronic Kidney Disease

The causes of CKD in children may be categorized into congenital and acquired conditions and are listed by anatomical location in Table 10.1 [6, 9–18]. Select significant causes are *italicized* and are the focus of the chapter.

Posterior Urethral Valves

Posterior urethral valves (PUV) are abnormal membranous folds unique to the male prostatic urethra. While there are other rare causes of congenital lower urinary tract (LUT) obstruction, such as urethral atresia and obstructive ureteroceles, PUV are undoubtedly the most common. They are encountered in 1 of 5000–25,000 live births [19–22].

Table 10.1 Urological causes of chronic kidney disease in children, *italicized* are discussed in this chapter

	Causes
Congenital	*Renal dysplasia* *Ureteropelvic junction obstruction* Ureterovesical junction obstruction Ureteroceles *Vesicoureteral reflux* *Neurogenic bladder* *Posterior urethral valves* *Prune belly syndrome*
Acquired	Obstructing urolithiasis Obstructing neoplasms Neurogenic bladder Urethral strictures

Advances in antenatal diagnosis, improved perinatal medicine, and early PUV management have led to a decrease in the neonatal mortality rate associated with PUV. In spite of these advances and antenatal intervention, there has been little improvement in the proportion of these patients ultimately developing CKD [23]. Twenty to sixty percent of boys with PUV will manifest with evidence of CKD in childhood, and 11–51% will eventually progress to ESKD during long-term follow-up [24–27].

Increasingly, the diagnosis is suggested in the antenatal period with ultrasound findings of oligohydramnios, bilateral hydroureteronephrosis, a thickened bladder wall, and a dilated posterior urethra (Fig. 10.1). Children without a prenatal diagnosis will present at different ages in the postnatal period with a variety of conditions, including respiratory insufficiency, kidney failure, urosepsis, failure to thrive, poor urinary stream, and urinary incontinence. The variation of PUV presentations represents a spectrum of disease, in which less severe forms of obstruction are often detected later in life and may be associated with a smaller impact on overall kidney function.

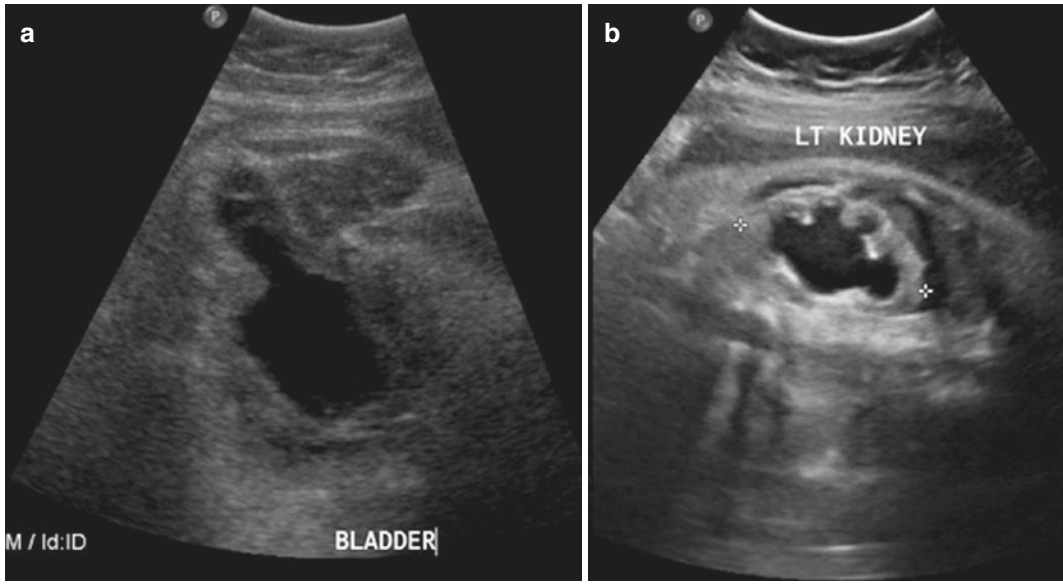

Fig. 10.1 Sonographic features suggestive of PUV detected during antenatal evaluation: (**a**) thick-walled bladder with prominent posterior urethra, the "key-hole" sign; (**b**) high-grade hydronephrosis

To prevent or attenuate kidney damage that occurs in utero, prenatal interventions have sought to bypass the urethral obstruction with open diversion, percutaneous diversion, or more recently cystoscopy of the fetal urinary system [28–30]. The decision to attempt antenatal intervention should be guided by selective criteria, aided by the analysis of amniotic fluid levels, imaging of renal dysplasia, and fetal urinary markers (sodium, chloride, osmolality, and B_2-microglobulin) [31]. Vesicoamniotic shunting achieves the required supra-urethral diversion while being minimally invasive, obviating the need for a maternal hysterotomy and fetal vesicostomy. Interventions to preserve kidney function would need to be performed early, probably before 22–23 weeks of gestation, although this is not well established [32]. Antenatal interventions are associated with a fetal mortality rate that ranges from 33% to 43%. Not all the reported deaths are directly related to the intervention, as many deaths recorded may be secondary to ensuing pulmonary hypoplasia. These procedures are also associated with significant morbidity in the form of urinary ascites, visceral herniation, shunt malfunction, and shunt migration [33–36].

Regardless of the timing of the postnatal presentation, an ultrasound of the kidneys, ureter, and bladder should be the first imaging study obtained. The ultrasound will often demonstrate a thick-wall bladder with a prominent posterior urethra, the "key-hole" sign, and high-grade hydroureteronephrosis. A voiding cystourethrogram (VCUG) is indicated to confirm the diagnosis of PUV. Typical features on VCUG include a dilated posterior urethra with a clear sharp transition to a normal (or attenuated due to reduced flow) distal channel, an associated valve cusp, a thickened open bladder neck, and a trabeculated bladder. Vesicoureteral reflux (VUR) is also often present (Fig. 10.2). While not always predictive of a favorable prognosis, the presence of a urinary "pop-off" has been reported to be protective in some children, by protecting at least one functioning kidney. Such "pop-off" mechanisms include unilateral high-grade VUR into an ipsilateral dysplastic/nonfunctioning kidney, a bladder diverticulum, a perinephric urinoma, urinary ascites, and a patent urachus [37–42].

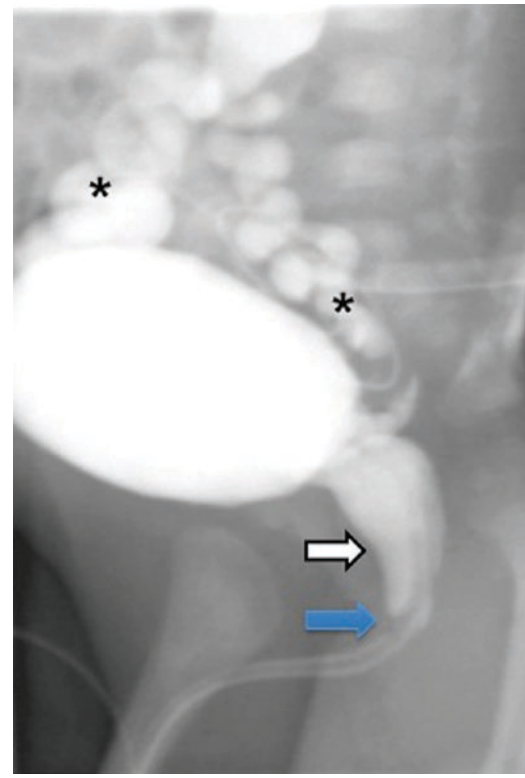

Fig. 10.2 Features of PUV on VCUG: dilated posterior urethra (*white arrow*) with a change in caliber compared with the anterior urethra at the site of the valves (*blue arrow*). Associated bilateral vesicoureteral reflux (*asterisk*)

At birth, many boys with PUV will have preexisting renal dysplasia and will eventually develop CKD regardless of treatment. An important goal of PUV management is to delay the onset of kidney failure, by optimizing function of the kidneys, ureters, bladder, and urethra. Management is initially directed at systemic stabilization and decompression of the urinary tract. Initial urological instrumentation usually involves urethral catheterization in the early neonatal period, prior to the confirmation of the diagnosis. The simple intervention of urethral catheterization temporarily bypasses the urinary obstruction, allows accurate monitoring of urine output, and helps avoid emergent surgical intervention, while associated abnormalities are identified and their management optimized. A VCUG can then be obtained by instilling contrast through the catheter with subsequent catheter removal to

image the urethra. Subsequent definitive urethroscopic valve ablation can be performed in most boys, except for the smallest of infants. Premature or small infants, whose urethras will not accommodate a cystoscope, are candidates for alternative forms of decompression. Similarly, in the occasional scenario, where valve ablation does not achieve decompression of the upper tracts, surgical diversion above the bladder outlet warrants consideration. This may be in part due to a functional ureterovesical junction obstruction as the ureter passes through a markedly thickened detrusor muscle. In such situations, segments of the urinary tract can be temporarily brought to the skin, in the form of a vesicostomy, ureterostomy, or pyelostomy (Fig. 10.3).

Bacterial colonization of the prepuce of uncircumcised boys predisposes them to urinary tract infection (UTI), particularly in the first year of life. Circumcision should be considered at the time of the valve ablation or vesicostomy to significantly decrease the risk of UTI [43]. This intervention is often heavily influenced by cultural and religious expectations.

Following valve ablation, the obstructive process is usually relieved; however, the functional improvements are less predictable. Urodynamic findings in these boys remain highly variable and prone to change over time, as kidney function, growth, and the acquisition of continence further challenge the stability of the bladder [44, 45]. The primary goal of the urological management in PUV is the preservation of upper tract function, which is achieved by ensuring an infection-free urinary tract with a bladder that stores urine at low pressure and empties efficiently. The secondary goals include urinary continence and a safe lower tract for those that require kidney transplantation.

Poorly controlled lower urinary tract (LUT) dysfunction can adversely affect existing kidney function. Residual bladder dysfunction in PUV is an independent risk factor for CKD [12, 25]. In 1980, Mitchell coined the term "valve bladder syndrome," identifying deleterious features of lower tract dysfunction that could reliably predict kidney deterioration. This term describes the development or persistence of hydroureteronephrosis in the presence of a poorly compliant, thick-walled bladder, incontinence, and polyuria [46].

Koff further clarified the role of the bladder in the deterioration of the upper tracts, suggesting that polyuria, insensitivity to overdistension, and high post void residual volumes were the three key factors contributing to kidney deterioration in valve patients [47].

An overwhelmed bladder with borderline function may lead to upper tract damage. *Polyuria*, caused by nephrogenic diabetes insipidus, has the potential to overload the bladder of the most diligent voider. *Insensitivity to overdis-*

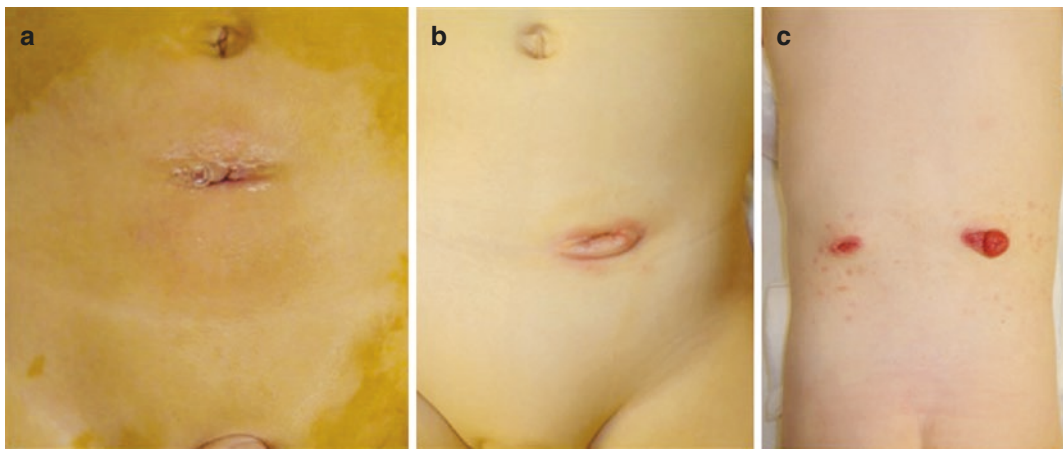

Fig. 10.3 Appearance on physical examination of different forms of cutaneous urinary diversion: (**a**) vesicostomy, (**b**) distal ureterostomy, and (**c**) bilateral pyelostomies (patient prone)

tension contributes to the potential for bladder overload and injury. *High post void residual volumes* decrease the functional capacity of the bladder and are not necessarily the result of myogenic failure [48]. Pseudo-residual volumes can be seen in children with PUV and VUR when urine refluxes into dilated ureters during filling and voiding, only to empty back into the bladder immediately after voiding. An additional cause of pseudo-residual volumes is a hypertrophied detrusor muscle that creates a functional ureterovesical junction obstruction during bladder filling, which is relieved after voiding, allowing the retained urine to drain from the dilated ureters (Fig. 10.4) [49].

With this understanding, hydroureteronephrosis is no longer considered unavoidable in PUV patients. Management has become proactive, focused on achieving complete urinary tract emptying (double voiding, timed voiding, and clean intermittent catheterization [CIC]), optimizing detrusor function (with judicious use of anticholinergics), and the selective use of alpha-blockers to assist voiding [50]. On occasion, routine daytime interventions are unsuccessful at preventing hydronephrosis in PUV, due to the polyuria and decreased functional capacity. To overcome this, nocturnal CIC or overnight indwelling catheterization has been shown to reduce diuresis, decrease the incidence of UTI, improve urinary continence, and decrease upper tract dilation [47, 51, 52].

VUR in PUV children is found in 50–70% of patients and is usually secondary to the obstructed bladder outlet [53, 54]. Because of its association with worse renal dysplasia, high-grade reflux can predict higher morbidity and mortality [55, 56]. Adequate treatment of the valvular obstruction will lead to spontaneous resolution of VUR in most cases (62%), and therefore VUR should be

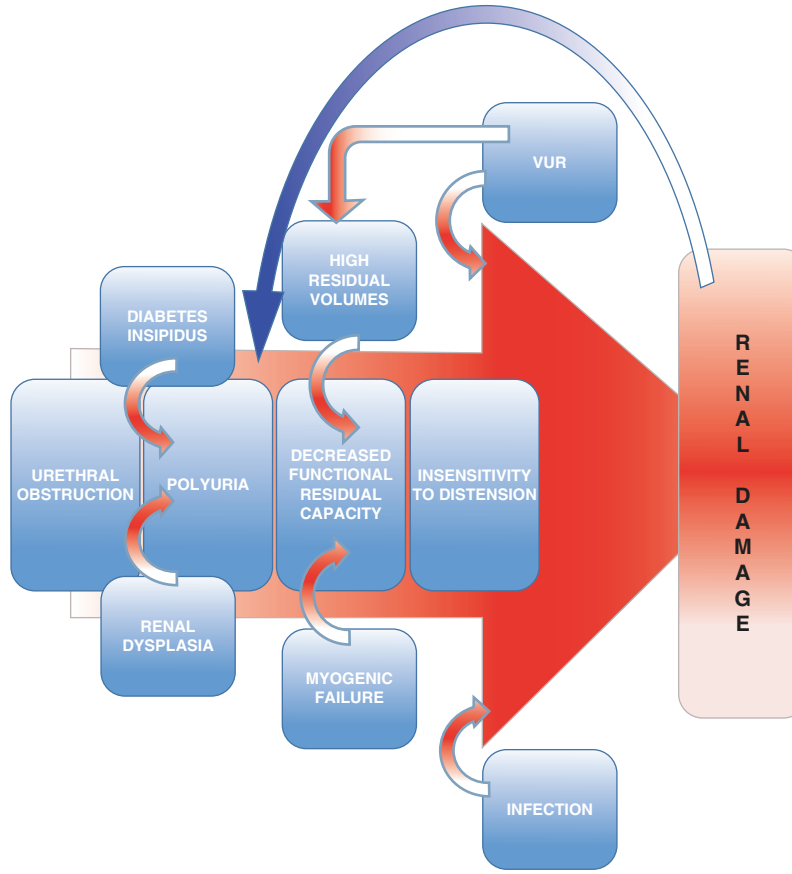

Fig. 10.4 Issues to consider in the monitoring of patients with PUV. Adequately addressing these problems helps prevent or slow kidney deterioration and provides a conceptual framework upon which to consider interventions and tailor treatment

managed conservatively [54, 57]. Rarely, surgical intervention is indicated for recurrent pyelonephritis, in cases where LUT dysfunction has been ruled out or controlled.

The presence of persistent unilateral reflux into a dysplastic nonfunctioning kidney in males with PUV, referred to as posterior urethral valve, unilateral vesicoureteral reflux and renal dysplasia (VURD) syndrome, has been associated with a better kidney functional prognosis than what is experienced by standard PUV patients in the short term [55, 58, 59]. The dysplastic kidney is thought to provide a protective effect as the renal pelvis and ureter absorb the high pressures generated by the bladder during voiding. Despite this protective effect, up to 50% of patients with VURD may develop some kidney scarring, voiding dysfunction, UTI, diurnal incontinence, and long-term hydroureteronephrosis [58]. Therefore, every boy with PUV, regardless of the presence of favorable prognostic features, should have close multidisciplinary team follow-up to identify and appropriately treat potential risk factors to the remaining kidney function.

When necessary, kidney transplantation is successful in patients with PUV with proper evaluation of the bladder for storage and emptying [60]. Vesicostomy or bladder augmentation may be needed in some PUV patients prior to kidney transplant. Patients with PUV are at a higher UTI risk after kidney transplantation [61].

Vesicoureteral Reflux in the Pediatric Dialysis Patient

Reflux nephropathy is kidney damage or abnormal kidney development related to VUR. The kidney damage may be congenital or acquired from repeated insults. Congenital sources of reflux nephropathy represent renal dysplasia that coexists with reflux rather than being directly caused by it (Fig. 10.5). Subsequently, postnatal kidney function may be worsened by pyelonephritis, which is facilitated by the reflux of infected urine into the abnormal kidney unit [62–65]. Differentiation between primary and secondary reflux has important therapeutic implications. Primary VUR is reflux, which occurs in the absence of secondary functional or anatomical causes, such as PUV, ureteroceles, or neurogenic bladder. Secondary reflux is associated with transmission of high bladder pressures to the upper tracts, which can further compromise the kidney parenchyma. This section will cover primary VUR, while secondary VUR is discussed under the specific primary conditions.

Primary VUR accounts for 7–25% of pediatric CKD cases [6, 66, 67]. Over half of children with VUR and CKD may require renal replacement therapy by the age of 20 years, suggesting that they have a relatively poor kidney prognosis and deserve particular attention [68]. Neither medical nor surgical management can alter the function of

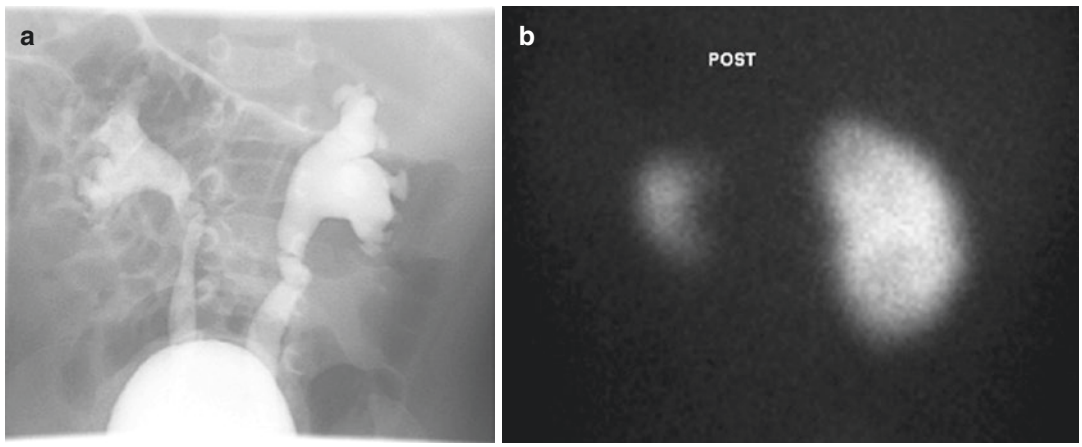

Fig. 10.5 Findings suggestive of renal dysplasia: (**a**) bilateral high-grade reflux detected in infant without a history of urinary tract infections; (**b**) DMSA scan demonstrates poor function of the left kidney moiety and photopenic defects

a dysplastic kidney, and treatment should therefore concentrate on preventing further UTI and kidney damage by early diagnosis and treatment of a febrile UTI (pyelonephritis) and correction of bladder and bowel dysfunction. Medical treatment may involve increased fluid intake, constipation management, biofeedback, bladder training, and prophylactic antibiotics.

Increased fluid intake allows for more urine production. This, in turn, increases the volume and frequency of voiding, effectively flushing the LUT and mechanically clearing out bacteria. Prophylactic antibiotics have long been held as the cornerstone of conservative management of VUR [69]. Recent large series have begun to question this conventional wisdom [70–73]. Selective use of antibiotics based on UTI risk factors is a reasonable approach.

Bladder training is helpful for children with an element of dysfunctional voiding. The process involves the education and retraining of the voiding process to achieve volitional, regular, and complete bladder emptying. Emphasis is placed on the awareness of the pelvic musculature and coordination of the detrusor muscle contraction with sphincter relaxation.

This training can be enhanced by biofeedback technology that registers and rewards the correct identification and control of pelvic musculature. The effective elimination of urine is very closely tied to the effective elimination of feces, i.e., bladder and bowel dysfunction. Active management of constipation has been shown to improve voiding dysfunction, incontinence, enuresis, urgency, and UTI frequency [74–76].

The surgical approach to the child with VUR and recurrent pyelonephritis who fails to respond to medical management is usually a graded escalation in intervention, which includes circumcision in males, endoscopic sub-ureteric injection of a bulking agent such as dextranomer/hyaluronic acid, and ureteral reimplantation. Although surgical reimplantation is more invasive than endoscopic therapy, it carries a higher overall success rate in terms of reflux correction and a lower future reflux recurrence rate. This is an important distinction when considering the child with borderline kidney function and a predisposition to recurrent, scarring UTIs. These patients may benefit from a more aggressive approach, consisting of early prophylactic circumcision and surgical reimplantation of the ureter.

As for the reflux patient with CKD who requires dialysis, the indications for medical management or surgical intervention are essentially no different from those patients with normal kidney function. One must be aware that once transplanted, these children will be immunosuppressed and have an additional kidney unit. Following kidney transplantation, UTIs may occur in children with VUR; approximately 60% of these patients experience at least one episode [77, 78]. The risk is highest in the first-year posttransplantation and then decreases over time [79]. VUR is associated with acute pyelonephritis in patients with kidney transplants, but this does not necessarily translate to kidney graft loss [79–83]. Thus, due to the increased morbidity in the setting of immunosuppression, proper evaluation should address pretransplant vesicoureteral reflux, especially in patients with a history of multiple episodes of pyelonephritis. In cases with high-grade reflux and an associated poorly functioning kidney, performing a nephroureterectomy rather than reimplantation should be considered.

Following kidney transplantation, VUR into the allograft is common and varies according to the ureteral implantation procedure used [79, 80, 84, 85]. As such, routine screening for VUR of the transplant kidney is not recommended. However, a VCUG is warranted to exclude reflux into the native or transplanted kidneys in the setting of recurrent UTI posttransplant. Treatment for posttransplant reflux-associated UTI is initially conservative. Patients who fail to improve are candidates for surgical intervention. This may involve efforts to stop the reflux or remove a poorly functioning, refluxing native kidney unit. Recently, the sub-ureteric injection of dextranomer/hyaluronic acid has gained wide acceptance as a minimally invasive method of correcting VUR. However, when compared to open reimplantation of the ureters, the success rate of ureteric injection is lower in both native and transplant kidneys. Reported reflux resolution rates in the transplant kidney following ure-

teric injection are only 29–44% [86, 87]. Similarly, surgical reimplantation has reported transient obstruction and a persistent increase in serum creatinine in 60% of reimplanted children [85]. Given the above issues, combined with the efficacy of conservative management and the concept that adult donor kidneys are less susceptible to the effects of refluxed bacteriuria, surgical intervention is rarely indicated in this patient population.

Neurogenic Voiding Dysfunction

Under normal bladder circumstances, the detrusor muscle and the sphincter complex function in a coordinated fashion, which optimizes both urine storage and emptying. During the filling phase, the detrusor muscle is relaxed and is compliant, as it fills in volume without an increase in bladder pressure. As capacity is reached, the intravesical pressure gradually rises. A full bladder is detected by stretch receptors and perceived in the central nervous system. During appropriate voiding, the sphincteric mechanism relaxes in anticipation of a coordinated detrusor contraction, expelling urine from the bladder. If voiding needs to be delayed, afferent nerves stimulate sympathetic and pudendal outflow activity, initiating the guarding reflex, which inhibits detrusor contraction and stimulates the rhabdosphincter to increase outflow resistance [88]. Disrupted innervation can lead to an alteration of this normal, coordinated interaction.

Neurogenic bladder dysfunction is an all-encompassing term that describes vesicourethral units with abnormal neural anatomy or function. Neurological lesions vary considerably in their influence on the key bladder functions of storage and emptying. Upper motor neuron lesions tend to produce a hyperreflexic bladder with sphincter dyssynergia. Lower motor neuron lesions tend to produce an areflexic bladder with variable sphincter function. Unfortunately, there are many neurological lesions that have various effects on the detrusor muscle, the striated urethral sphincter, and the smooth muscle of the bladder neck. This high variability makes classification of neurogenic voiding dysfunction difficult. As a result, popular classifications tend to focus on the dysfunction rather than on the underlying cause [89].

Wein developed a clinical classification for patients with urinary incontinence, dividing the etiology into two broad categories: a failure of storage and a failure of emptying [90]. Adequate storage requires high bladder compliance, reasonable capacity, and the absence of detrusor overactivity combined with adequate sphincteric function. Efficient emptying requires a coordinated interaction of detrusor contraction and a lowering of the outlet resistance. Four broad, simplified scenarios exist: (1) a bladder with adequate storage and an outlet with low resistance, (2) a bladder with adequate storage and an outlet with increased resistance, (3) a bladder with inadequate storage and an outlet with low resistance, and (4) a bladder with inadequate storage and an outlet with increased resistance (Fig. 10.6). With this understanding, it is not uncommon for the neurogenic bladder to be either incontinent, continent, or dyssynergic (i.e., lack of coordination between detrusor muscle and bladder outlet, resulting in outlet occlusion in response to detrusor contraction leading to dangerously elevated intravesical pressures).

Regardless of detrusor compliance, poor tone in the sphincter mechanism typically results in urinary incontinence. However, as long as the incontinence is associated with low leak point pressures, there is little risk of damage to the upper tracts. In contrast, the “hostile bladder” is found in situations of a hyperreflexic, poorly compliant, and small capacity bladder that is combined with high outlet resistance. This resistance is caused by sphincter hypertonia and detrusor-sphincter dyssynergia. In these situations, high filling and voiding pressures are transmitted to the kidney, leading to kidney dysfunction and, if not corrected (especially if associated with UTI), permanent kidney damage [91].

Following the diagnosis of neurogenic voiding dysfunction, initial management is directed at maintaining acceptable bladder storage pressures, ensuring efficient emptying, and preventing UTIs [92]. Early medical management and close monitoring are the cornerstones of a suc-

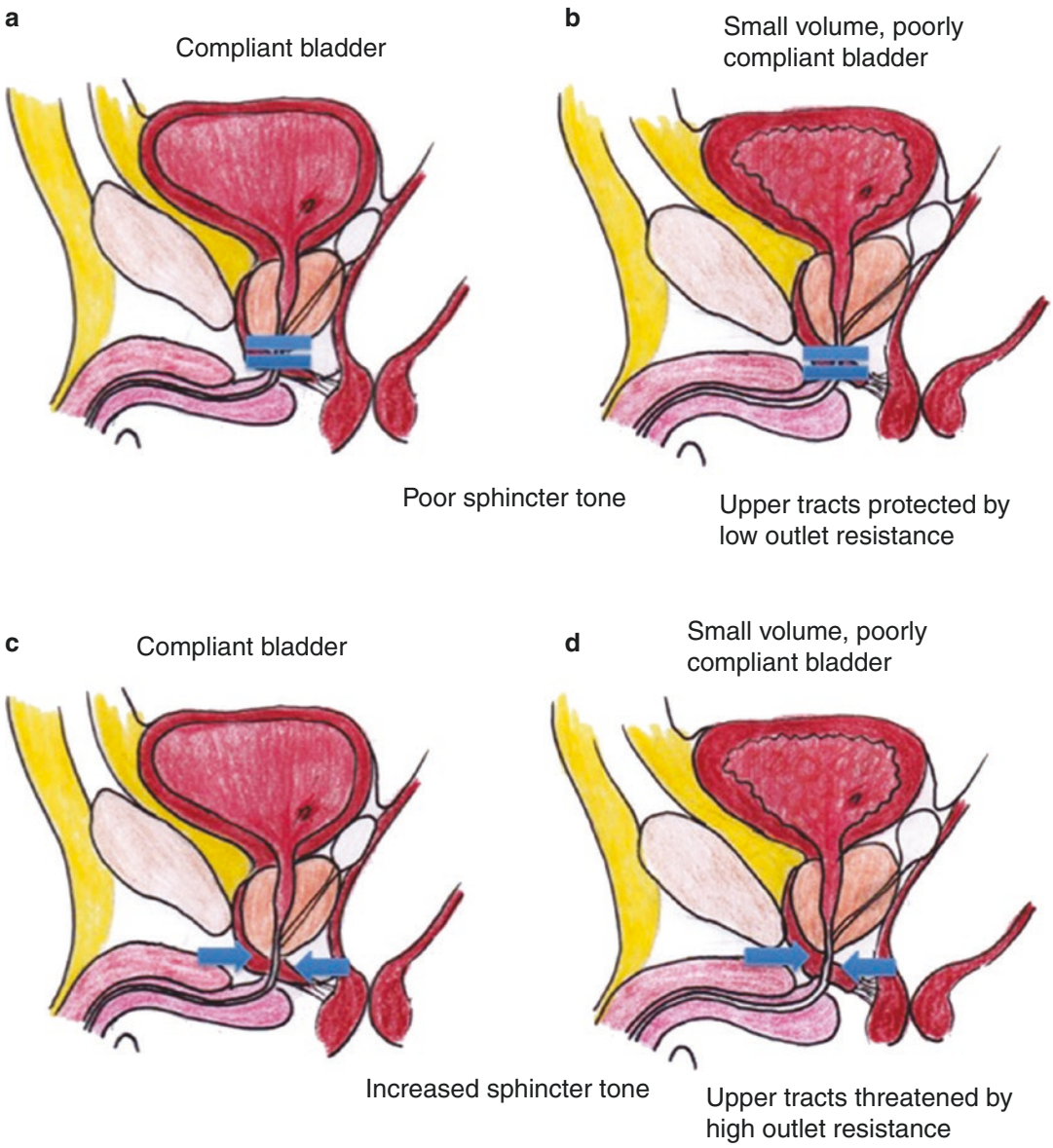

Fig. 10.6 The four broad scenarios based on bladder and sphincter functionality: (**a**) good bladder compliance with poor sphincter tone, (**b**) poor bladder compliance with poor sphincter tone, (**c**) good bladder compliance with increased sphincter tone, (**d**) poor bladder compliance with increased sphincter tone

Table 10.2 Basic concepts of management for neurogenic voiding dysfunction based on Wein's classification [90]

	Bladder	Outlet	Bypass
Facilitate storage	*Decrease tone* Bladder muscle relaxants *Increase capacity* Bladder augment	*Increase resistance* α-Agonists Mechanical compression	CIC Diversion
Facilitate emptying	*Increase bladder pressure* Trigger zones Bladder training	*Decrease resistance* α-Blockade Sphincterotomy Bladder neck disruption Urethral dilation	CIC Diversion

cessful outcome for these children. Patients vary in their need for specific medical interventions but should be managed according to their unique urodynamic dysfunction. The basic concepts of this management are outlined in Table 10.2. The majority of children with "hostile bladders" are managed with a combination of CIC to ensure regular and complete emptying [93–95]; anticholinergics to attenuate neurogenic detrusor overactivity, increase capacity, and decrease tone [96, 97]; α-blockers to decrease the sphincter muscle tone [98, 99]; and prophylactic antibiotics to prevent recurrent UTI.

Surveillance is a crucial component of the management of the neurologically impaired child. In myelodysplasia, the neurological consequences are often dynamic, with changes taking place throughout childhood but particularly at puberty when linear growth is accelerated. The entire urinary system should be screened regularly for evidence of deterioration. Ultrasound of the kidneys, ureter, and bladder is useful in detecting kidney growth failure, scarring, loss of cortico-medullary differentiation, hydronephrosis, bladder wall thickening, and significant residual bladder volumes. In the patients who are able to void, urinary flow rates may demonstrate abnormal flow curves and, combined with electromyography, may demonstrate detrusor-sphincter dyssynergia. Urodynamic studies are useful in monitoring bladder dynamics during the filling and emptying phases. Spinal MRI is indicated for the initial workup of many of these patients and may be indicated during the surveillance period when changing clinical features suggest the development of a potentially correctable cause, such as a tethered spinal cord.

If the medical management is ineffective or not tolerated, treatment will need to be escalated. Surgical strategies are mainly aimed at addressing three different issues: decreasing bladder outlet resistance, providing alternative access for catheterization, and enhancing bladder capacity and compliance. For patients in whom continence is not necessary, strategies aimed at reducing outlet resistance include urethral dilation [100, 101] and sphincterotomy (in older male patients) [102]. Vesicostomy produces an incontinent diversion, a safe and reliable method of decompressing the upper tracts in young children with neurogenic bladders [103].

When continence is the goal of treatment, bladder emptying aided by CIC through the urethra is favored. In some children, this is not feasible, as catheterization may be anatomically difficult or impossible (as seen in children with urethral strictures), poorly tolerated (in patients with a sensate urethra), or difficult to perform (related to body habitus and poor manual dexterity) [9]. These patients may benefit from a surgically constructed continent catheterizable channel, usually fashioned with the appendix (Mitrofanoff channel) or reconfigured small bowel (Monti channel) [104]. These conduits should be as short and straight as possible, to avoid catherization issues, and enter the bladder from an easily accessible, cosmetically appropriate site. Accessibility is the principal goal and is ideally determined preoperatively by the surgeon, patient, and a stoma nurse. Cosmesis is a secondary concern to function, often best achieved with the stoma placed at the umbilicus (Fig. 10.7).

Surgical interventions that augment the bladder are aimed to improve compliance, increase capacity, and decrease uninhibited detrusor contractions. Bladder augmentation with enterocystoplasty is the most commonly used technique,

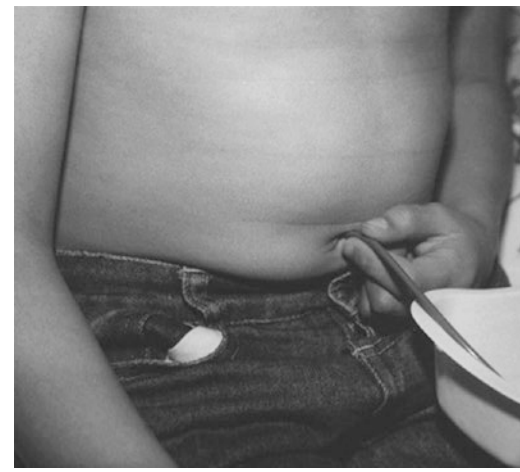

Fig. 10.7 Patient with an appendicovesicostomy (Mitrofanoff channel), performing self-catheterization through stoma located at the umbilicus

and it involves the use of a portion of the intestine that has been detubularized, reconfigured into a patch, and then sutured into the defect of a widely incised bladder. The gastrointestinal patch can be ileum or colon, but the most commonly used is the ileum, due to its preferred absorptive and secretory profile [105, 106]. Following enterocystoplasty, metabolic abnormalities may develop over time, due to the exposure of intestinal epithelium, with its absorptive and secretory characteristics, to urine. This is more clinically relevant in children with marginal kidney function.

To avoid the metabolic impact of the intestinal augments, the bladder may be augmented using tissue naturally lined by urothelium, such as the ureter. While most urothelium-lined augmentations create only modest urodynamic improvement, the best improvement is seen with the use of a dilated tortuous ureter of a poorly functioning kidney unit [107, 108]. While now uncommonly performed due to inferior results, an auto-augmentation of the bladder was proposed to excise the hypertrophied detrusor muscle, thus creating a diverticulum of bladder mucosa through the detrusor muscle, thereby increasing compliance and capacity. A summary of the advantages and disadvantages of common bladder augmentation procedures is provided in Table 10.3.

Table 10.3 A summary of the advantages and disadvantages of common augmentation procedures

Auto-augmentation
Lined by urothelium
No metabolic sequelae
No bowel harvesting
Extraperitoneal approach
Not reliable at increasing bladder volume
Ureterocystoplasty
Native ureter
Lined by urothelium
No metabolic sequelae
No bowel harvesting
Mucosa backed by muscle
Not always available
Not always sufficient
Additional exposure required (laparoscopic/open)
Colocystoplasty
Sigmoid/ileocolic
Large diameter
Reliable blood supply
Mobile segments
Ileocecal valve can be used to prevent urinary reflux
Can be tunneled
Not always available
Can impact gut function
Bowel surgery required
Absorption of urinary waste
Lifelong alkalinization required if kidney function impaired
Mucus production +++
Bladder stone and UTI risks +++
Higher perforation rate
Tumor risk
Ileocystoplasty
Preterminal ileum
Reliable blood supply and length
Most compliant bowel segment
Hyperchloremic metabolic acidosis
Mucus production ++
Bladder stone and UTI risk ++
Vitamin B12 deficiency
Tumor risk

Bladder Augmentation and End-Stage Kidney Disease

A severely dysfunctional bladder that has caused or facilitated failure of the native kidneys will put a transplanted kidney at risk. If this hostile environment is left untreated, a transplanted kidney will fail. Prior to effective reconstruction of the lower urinary tract to create a safe reservoir for urine storage, severe bladder dysfunction was a contraindication to kidney transplantation. This has allowed for a successful kidney transplantation in children with stage 5 CKD and severe LUT dysfunction.

The safety and timing of bladder augmentation in the child with ESKD in the context of kidney transplantation has been controversial [109–117]. The cumulative graft survival rates for children who underwent major LUT reconstruction seem favorable, despite the lack of standardized follow-up between cohorts [111, 113, 114, 118]. The safety of transplantation in patients with bladder augmentation has been established; however, the timing of the reconstruction in relation to the timing of the kidney transplant is debated. If bladder augmentation occurs before transplantation, adequate capacity

may not be achieved due to lack of cycling. However, if bladder augmentation occurs after transplantation, the kidney graft could be jeopardized by the abnormal functioning bladder and the healing process could be hindered by the immunosuppression.

Insight is gained from a retrospective review of three groups of transplant patients: those who underwent bladder augmentation *prior* to transplant, those who had augmentation *post*transplant, and those transplanted patients who did not require LUT reconstruction. In this cohort, graft survival and the incidence of symptomatic UTI were no different in the two augmented groups, but the non-augment group did significantly better in both outcomes. It is suggested that the increased incidence of UTI could be the cause of lower graft survival rates in the augmented groups [112]. Posttransplant sepsis rates in augmented patients may be lower with prophylactic antibiotics use or the use of stomach instead of ileum for augmentation [111, 114, 118].

In summary, major LUT reconstruction appears safe prior to kidney transplantation. It should be remembered that these bladders are inherently dysfunctional, and augmentation cannot completely negate the consequences of that dysfunction. The reconstructive procedures carry with them inherent metabolic, functional, and surgical risks that often persist throughout life. While kidney graft survival is better in children with normal bladders, children who undergo bladder reconstruction for a defunctionalized bladder are kidney transplant candidates with an acceptable increased risk.

Prune Belly Syndrome

Prune belly syndrome (PBS) is defined by three abnormalities: an absence or deficiency of abdominal wall musculature, bilateral cryptorchidism, and dilated uropathy involving the urethra, bladder, and ureters (Fig. 10.8). PBS has an incidence of 1 in 29,000 to 1 in 40,000 live births, but the etiology remains unknown [119, 120]. The complete syndrome is unique to the male patient; however, a "pseudo-prune" disorder with similar PBS pathology without the complete triad and features may occur in both males and females [121–123]. Associated pulmonary, cardiac, orthopedic, and gastrointestinal abnormalities are relatively common and contribute to overall morbidity and mortality [124]. The underlying pathology and possible clinical presentation are summarized in detail in Table 10.4 [125, 126].

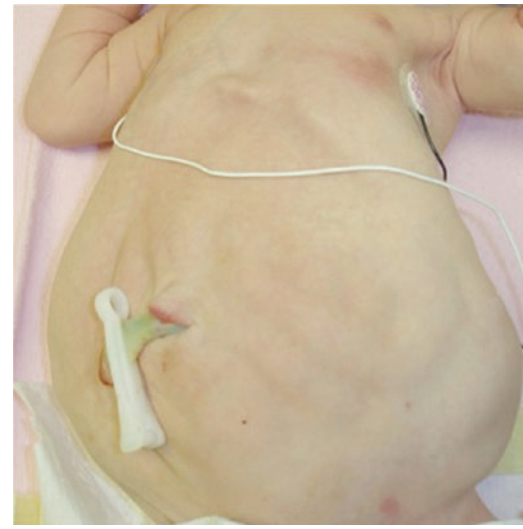

Fig. 10.8 Characteristic abdominal wall appearance in a newborn boy with prune belly syndrome

From a urological perspective, the initial workup aims to exclude obstruction, VUR, and renal dysplasia. The passage of urine in these diffusely dilated urinary tracts is usually not obstructed but is often inefficient as a consequence of gross dilation. If obstruction is present, the initial ultrasound may reveal an unusually thickened bladder wall or serial ultrasounds may reveal progressive dilation of the upper tracts. Furosemide washout studies are imperfect at diagnosing obstruction and should be interpreted with caution in the setting of gross distension. Thickening of the bladder wall should raise the suspicion of a urethral obstruction. A VCUG will define urethral and bladder anatomy, confirm VUR and, as a result, should be done early in the workup of PBS patients. Where renal dysplasia is suspected or there have been recurrent febrile UTI, a nuclear medicine scan is indicated. Imaging findings in PBS are demonstrated in Fig. 10.9.

Table 10.4 Clinical features of prune belly syndrome with pertinent urological issues highlighted

Anterior urethra	Ranges from *urethral atresia* to fusiform megalourethra Complete obstruction is lethal unless urachus is patent Variably deficient corpora cavernosa and spongiosum
Testicles	Bilaterally cryptorchid Usually intra-abdominal location Intrinsically abnormal testis with marked Leydig cell hyperplasia Increased risk of malignancy Decreased spermatogonia or azoospermia Paternity may be possible with assisted reproductive techniques
Genital conduits	Epididymal-testicular dissociation Ectopic, thickened vas deferens Seminal vesicles are usually absent or atretic but may be ectatic in some cases All contribute to infertility Retrograde ejaculation
Prostate and prostatic urethra	Prostatic hypoplasia Epithelial glandular development consistently lacking – contributes to infertility Prostatic urethra is dilated, in continuity with an open bladder neck and tapering to the membranous urethra Utricular diverticula common Hypoplastic or absent verumontanum Reflux into the vas deferens can be seen Prostatic urethral lesions are seen in 20% – poorer prognosis
Bladder	*Grossly enlarged* Trabeculation unusual Pseudo-diverticulum or urachal remnant *Urachus may be patent* Widely separated ureteric orifices due to splayed trigone and *predisposing to reflux* Open bladder neck *Efficient storage with good compliance* *Poor emptying due to hypo-contractility and VUR (CIC may be required)* *Delayed sensation to void* Instability and uninhibited contractions unusual *Requires regular assessment for altered voiding efficiency*
Ureters	*Elongated, dilated, and tortuous* Lower third more severely affected *Peristalsis present but ineffective* *True obstruction rare* *VUR present in 85%*
Kidneys	*Variable renal dysplasia* *Hydronephrosis* May have hydronephrosis without renal dysplasia Ureteropelvic junction obstruction has been reported
Abdominal wall	*Variable deficiency of underlying anterior abdominal wall muscle* Transversus abdominus most affected followed by infraumbilical rectus, internal oblique, external oblique, and the supraumbilical rectus abdominus Can cause developmental delay due to axial instability (sitting and walking) Can predispose to constipation and pneumonia as a result of poor Valsalva

As with many syndromes, PBS represents a spectrum of disease with a wide range of impairment due to the underlying congenital abnormalities. As a consequence, management must be individualized. It is useful to consider the child with PBS as fitting into three broad categories as outlined by Woodard [127] (Table 10.5). Category 1 children have severe pulmonary and renal dysplasia and have a very poor prognosis. The outcome is largely determined by pulmonary function and possible associated cardiac defects. Urological manage-

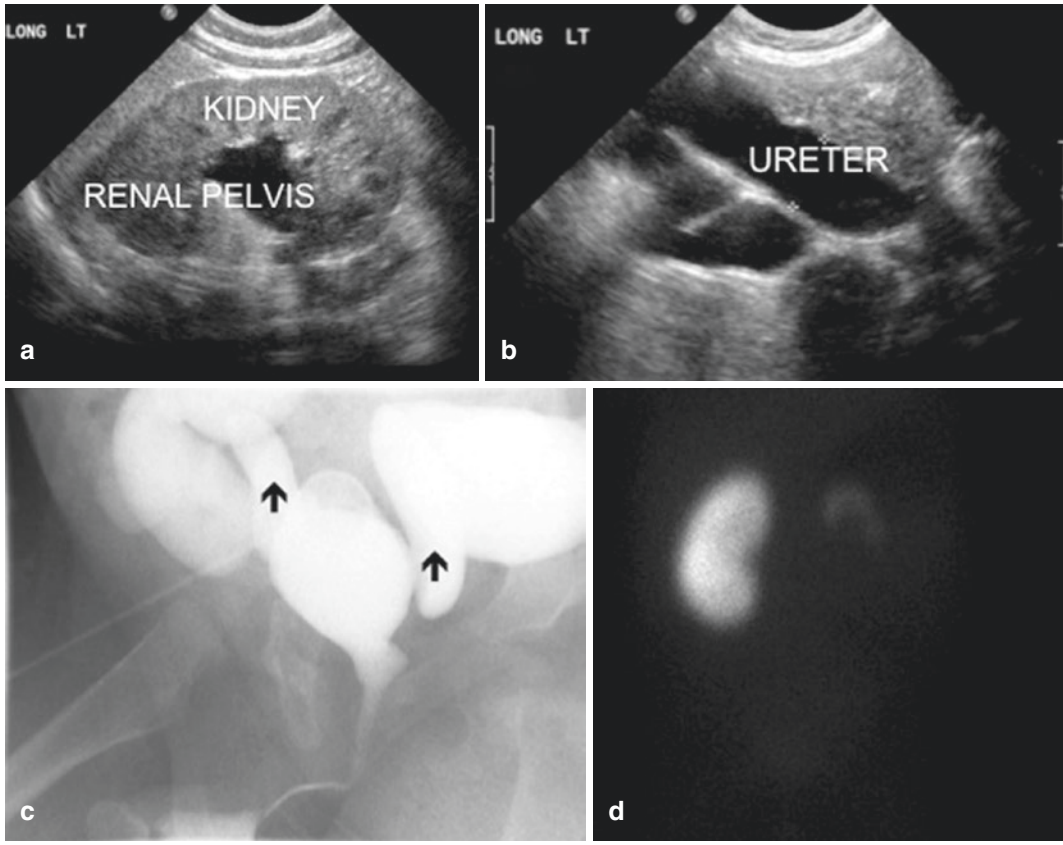

Fig. 10.9 Imaging studies in a patient with prune belly syndrome: (**a**, **b**) hydroureteronephrosis with dilated and tortuous ureter; (**c**) VCUG after vesicostomy creation demonstrating bilateral high-grade reflux into dilated distal ureters (*arrows*); (**d**) posterior view of a DMSA scan demonstrating poor right kidney differential function

Table 10.5 Outcomes of prune belly syndrome based on salient features and Woodard category

Category	Salient features	Outcome
1	Severe renal dysplasia Pulmonary hypoplasia	Few survive beyond neonatal period
2	Mild to severe renal dysplasia No pulmonary hypoplasia	Survival with variably impaired kidney function
3	No renal dysplasia No pulmonary hypoplasia	Excellent prognosis, provided upper tracts are protected

ment should aim to identify obstructing uropathy and may involve diverting the upper tracts, if appropriate for the individual patient. Category 2 patients tend to have no immediate threat to life, but kidney dysfunction is significant. Baseline kidney function must be monitored and optimized. Management should involve a multidisciplinary team with active participation of pediatric nephrologists and urologists. The structural integrity of the kidney tracts must be regularly assessed, and conditions that threaten the kidneys need to be identified and treated early. Category 3 patients demonstrate good kidney function despite their grossly dilated urinary tracts. Their prognosis is good because they lack renal dysplasia, but they still require close monitoring for signs of deteriorating kidney or urinary tract function.

Management of these complex patients is aimed at delaying the onset of kidney failure. It should include prophylactic antibiotics, because of the potential for high-grade VUR and urinary stasis. Timed voiding, double voiding, and CIC, when necessary, are recommended to facilitate complete bladder emptying. Pyelostomies, ureterostomies, or vesicostomies are unusual interventions that may be required to divert the urinary stream proximal to an obstruction or poorly draining segment. Early orchidopexies are indicated to optimize spermatogenic potential and facilitate testicular examination. Abdominoplasty, where necessary, improves psychosocial well-being and has recently been shown to improve pulmonary function, defecation, and voiding efficiency [128, 129]. The timing of and indication for the above interventions vary with each patient and institutional protocols.

The goal of management in PBS is preservation of kidney function, prevention of UTI, and management of the testes. There is debate on the optimal management of children with PBS, varying from conservative to aggressive early surgery. Aggressive reconstruction involves simultaneous and early (3 months to 1 year of age) resection, tapering and reimplantation of the ureters, bilateral transabdominal orchidopexy and abdominoplasty and may include reduction cystoplasty or resection of the urachal diverticulum [130]. With the lack of a clear benefit in bladder capacity or voiding efficiency, reduction cystoplasty is not recommended by all proponents of the more aggressive approach [131, 132]. Conversely, the conservative approach argues that surgery cannot improve baseline kidney function; instead, it should be reserved for those patients in whom obstruction, stasis, or reflux cause dysfunction [129, 133].

Despite proper management of children with PBS, some will progress to ESKD. In this event, PBS is not a contraindication to either peritoneal dialysis (PD) or kidney transplantation. While PD does pose some unique challenges with respect to anchoring the PD catheter to the attenuated abdominal wall [134], it is successful at temporarily replacing kidney function. Kidney transplantation in children with PBS has not shown a statistically significant difference in graft or patient survival [135, 136].

Urological Issues in the Pretransplant Workup

Unlike adult patients, pediatric transplant recipients often have urological issues that have caused or contributed to their kidney failure. It is therefore imperative that the pediatric urologist is integrally involved in the pretransplant workup and optimization of the evaluation of these patients. The pretransplant assessment is aimed at identifying those factors that may complicate transplant surgery, as well as those factors that pose a potential threat to graft or patient survival following transplantation. These factors include previous surgeries and existing stomas, a history of a hypercoagulable state or inguinal vascular access (Fig. 10.10), and, in the case of a living donor, the kidney and vascular anatomy of the donor allograft. All this information is necessary for planning the surgical approach, including the side and site of the transplant vascular anastomosis. With particular relevance to nephrectomy, the need for simultaneous or pretransplant procedures should be established and well-coordinated prior to the procedure.

The anatomy and functioning of the bladder and its outflow tract must be assessed for factors that could compromise postoperative graft survival. If there is voiding dysfunction or features of a hostile bladder, these need to be addressed prior to transplantation. In the case of a defunctionalized bladder or a bladder of an oliguric patient, it is important to ascertain the relative likelihood of underlying bladder dysfunction. Generally, a normal bladder that has been defunctionalized by diversion or anuria will reestablish normal function over time. This contrasts with the dysfunctional bladder that could threaten the survival of the allograft if not addressed prior to surgery. In this regard, pretransplant undiversion or bladder cycling via urethral or suprapubic catheter has been suggested as an important diagnostic step in the workup of these patients.

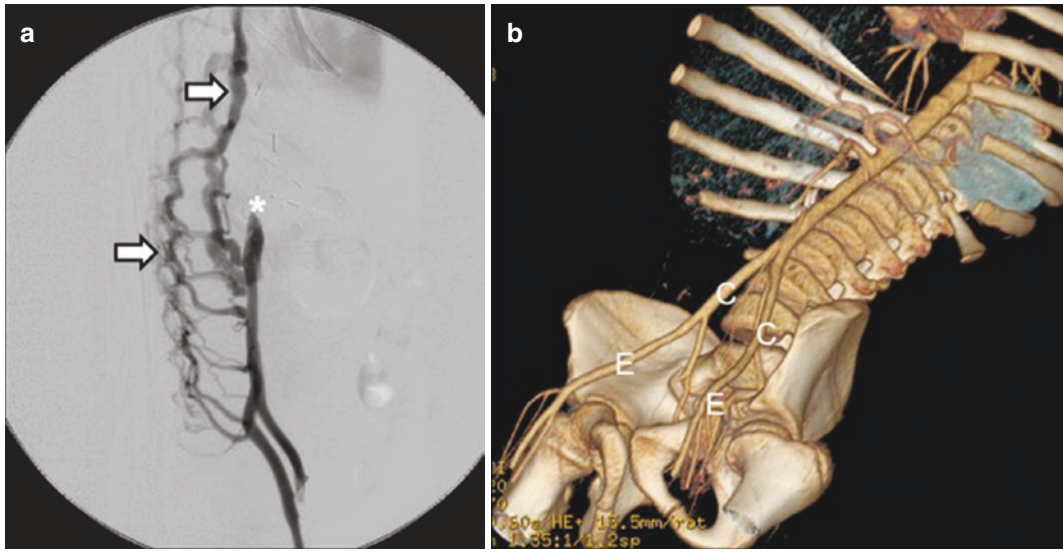

Fig. 10.10 Imaging studies used to further evaluate abdominopelvic vascular anatomy following abnormal Doppler ultrasound screening: (**a**) Venogram demonstrating occluded inferior vena cava (*) with prominent collaterals into lumbar veins and the azygos system (*arrows*). (**b**) CT scan reconstruction of arterial phase demonstrating acceptable targets for transplantation at the level of common (c) and external (e) iliac arteries

Conditions predisposing the immunosuppressed patient to infection could compromise patient survival. VUR into the native kidneys or the allograft has been associated with an increased incidence of UTI in graft recipients [79, 82]. This is especially true of patients with underlying voiding dysfunction and those with high-grade reflux (grade IV–V) [67, 82]. Basiri found that preemptive ureteral reimplantation failed to reduce the risk of infection in patients with VUR who underwent transplantation. However, a subset analysis of patients with high-grade reflux did show a reduction in the incidence of UTI. Based on this observation, Basiri suggested that patients with high-grade reflux into native kidneys should be considered for pretransplant, anti-reflux surgery, or nephrectomy.

Among the many possible investigations of the potential transplant recipient's urinary tract, not all need be routinely performed. Urologic workup should be individualized with studies chosen according to their ability to define relevant anatomical or functional abnormalities. An ultrasound of the kidneys, ureters, and bladder is a very commonly performed, noninvasive investigation that will detect abnormalities in structure or position of the kidneys. A VCUG is indicated in patients with underlying urological abnormalities or where VUR was suspected. Additionally, the VCUG can assess bladder capacity, anatomy, and emptying efficiency. Where voiding dysfunction is suspected, a urinary flow rate with or without electromyography can be done. Urodynamic studies are indicated if abnormal bladder function is suspected based on underlying pathology, preceding surgical interventions, or present clinical evidence. Computerized tomography would be indicated if native kidney tumors or stones were suspected. Doppler ultrasound of the pelvic and abdominal vasculature is performed to confirm normal vascular anatomy where doubt of its patency exists.

Nephrectomy

As a general rule, the kidneys of a stage 5 CKD patient should not be removed prior to transplantation. Even poorly functioning kidneys can provide a valuable homeostatic adjunct to dialysis. However, there are several situations in which nephrectomy is indicated (Table 10.6).

Table 10.6 Indications for pretransplant nephrectomy

Pathology	Systemic impact
Hypertension	Lifelong antihypertensive medication Potential for end-organ dysfunction
Proteinuria	Immunosuppression Hypercoagulable state Malnutrition
Infection	Urinary infections Kidney parenchymal infections (fungal infection)
Polyuria	Dehydration Electrolyte abnormalities Inefficient voiding
Kidney calculi	Pain Infections
Neoplastic potential	Recurrence after previous partial nephrectomy Genetic predisposition to kidney malignancies (Beckwith Wiedemann)
Mass effect	Lack of space for the allograft Lack of peritoneal domain for peritoneal dialysis

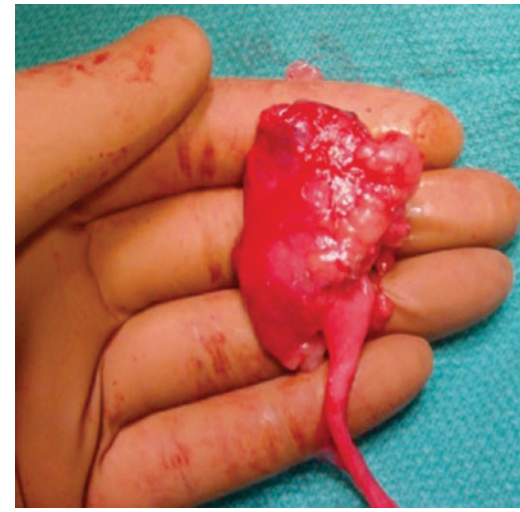

Fig. 10.11 A small atrophic kidney removed laparoscopically in a patient with stage 5 CKD and renin-mediated hypertension, performed in preparation for kidney transplantation, with improvement in blood pressure control

Renin-dependent hypertension is common to focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome, reflux nephropathy, and cystinosis. Pretransplant nephrectomy may be indicated in these patients, as steroid medication and fluid overload could precipitate malignant hypertension in the postoperative period. In these particular children, nephrectomy is often curative and can obviate the need for long-term antihypertensive therapy (Fig. 10.11). Additionally, the vasoactive effects of hyperreninemia may decrease perfusion of the grafted kidney in the immediate postoperative period. Persistent proteinuria can lead to malnutrition, hypercoagulable states, and immune suppression. It can also confound the significance of proteinuria in the posttransplant urine. If the proteinuria is clinically significant, bilateral nephrectomy is indicated. Intractable polyuria can cause dehydration, electrolyte abnormalities, and urinary tract dysfunction and, if present, is an indication for nephrectomy [137]. High-grade native VUR not only predisposes to UTI but can also cause bladder dysfunction as refluxed urine drains into the bladder post void, causing high residual volumes and decreasing functional bladder capacity. If this is the case, nephrectomy with ureterectomy is curative. Prior to excising the ureters, one should exclude the need for a future bladder augmentation, as massively dilated ureters are an ideal material for augmentation cystoplasty. Tuberculosis, xanthogranulomatous pyelonephritis, and fungal infections are just some of the chronic or recurrent infections that are best treated with excision of the entire kidney unit ahead of immunosuppressive therapy. The kidney that is predisposed to symptomatic stone formation should also be removed. The risk of malignancy is an unusual indication for unilateral or bilateral nephrectomy. It is encountered in situations where genetic disorders predispose to malignancy (e.g., Denys-Drash and Beckwith Wiedemann syndromes). Where a partial nephrectomy has been performed for malignancy, the remnant parenchyma should be removed before transplantation. Nephrectomy is further indicated in the case of multicystic dysplastic kidneys with significant parenchyma or demonstrable growth of the remnant [138]. Rarely one sees large, pathological kidneys that produce a significant mass effect. These kidneys may need to be removed to make space for the donor kidney or to facilitate PD (Fig. 10.12).

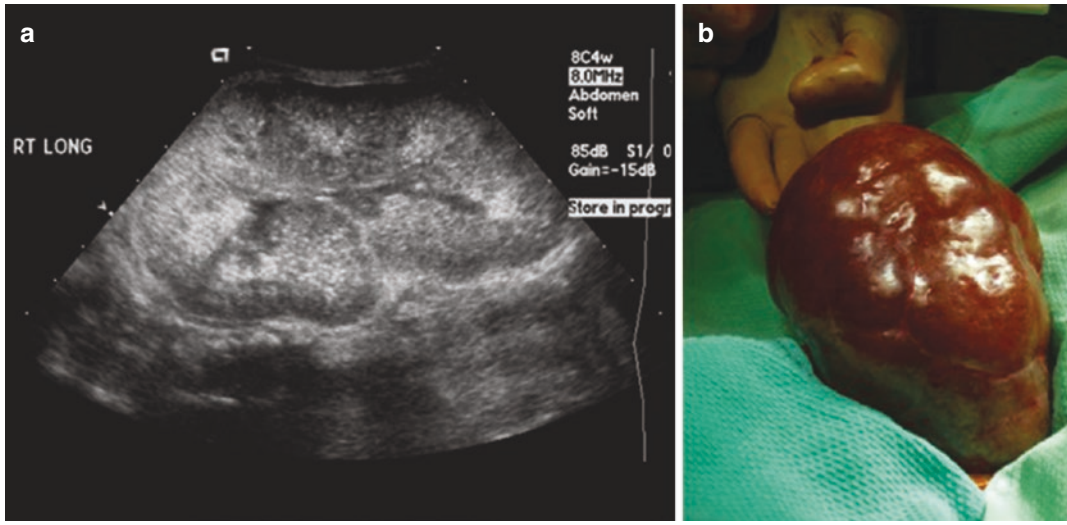

Fig. 10.12 Large kidney removed from patient with autosomal recessive polycystic kidney disease due to inability to effectively carry out peritoneal dialysis. Patient subsequently received a deceased donor kidney transplantation. Notice large size of the native kidney on ultrasound (**a**) and at the time of open nephrectomy (**b**, compare size to surgeon's hand in the background)

When nephrectomy is being considered in the child with ESKD, one must take many factors into account. In practice, the balance between the severity of native kidney dysfunction and the relative contribution of these failing kidneys to the management of the patient often dictates timing and staging of nephrectomy. The likely time to transplantation and the possible need for PD should be included in any decision-making.

Once the decision to perform nephrectomy has been made, the operational approach and technique are considered next. The nephrectomy can either be done laparoscopically or as an open procedure. The surgical approach can be transperitoneal or retroperitoneal. The technique and approach should be tailored to the individual patient and the relative skills of the surgical team. The goal is to have the safest, most efficient, least invasive operation that aims to preserve as much of the peritoneal domain as possible [137, 139, 140].

Any surgery is subject to complications, and nephrectomy is no different. CKD and dialysis can both predispose to perioperative bleeding. Immunosuppressive therapy can predispose to infections in the immediate postoperative period. Bowel injuries have been reported following nephrectomy, as have infections of incision sites. Some kidneys are notoriously difficult to remove (polycystic kidneys, chronic parenchymal infection/inflammation) and are often approached with an open technique to avoid the higher than usual complication rates that can be seen when minimally invasive techniques are used [141, 142].

Inguinal Hernias and Peritoneal Dialysis

The incidence of inguinal hernias developing in children while on PD ranges from 8% to 30%. The incidence is highest in patients under 2 years of age. Most of the hernias will develop within 3 months of the initiation of PD [143].

The persistence of a patent processus vaginalis is found in 90% of neonates and predisposes them to the development of an indirect inguinal hernia [144]. The processus vaginalis tends to close spontaneously during childhood, and with this, the incidence of inguinal hernia drops. PD, however, creates an abnormal peritoneal fluid volume and consequently an increase in hydrostatic pressure within the peritoneal cavity. This

pressure is amplified in sitting or ambulatory patients and is capable of exposing any weakness or potential space that exists in previous incisions, the umbilical remnant, or the inguinal canals and is the most likely factor accounting for the higher incidence of inguinal, umbilical, and incisional hernias in PD patients [145]. Management of the inguinal hernia in the patient on PD depends on the surgical approach of the managing physicians. Preemptive diagnosis and prophylactic ligation of the patent processus vaginalis is easily performed at laparoscopic catheter insertion and safely eliminates the problem before PD begins. However, many surgeons use an open technique for catheter insertion that does not allow for visualization of the internal ring. In this case, one simply waits for the development of a hernia before repairing it via a standard inguinal approach. When suspicion of a hernia exists in a patient who is receiving PD, ultrasound and peritoneography can be effective at confirming the diagnosis prior to any surgical intervention [146]. Inguinal hernias are usually hydroceles (fluid hernia), but because there is always a risk of bowel herniation and incarceration, herniotomy is advocated. While timing of hernia repair is determined by the relative risk of bowel incarceration and the health of the patient, it should not be unduly delayed. While waiting for surgery, the patients and their families should be educated on the features of an incarcerated hernia, so they can identify the problem and respond appropriately, should it occur. Because of the high incidence of recurrent inguinal hernias in young children on PD, the internal ring should be actively reinforced in addition to the standard high ligation of the hernia sac. Bilateral herniotomies should be performed in all cases because of the relatively high risk of developing a contralateral hernia [147, 148].

Stomas, Catheters, Vascular Access, and Incisions

Children with CKD frequently require multiple surgeries. Operations common to this group include ureteric reimplantation (Pfannenstiel incision), nephrectomy (bilateral flank incisions), bladder augmentation (midline lower abdominal incision), PD catheter placement (paramedian incision), hernia repair (inguinal/umbilical incisions), ventriculoperitoneal shunt placement (horizontal upper quadrant), and kidney transplantation (Gibson/curved iliac fossa incision). In conjunction with this, they often require stomas (colostomy or vesicostomy). Catheterizable channels for bladder drainage or bowel irrigation are commonly placed in the iliac fossae or umbilicus (Fig. 10.13). Some children may have gastrostomy tubes in the epigastrium. The issue that arises from the multitude of possible surgeries that these patients undergo is the need for careful preoperative planning and careful consideration of the follow-up management that may be required. The potential for stomas to be too close to PD catheters or to be placed in the path of ideal surgical incision lines is high if they are not well planned. There is the potential to devascularize segments of the abdominal wall if care is not taken to avoid intersecting and parallel, horizontal incisions. Phlebotomy, temporary intravenous access, and hemodialysis catheters should avoid the groin vessels if possible, as a small but significant number of patients will have obliterated iliac vasculature secondary to these interventions. This can make the vascular anastomosis at the time of transplant difficult or impossible, necessitating an alternate site for the implantation of the donor kidney.

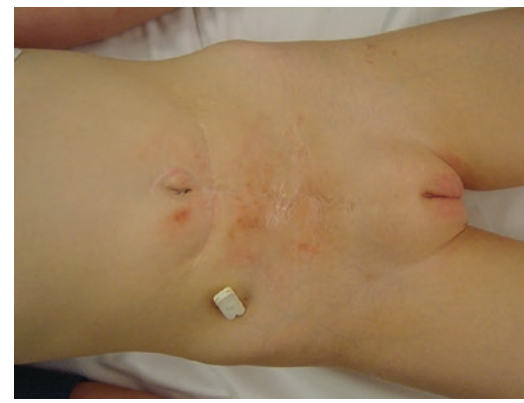

Fig. 10.13 The scarred lower abdomen of a patient with CKD following multiple surgical interventions

Summary

Pediatric patients with CKD and underlying urological issues are uniquely challenging and are ideally suited to management by a multidisciplinary team. It is unusual in modern medicine to find urological issues destroying normal kidneys. It is far more common that kidney dysfunction preexists as part of, or secondary to, early fetal urological pathology. Despite fetal interventions, congenital kidney dysfunction cannot be significantly altered. This restricts the treatment options prolonging native kidney function by optimizing urinary drainage, preventing urinary infection and reducing bladder and kidney pressures. Many patients will require surgical interventions to achieve these goals. Early urological management may have lifelong implications to slow and prevent the need for future renal transplantation.

References

1. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27(3):363–73.
2. Orr NI, McDonald SP, McTaggart S, Henning P, Craig JC. Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. Pediatr Nephrol. 2009;24(9):1719–26.
3. Chua A, Cramer C, Moudgil A, Martz K, Smith J, Blydt-Hansen T, et al. Kidney transplant practice patterns and outcome benchmarks over 30 years: the 2018 report of the NAPRTCS. Pediatr Transplant. 2019;23(8):e13597.
4. Deleau J, Andre JL, Briancon S, Musse JP. Chronic renal failure in children: an epidemiological survey in Lorraine (France) 1975-1990. Pediatr Nephrol. 1994;8(4):472–6.
5. Neu AM, Ho PL, McDonald RA, Warady BA. Chronic dialysis in children and adolescents. The 2001 NAPRTCS Annual Report. Pediatr Nephrol. 2002;17(8):656–63.
6. Ardissino G, Dacco V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003;111(4 Pt 1):e382–7.
7. Chesney RW, Brewer E, Moxey-Mims M, Watkins S, Furth SL, Harmon WE, et al. Report of an NIH task force on research priorities in chronic kidney disease in children. Pediatr Nephrol. 2006;21(1):14–25.
8. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. Pediatr Nephrol. 2003;18(8):796–804.
9. de Jong TP, Chrzan R, Klijn AJ, Dik P. Treatment of the neurogenic bladder in spina bifida. Pediatr Nephrol. 2008;23(6):889–96.
10. Kari JA. Neuropathic bladder as a cause of chronic renal failure in children in developing countries. Pediatr Nephrol. 2006;21(4):517–20.
11. Kari JA, Safdar O, Jamjoom R, Anshasi W. Renal involvement in children with spina bifida. Saudi J Kidney Dis Transpl. 2009;20(1):102–5.
12. DeFoor W, Clark C, Jackson E, Reddy P, Minevich E, Sheldon C. Risk factors for end stage renal disease in children with posterior urethral valves. J Urol. 2008;180(4 Suppl):1705–8. discussion 8
13. Dik P, Klijn AJ, van Gool JD, de Jong-de Vos van Steenwijk CC, de Jong TP. Early start to therapy preserves kidney function in spina bifida patients. Eur Urol. 2006;49(5):908–13.
14. Coulthard MG, Keir MJ. Reflux nephropathy in kidney transplants, demonstrated by dimercaptosuccinic acid scanning. Transplantation. 2006;82(2):205–10.
15. Strand WR. Initial management of complex pediatric disorders: prunebelly syndrome, posterior urethral valves. Urol Clin North Am. 2004;31(3):399–415, vii.
16. Marra G, Oppezzo C, Ardissino G, Dacco V, Testa S, Avolio L, et al. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J Pediatr. 2004;144(5):677–81.
17. Roth KS, Koo HP, Spottswood SE, Chan JC. Obstructive uropathy: an important cause of chronic renal failure in children. Clin Pediatr (Phila). 2002;41(5):309–14.
18. Woolf AS, Thiruchelvam N. Congenital obstructive uropathy: its origin and contribution to end-stage renal disease in children. Adv Ren Replace Ther. 2001;8(3):157–63.
19. Casale AJ. Early ureteral surgery for posterior urethral valves. Urol Clin North Am. 1990;17(2):361–72.
20. Thomas DF, Gordon AC. Management of prenatally diagnosed uropathies. Arch Dis Child. 1989;64(1 Spec No):58–63.
21. Tsingoglou S, Dickson JA. Lower urinary obstruction in infancy. A review of lesions and symptoms in 165 cases. Arch Dis Child. 1972;47(252):215–7.
22. Jesus LE, Pippi Salle JL. Pre-transplant management of valve bladder: a critical literature review. J Pediatr Urol. 2015;11(1):5–11.
23. Roth KS, Carter WH Jr, Chan JC. Obstructive nephropathy in children: long-term progression after relief of posterior urethral valve. Pediatrics. 2001;107(5):1004–10.
24. Holmdahl G, Sillen U. Boys with posterior urethral valves: outcome concerning renal function, bladder function and paternity at ages 31 to 44 years. J Urol. 2005;174(3):1031–4; discussion 4.
25. Ansari MS, Gulia A, Srivastava A, Kapoor R. Risk factors for progression to end-stage renal disease

in children with posterior urethral valves. J Pediatr Urol. 2010;6(3):261–4.
26. Warren J, Pike JG, Leonard MP. Posterior urethral valves in Eastern Ontario - a 30 year perspective. Can J Urol. 2004;11(2):2210–5.
27. Smith GH, Canning DA, Schulman SL, Snyder HM 3rd, Duckett JW. The long-term outcome of posterior urethral valves treated with primary valve ablation and observation. J Urol. 1996;155(5):1730–4.
28. Welsh A, Agarwal S, Kumar S, Smith RP, Fisk NM. Fetal cystoscopy in the management of fetal obstructive uropathy: experience in a single European centre. Prenat Diagn. 2003;23(13):1033–41.
29. Johnson MP, Bukowski TP, Reitleman C, Isada NB, Pryde PG, Evans MI. In utero surgical treatment of fetal obstructive uropathy: a new comprehensive approach to identify appropriate candidates for vesicoamniotic shunt therapy. Am J Obstet Gynecol. 1994;170(6):1770–6; discussion 6-9.
30. Farrugia MK, Braun MC, Peters CA, Ruano R, Herndon CD. Report on The Society for Fetal Urology panel discussion on the selection criteria and intervention for fetal bladder outlet obstruction. J Pediatr Urol. 2017;13(4):345–51.
31. Ruano R, Sananes N, Wilson C, Au J, Koh CJ, Gargollo P, et al. Fetal lower urinary tract obstruction: proposal for standardized multidisciplinary prenatal management based on disease severity. Ultrasound Obstet Gynecol. 2016;48(4):476–82.
32. Nassr AA, Shazly SAM, Abdelmagied AM, Araujo Junior E, Tonni G, Kilby MD, et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;49(6):696–703.
33. Holmes N, Harrison MR, Baskin LS. Fetal surgery for posterior urethral valves: long-term postnatal outcomes. Pediatrics. 2001;108(1):E7.
34. McLorie G, Farhat W, Khoury A, Geary D, Ryan G. Outcome analysis of vesicoamniotic shunting in a comprehensive population. J Urol. 2001;166(3):1036–40.
35. Salam MA. Posterior urethral valve: outcome of antenatal intervention. Int J Urol. 2006;13(10):1317–22.
36. Freedman AL, Johnson MP, Smith CA, Gonzalez R, Evans MI. Long-term outcome in children after antenatal intervention for obstructive uropathies. Lancet. 1999;354(9176):374–7.
37. Georgieva M, Thieme M, Pernice W, Trobs RB. Urinary ascites and perirenal urinoma - a renoprotective "Complication" of posterior urethral valves. Aktuelle Urol. 2003;34(6):410–2.
38. Rittenberg MH, Hulbert WC, Snyder HM 3rd, Duckett JW. Protective factors in posterior urethral valves. J Urol. 1988;140(5):993–6.
39. Oliveira EA, Rabelo EA, Pereira AK, Diniz JS, Cabral AC, Leite HV, et al. Prognostic factors in prenatally-detected posterior urethral valves: a multivariate analysis. Pediatr Surg Int. 2002;18(8):662–7.
40. Mizra K, Onuora V, Al-Sowailem A. Protective factors in posterior urethral valves in Saudi children. Ann Saudi Med. 1998;18(3):263–5.
41. Kaefer M, Keating MA, Adams MC, Rink RC. Posterior urethral valves, pressure pop-offs and bladder function. J Urol. 1995;154(2 Pt 2):708–11.
42. Silveri M, Adorisio O, Pane A, Zaccara A, Bilancioni E, Giorlandino C, et al. Fetal monolateral urinoma and neonatal renal function outcome in posterior urethral valves obstruction: the pop-off mechanism. Pediatr Med Chir. 2002;24(5):394–6.
43. Mukherjee S, Joshi A, Carroll D, Chandran H, Parashar K, McCarthy L. What is the effect of circumcision on risk of urinary tract infection in boys with posterior urethral valves? J Pediatr Surg. 2009;44(2):417–21.
44. De Gennaro M, Capitanucci ML, Mosiello G, Caione P, Silveri M. The changing urodynamic pattern from infancy to adolescence in boys with posterior urethral valves. BJU Int. 2000;85(9):1104–8.
45. Emir H, Eroglu E, Tekant G, Buyukunal C, Danismend N, Soylet Y. Urodynamic findings of posterior urethral valve patients. Eur J Pediatr Surg. 2002;12(1):38–41.
46. Mitchell ME, editor Valve bladder syndrome. American Urological Association, Annual meeting of the North Central Section; 1980: Hamilton.
47. Koff SA, Mutabagani KH, Jayanthi VR. The valve bladder syndrome: pathophysiology and treatment with nocturnal bladder emptying. J Urol. 2002;167(1):291–7.
48. De Gennaro M, Capitanucci ML, Capozza N, Caione P, Mosiello G, Silveri M. Detrusor hypocontractility in children with posterior urethral valves arises before puberty. Br J Urol. 1998;81(Suppl 3):81–5.
49. Glassberg KI, Schneider M, Haller JO, Moel D, Waterhouse K. Observations on persistently dilated ureter after posterior urethral valve ablation. Urology. 1982;20(1):20–8.
50. Abdelhalim A, El-Hefnawy AS, Dawaba ME, Bazeed MA, Hafez AT. Effect of early oxybutynin treatment on posterior urethral valve outcomes in infants: a randomized controlled trial. J Urol. 2019;203:826.
51. Nguyen MT, Pavlock CL, Zderic SA, Carr MC, Canning DA. Overnight catheter drainage in children with poorly compliant bladders improves postobstructive diuresis and urinary incontinence. J Urol. 2005;174(4 Pt 2):1633–6; discussion 6.
52. Fumo MJ, McLorie GA. Management of the valve-bladder syndrome and congenital bladder obstruction: the role of nocturnal bladder drainage. Nat Clin Pract Urol. 2006;3(6):323–6.
53. Hassan JM, Pope JC, Brock JW 3rd, Adams MC. Vesicoureteral reflux in patients with posterior urethral valves. J Urol. 2003;170(4 Pt 2):1677–80; discussion 80.
54. Priti K, Rao KL, Menon P, Singh N, Mittal BR, Bhattacharya A, et al. Posterior urethral valves: incidence and progress of vesicoureteric reflux after primary fulguration. Pediatr Surg Int. 2004;20(2):136–9.
55. Cuckow PM, Dinneen MD, Risdon RA, Ransley PG, Duffy PG. Long-term renal function in the posterior

urethral valves, unilateral reflux and renal dysplasia syndrome. J Urol. 1997;158(3 Pt 2):1004–7.
56. Parkhouse HF, Barratt TM, Dillon MJ, Duffy PG, Fay J, Ransley PG, et al. Long-term outcome of boys with posterior urethral valves. Br J Urol. 1988;62(1):59–62.
57. Heikkila J, Rintala R, Taskinen S. Vesicoureteral reflux in conjunction with posterior urethral valves. J Urol. 2009;182(4):1555–60.
58. Narasimhan KL, Mahajan JK, Kaur B, Mittal BR, Bhattacharya A. The vesicoureteral reflux dysplasia syndrome in patients with posterior urethral valves. J Urol. 2005;174(4 Pt 1):1433–5; discussion 5.
59. Hoag NA, MacNeily AE, Abdi H, Figueroa V, Afshar K. VURD syndrome--does it really preserve long-term renal function? J Urol. 2014;191(5 Suppl):1523–6.
60. Hebenstreit D, Csaicsich D, Hebenstreit K, Muller-Sacherer T, Berlakovich G, Springer A. Long-term outcome of pediatric renal transplantation in boys with posterior urethral valves. J Pediatr Surg. 2018;53(11):2256–60.
61. Lopez Pereira P, Ortiz R, Espinosa L, Martinez Urrutia MJ, Lobato R, Alonso A, et al. Does bladder augmentation negatively affect renal transplant outcome in posterior urethral valve patients? J Pediatr Urol. 2014;10(5):892–7.
62. Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol. 1973;1(3):132–41.
63. Rolleston GL, Shannon FT, Utley WL. Relationship of infantile vesicoureteric reflux to renal damage. Br Med J. 1970;1(5694):460–3.
64. Roberts JA. Pathogenesis of pyelonephritis. J Urol. 1983;129(6):1102–6.
65. Roberts JA. Vesicoureteral reflux in the monkey: a review. Urol Radiol. 1983;5(3):211–7, 9.
66. Fenton S, Desmeules M, Copleston P, Arbus G, Froment D, Jeffery J, et al. Renal replacement therapy in Canada: a report from the Canadian Organ Replacement Register. Am J Kidney Dis. 1995;25(1):134–50.
67. Casale P, Grady RW, Mitchell ME, Healey P. Recurrent urinary tract infection in the post-transplant reflux nephropathy patient: is reflux in the native ureter the culprit? Pediatr Transplant. 2005;9(3):324–7.
68. Ardissino G, Avolio L, Dacco V, Testa S, Marra G, Vigano S, et al. Long-term outcome of vesicoureteral reflux associated chronic renal failure in children. Data from the ItalKid Project. J Urol. 2004;172(1):305–10.
69. Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev. 2001;(4):CD001534.
70. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW, Keren R. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. JAMA. 2007;298(2):179–86.
71. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics. 2008;121(6):e1489–94.
72. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol. 2008;179(2):674–9; discussion 9.
73. Wang ZT, Wehbi E, Alam Y, Khoury A. A reanalysis of the RIVUR trial using a risk classification system. J Urol. 2018;199(6):1608–14.
74. Hadjizadeh N, Motamed F, Abdollahzade S, Rafiei S. Association of voiding dysfunction with functional constipation. Indian Pediatr. 2009;46(12):1093–5.
75. Halachmi S, Farhat WA. The impact of constipation on the urinary tract system. Int J Adolesc Med Health. 2008;20(1):17–22.
76. Kasirga E, Akil I, Yilmaz O, Polat M, Gozmen S, Egemen A. Evaluation of voiding dysfunctions in children with chronic functional constipation. Turk J Pediatr. 2006;48(4):340–3.
77. Mathew TH, Kincaid-Smith P, Vikraman P. Risks of vesicoureteric reflux in the transplanted kidney. N Engl J Med. 1977;297(8):414–8.
78. Prat V, Horcickova M, Matousovic K, Hatala M, Liska M. Urinary tract infection in renal transplant patients. Infection. 1985;13(5):207–10.
79. Ranchin B, Chapuis F, Dawhara M, Canterino I, Hadj-Aissa A, Said MH, et al. Vesicoureteral reflux after kidney transplantation in children. Nephrol Dial Transplant. 2000;15(11):1852–8.
80. Fontana I, Ginevri F, Arcuri V, Basile G, Nocera A, Beatini M, et al. Impact of vesicoureteral reflux on graft survival in paediatric kidney transplants. Transplant Proc. 1998;30(5):2000–1.
81. Dunn SP, Vinocur CD, Hanevold C, Wagner CW, Weintraub WH. Pyelonephritis following pediatric renal transplant: increased incidence with vesicoureteral reflux. J Pediatr Surg. 1987;22(12):1095–9.
82. Basiri A, Otookesh H, Simforoosh N, Hosseini R, Hosseini-Moghaddam SM, Sharifian M. Does pre-transplantation antireflux surgery eliminate post-renal transplantation pyelonephritis in children? J Urol. 2006;175(4):1490–2.
83. Barrero R, Fijo J, Fernandez-Hurtado M, Garcia-Merino F, Leon E, Torrubia F. Vesicoureteral reflux after kidney transplantation in children. Pediatr Transplant. 2007;11(5):498–503.
84. Engelstein D, Dorfman B, Yussim A, Shmueli D, Bar Nathan N, Shaharabani E, et al. A critical appraisal of vesicoureteral reflux in long-term renal transplantation recipients: prospective study. Transplant Proc. 1997;29(1–2):136–7.

85. Neuhaus TJ, Schwobel M, Schlumpf R, Offner G, Leumann E, Willi U. Pyelonephritis and vesicoureteral reflux after renal transplantation in young children. J Urol. 1997;157(4):1400–3.
86. Cloix P, Gelet A, Desmettre O, Cochat P, Garnier JL, Dubernard JM, et al. Endoscopic treatment of vesicoureteric reflux in transplanted kidneys. Br J Urol. 1993;72(1):20–2.
87. Williams MA, Giel DW, Colleen HM. Endoscopic Deflux injection for pediatric transplant reflux: a feasible alternative to open ureteral reimplant. J Pediatr Urol. 2008;4(5):341–4.
88. Wan J, Park JM. Neurologic control of storage and voiding. In: Docimo SG, Canning DA, Khoury AE, editors. The Kelalis-King-Belman textbook of clinical pediatric urology. London: Informa Healthcare; 2007.
89. Neveus T, von Gontard A, Hoebeke P, Hjalmas K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176(1):314–24.
90. Wein AJ. Classification of neurogenic voiding dysfunction. J Urol. 1981;125(5):605–9.
91. Joseph DB. Current approaches to the urologic care of children with spina bifida. Curr Urol Rep. 2008;9(2):151–7.
92. Hopps CV, Kropp KA. Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup. J Urol. 2003;169(1):305–8.
93. Kaefer M, Pabby A, Kelly M, Darbey M, Bauer SB. Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomentingocele. J Urol. 1999;162(3 Pt 2):1068–71.
94. Edelstein RA, Bauer SB, Kelly MD, Darbey MM, Peters CA, Atala A, et al. The long-term urological response of neonates with myelodysplasia treated proactively with intermittent catheterization and anticholinergic therapy. J Urol. 1995;154(4):1500–4.
95. Lapides J, Diokno AC, Silber SJ, Lowe BS. Clean, intermittent self-catheterization in the treatment of urinary tract disease. J Urol. 1972;107(3):458–61.
96. Goto M, Kato K, Kondo A, Otani T, Takita T, Kobayashi M. Clinical effects of oxybutynin hydrochloride in the treatment of unstable bladder and overactive neurogenic bladder: a long-term clinical trial. Hinyokika Kiyo. 1988;34(3):541–50.
97. Thompson IM, Lauvetz R. Oxybutynin in bladder spasm, neurogenic bladder, and enuresis. Urology. 1976;8(5):452–4.
98. Koyanagi T. Further observation on the denervation supersensitivity of the urethra in patients with chronic neurogenic bladders. J Urol. 1979;122(3):348–51.
99. Takimoto Y, Kitamura K, Fuse T, Kawazoe K, Hirano D, Amagai T, et al. Clinical effect of new alpha-adrenergic blocker on micturition disturbance of neurogenic bladder and lower urinary tract obstruction. Hinyokika Kiyo. 1983;29(2):255–63.
100. Wan J. The role of urethral dilation in managing pediatric neurogenic bladder dysfunction. Curr Urol Rep. 2009;10(2):153–8.
101. Park JM, McGuire EJ, Koo HP, Schwartz AC, Garwood CK, Bloom DA. External urethral sphincter dilation for the management of high risk myelomeningocele: 15-year experience. J Urol. 2001;165(6 Pt 2):2383–8.
102. Pan D, Troy A, Rogerson J, Bolton D, Brown D, Lawrentschuk N. Long-term outcomes of external sphincterotomy in a spinal injured population. J Urol. 2009;181(2):705–9.
103. Morrisroe SN, O'Connor RC, Nanigian DK, Kurzrock EA, Stone AR. Vesicostomy revisited: the best treatment for the hostile bladder in myelodysplastic children? BJU Int. 2005;96(3):397–400.
104. Lemelle JL, Simo AK, Schmitt M. Comparative study of the Yang-Monti channel and appendix for continent diversion in the Mitrofanoff and Malone principles. J Urol. 2004;172(5 Pt 1):1907–10.
105. Chen JL, Kuo HC. Long-term outcomes of augmentation enterocystoplasty with an ileal segment in patients with spinal cord injury. J Formos Med Assoc. 2009;108(6):475–80.
106. Gurocak S, Nuininga J, Ure I, De Gier RP, Tan MO, Feitz W. Bladder augmentation: review of the literature and recent advances. Indian J Urol. 2007;23(4):452–7.
107. Churchill BM, Aliabadi H, Landau EH, McLorie GA, Steckler RE, McKenna PH, et al. Ureteral bladder augmentation. J Urol. 1993;150(2 Pt 2):716–20.
108. Landau EH, Jayanthi VR, Khoury AE, Churchill BM, Gilmour RF, Steckler RE, et al. Bladder augmentation: ureterocystoplasty versus ileocystoplasty. J Urol. 1994;152(2 Pt 2):716–9.
109. Capizzi A, Zanon GF, Zacchello G, Rigamonti W. Kidney transplantation in children with reconstructed bladder. Transplantation. 2004;77(7):1113–6.
110. Djakovic N, Wagener N, Adams J, Gilfrich C, Haferkamp A, Pfitzenmaier J, et al. Intestinal reconstruction of the lower urinary tract as a prerequisite for renal transplantation. BJU Int. 2009;103(11):1555–60.
111. DeFoor W, Minevich E, McEnery P, Tackett L, Reeves D, Sheldon C. Lower urinary tract reconstruction is safe and effective in children with end stage renal disease. J Urol. 2003;170(4 Pt 2):1497–500; discussion 500.
112. Basiri A, Otoukesh H, Simforoosh N, Hosseini R, Farrokhi F. Kidney transplantation in children with augmentation cystoplasty. J Urol. 2007;178(1):274–7; discussion 7.
113. Fontaine E, Gagnadoux MF, Niaudet P, Broyer M, Beurton D. Renal transplantation in children with augmentation cystoplasty: long-term results. J Urol. 1998;159(6):2110–3.

114. Hatch DA, Koyle MA, Baskin LS, Zaontz MR, Burns MW, Tarry WF, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. J Urol. 2001;165(6 Pt 2):2265–8.
115. Power RE, O'Malley KJ, Khan MS, Murphy DM, Hickey DP. Renal transplantation in patients with an augmentation cystoplasty. BJU Int. 2000;86(1):28–31.
116. Rigamonti W, Capizzi A, Zacchello G, Capizzi V, Zanon GF, Montini G, et al. Kidney transplantation into bladder augmentation or urinary diversion: long-term results. Transplantation. 2005;80(10):1435–40.
117. Riley P, Marks SD, Desai DY, Mushtaq I, Koffman G, Mamode N. Challenges facing renal transplantation in pediatric patients with lower urinary tract dysfunction. Transplantation. 2010;89(11):1299–307.
118. Koo HP, Bunchman TE, Flynn JT, Punch JD, Schwartz AC, Bloom DA. Renal transplantation in children with severe lower urinary tract dysfunction. J Urol. 1999;161(1):240–5.
119. Ives EJ. The abdominal muscle deficiency triad syndrome--experience with ten cases. Birth Defects Orig Artic Ser. 1974;10(4):127–35.
120. Williams DI, Burkholder GV. The prune belly syndrome. J Urol. 1967;98(2):244–51.
121. Rabinowitz R, Schillinger JF. Prune belly syndrome in the female subject. J Urol. 1977;118(3):454–6.
122. Aaronson IA, Cremin BJ. Prune belly syndrome in young females. Urol Radiol. 1979;1(3):151–5.
123. Bellah RD, States LJ, Duckett JW. Pseudoprune-Belly syndrome: imaging findings and clinical outcome. AJR Am J Roentgenol. 1996;167(6):1389–93.
124. Ely B, Gustafson RA, Karnsakul W. Pseudoprune-belly syndrome in vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects association. Clin Gastroenterol Hepatol. 2008;6(7):e26.
125. Woods AG, Brandon DH. Prune belly syndrome. A focused physical assessment. Adv Neonatal Care. 2007;7(3):132–43; quiz 44-5.
126. DeMarco R. Prune belly syndrome. In: Holcomb GW, III MJP, editors. Ashcraft's Pediatric Surgery. 5th ed. Philadelphia, PA: Saunders. 2009;796–804.
127. Woodard JR. Prune belly syndrome. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1985. p. 805–24.
128. Smith CA, Smith EA, Parrott TS, Broecker BH, Woodard JR. Voiding function in patients with the prune-belly syndrome after Monfort abdominoplasty. J Urol. 1998;159(5):1675–9.
129. Diao B, Diallo Y, Fall PA, Ngom G, Fall B, Ndoye AK, et al. Prune Belly syndrome: epidemiologic, clinic and therapeutic aspects. Prog Urol. 2008;18(7):470–4.
130. Fallat ME, Skoog SJ, Belman AB, Eng G, Randolph JG. The prune belly syndrome: a comprehensive approach to management. J Urol. 1989;142(3):802–5.
131. Kinahan TJ, Churchill BM, McLorie GA, Gilmour RF, Khoury AE. The efficiency of bladder emptying in the prune belly syndrome. J Urol. 1992;148(2 Pt 2):600–3.
132. Bukowski TP, Perlmutter AD. Reduction cystoplasty in the prune belly syndrome: a long-term followup. J Urol. 1994;152(6 Pt 1):2113–6.
133. Hubinois P, Valayer J, Cendron J. A series of 34 cases of prune belly syndrome in children. Sem Hop. 1983;59(40):2769–77.
134. Crompton CH, Balfe JW, Khoury A. Peritoneal dialysis in the prune belly syndrome. Perit Dial Int. 1994;14(1):17–21.
135. Fontaine E, Salomon L, Gagnadoux MF, Niaudet P, Broyer M, Beurton D. Long-term results of renal transplantation in children with the prune-belly syndrome. J Urol. 1997;158(3 Pt 1):892–4.
136. Reinberg Y, Manivel JC, Fryd D, Najarian JS, Gonzalez R. The outcome of renal transplantation in children with the prune belly syndrome. J Urol. 1989;142(6):1541–2.
137. Shoma AM, Eraky I, El-Kappany HA. Pretransplant native nephrectomy in patients with end-stage renal failure: assessment of the role of laparoscopy. Urology. 2003;61(5):915–20.
138. Broyer M. What are the indications for nephrectomy, either bilateral or unilateral, prior to transplantation in children? Pediatr Nephrol. 1991;5(1):11.
139. Gundeti MS, Taghizaedh A, Mushtaq I. Bilateral synchronous posterior prone retroperitoneoscopic nephrectomy with simultaneous peritoneal dialysis: a new management for end-stage renal disease in children. BJU Int. 2007;99(4):904–6.
140. Doublet JD, Peraldi MN, Monsaint H, Tligui M, Sraer JD, Gattegno B, et al. Retroperitoneal laparoscopic nephrectomy of native kidneys in renal transplant recipients. Transplantation. 1997;64(1):89–91.
141. Keeley FX, Tolley DA. A review of our first 100 cases of laparoscopic nephrectomy: defining risk factors for complications. Br J Urol. 1998;82(5):615–8.
142. Dunn MD, Portis AJ, Elbahnasy AM, Shalhav AL, Rothstein M, McDougall EM, et al. Laparoscopic nephrectomy in patients with end-stage renal disease and autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2000;35(4):720–5.
143. von Lilien T, Salusky IB, Yap HK, Fonkalsrud EW, Fine RN. Hernias: a frequent complication in children treated with continuous peritoneal dialysis. Am J Kidney Dis. 1987;10(5):356–60.
144. White JJ, Haller JA. Groin hernia in infants and children. In: Nyphus LM, Condon RE, editors. Hernia. Philadelphia: Lippincott; 1978.

145. Aranda RA, Romao Junior JE, Kakehashi E, Domingos W, Sabbaga E, Marcondes M, et al. Intraperitoneal pressure and hernias in children on peritoneal dialysis. Pediatr Nephrol. 2000;14(1):22–4.
146. Wetherington GM, Leapman SB, Robison RJ, Filo RS. Abdominal wall and inguinal hernias in continuous ambulatory peritoneal dialysis patients. Am J Surg. 1985;150(3):357–60.
147. Khoury AE, Charendoff J, Balfe JW, McLorie GA, Churchill BM. Hernias associated with CAPD in children. Adv Perit Dial. 1991;7:279–82.
148. Tank ES, Hatch DA. Hernias complicating chronic ambulatory peritoneal dialysis in children. J Pediatr Surg. 1986;21(1):41–2.

11 Preservation of Residual Renal Function in Children Reaching End-Stage Renal Disease

Il-Soo Ha and Franz Schaefer

Introduction

In children, chronic kidney disease (CKD) progresses at a variable rate (Fig. 11.1) [1], and when renal function deteriorates below the level that cannot maintain the patient's homeostasis by conservative management, dialysis is initiated (see Chap. 6). From this point, most of the physician's concern shifts to optimal delivery of dialysis because native renal function seems to be negligible and beyond control.

However, when dialysis is initiated, patients still have some degree of residual renal function (RRF), and evidence is accumulating that RRF plays critical roles in volume control; clearance of medium- and high-molecular-weight uremic toxins and proinflammatory cytokines; and maintenance of optimal cardiovascular status, nutrition, growth, and quality of life with minimal mortality [2–4]. Hence, careful attention to preserving RRF is a crucial component in dialytic management, especially when an extended duration of dialysis is expected [5].

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Experimental and clinical investigations have not only advanced our understanding of the mechanisms underlying CKD progression before and after dialysis initiation but also revealed the risk factors predisposing to it. Based on these insights, interventional strategies aimed at slowing the progression of CKD and preserving RRF have been developed. They promise to decelerate, halt, or even reverse the disease progression at least in a subgroup of patients. In this chapter, the factors associated with deterioration of RRF and interventions to slow the rate of RRF loss are reviewed.

Measurement of RRF

RRF is assessed as a part of the dialysis adequacy assessment (see Chaps. 11 and 18). The amount of urine volume, normalized to body surface area, is the most commonly used surrogate marker of RRF. The most widely applied, and sufficiently accurate, measurement of residual GFR is the arithmetic mean of the urinary creatinine and urea clearances. Recently, serum levels of cystatin C, beta2-microglobulin, beta-trace protein, and protein-bound organic anions such as hippuric acid, indoxyl sulfate, and p-cresol sulfate have been proposed as alternative measures of RRF [6–10]. While these parameters are appealing due to the omissibility of timed urine collection and the added information regarding

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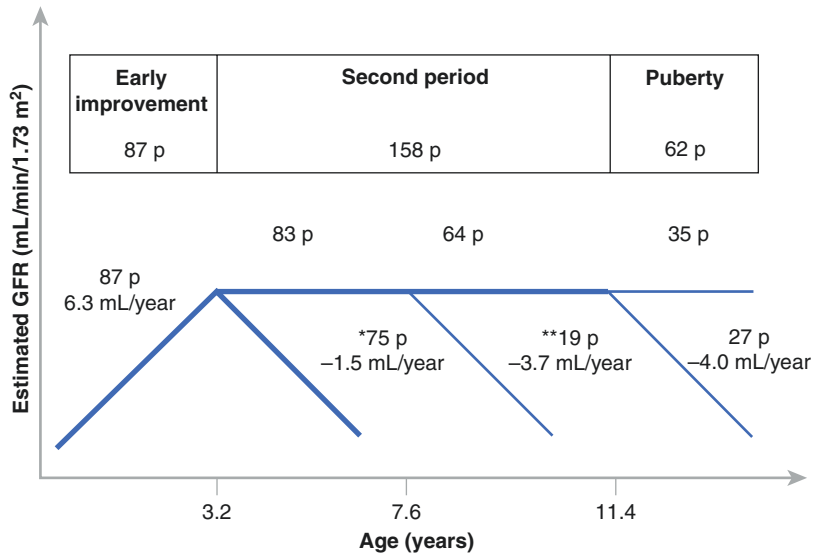

Fig. 11.1 Natural course of renal function in children with renal hypodysplasia. Early postnatal GFR increase followed by progressive deterioration after a stable interim period of variable duration. (Modified from Ref. [1])

tubular secretory function, their reproducibility, specificity and prognostic value still need to be corroborated [10, 11].

Clinical Benefits of RRF

Most studies exploring the clinical value of RRF in dialysis patients have focused on adults receiving chronic peritoneal dialysis (PD). The CANUSA study observed a correlation of dialysis adequacy as determined by small molecule clearance with patient death while on PD [12]. However, reanalysis of the CANUSA study revealed that patient *mortality* was associated with renal clearance and urine volume and not with dialytic clearance [13]. Later studies separating the effects of renal and peritoneal clearance components confirmed that patient survival is correlated with renal clearance and not with peritoneal clearance [14, 15]. The mortality of adult patients on hemodialysis (HD) has also been found to depend on the presence of RRF [16].

A recent study in adults showed a significantly closer association of patient survival with residual urine volume than with residual GFR [17], supporting the notion that *volume control* constitutes the primary link between loss of RRF and mortality. The higher overall mortality rate in anuric adults on PD is almost entirely attributable to *cardiovascular diseases* [18]. Low urine output has been associated with hypertension, left ventricular hypertrophy, and valvular calcification in both chronic PD and HD [19, 20]. Similarly, RRF is the most important single factor protecting from hypervolemia, [21], and lower residual urine volume predicts diastolic dysfunction in children on PD [22].

Hyperphosphatemia and hypercalcemia are essential mediators of the cardiovascular "toxicity" of ESRD. RRF is a crucial determinant of serum phosphate level in PD [23, 24], serum *fibroblast growth factor-23* (*FGF-23*) level in hemodialysis [25], and urinary Klotho excretion in PD patients [26]. As a consequence, anuric PD patients show a high calcium-phosphorus product [27] and may be more prone to vascular calcifications.

Also, the clearance of middle molecules critically depends on RRF. In pediatric hemodialysis patients, those with RRF had significantly lower serum levels of beta2-microglobulin [28]. In children on PD, beta2-microglobulin, cystatin C, and inulin were removed mainly by renal clearance [9].

Maintenance of adequate cardiovascular status and bone mineral metabolism with efficient removal of uremic toxins by RRF may help to maintain better *growth and nutrition* in dialyzed children. Statural growth, expressed as change in

height SDS over time, was also found to be related with RRF rather than with peritoneal solute removal [29]. In a large cohort of PD patients, serum albumin levels correlated positively with RRF [30]. In a study in children and adolescents on chronic hemodialysis, RRF positively affected nutritional status independently of dialysis efficacy and rhGH treatment [4]. RRF also correlated with *quality of life* in adult patients on both hemodialysis and PD [31–33] and serum erythropoietin levels in children [34].

General Risk Factors for Loss of Renal Function

Numerous factors have been associated with the rate of progression of CKD. The strongest evidence exists for the pathophysiological roles of blood pressure and proteinuria.

Observational data unequivocally show an association between the prevailing blood pressure and the rate of CKD progression in adults with CKD [35]. Observations in adults and children suggest that *hypertension* remains associated with loss of RRF when ESRD is reached [36–40]. Data from the NAPRTCS registry suggested that systolic hypertension predicts CKD progression also in pediatric nephropathies [41]. In a study evaluating 24-h blood pressure in children with congenital uropathies, casual systolic and mean arterial pressure at night affected the risk of progression [42]. In a recent study, visit-to-visit blood pressure variability affects RRF in adult PD patients [43].

Proteinuria is an accepted surrogate marker of CKD progression in adult nephropathies and correlates with a faster GFR decline also in children with CKD due to hypodysplasia [42, 44]. The predictive role of proteinuria was also confirmed in studies that included glomerular disorders [1] and in a pediatric prospective multicenter cohort study [46, 47]. The ESCAPE trial showed an association of proteinuria at baseline, as well as of residual proteinuria during ACE inhibition, with progression [48, 49]. Observational studies in adult patients suggest that the relationship between proteinuria and the rate of loss of RRF persists even after attainment of ESRD [37, 38, 50], providing a rationale for continued antiproteinuric treatment after initiation of dialysis. Proteinuria was also a risk factor for RRF loss in children on PD [39, 51].

The *underlying kidney disorder* is an important predictor of CKD progression. CKD with primary glomerulopathies tends to progress more rapidly than those associated with congenital anomaly of kidney and urinary tract (CAKUT) or tubulointerstitial diseases [41]. In children with ESRD on PD, the diagnosis of a glomerulopathy is a predictor of rapid RRF loss (Fig. 11.2)

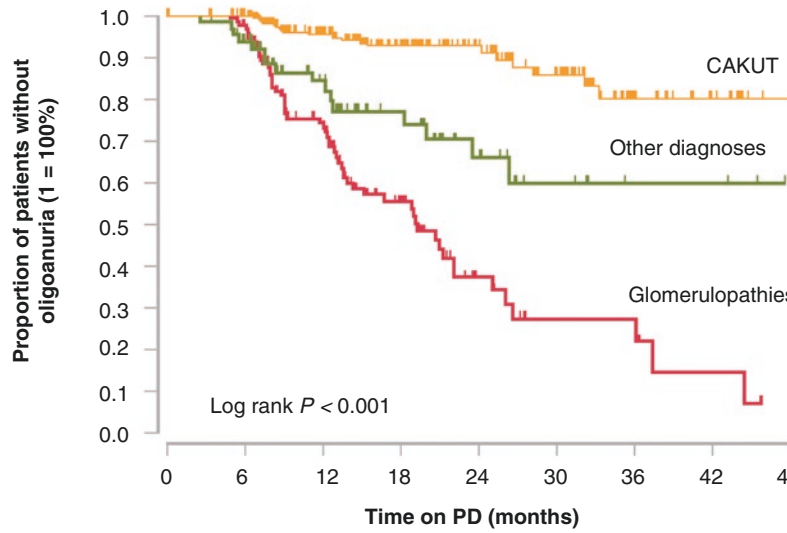

Fig. 11.2 Evolution of residual diuresis according to underlying renal diagnosis in 400 children undergoing chronic PD. (Modified from Ref. [45])

[45, 51], although this difference may not be relevant when HD patients are included [37]. In children with renal malformations, occurrence of more than two *episodes of febrile UTI* was associated with a faster decline of renal function [1].

Study results on the effect of *baseline renal impairment* on subsequent loss of renal function can be different depending on the evaluation methods and may be misunderstood as opposing each other. In adult patients on PD, an exponential rather than linear decline of RRF is observed [52, 53]. This is consistent with the finding that the RRF loss is faster when urine volume is larger and residual GFR is higher [38, 39, 54, 55]. However, when the total duration maintaining urine volume above a certain amount or the proportion of patients with residual diuresis is measured, results must be different. The children with larger urine volume at the beginning of dialysis keep their urine volume longer than those who have less baseline urine volume [45, 51, 56]. In addition, it was reported that an earlier start of PD was associated with better subsequent preservation of RRF in adult patients [57]. These apparently contradictory findings due to different methods to measure RRF actually do not conflict with each other.

Furthermore, GFR declined more rapidly in adolescent CKD patients with significant *anemia* [58]. In a randomized controlled study in adults, early administration of erythropoietin targeting at a higher hemoglobin level significantly slowed the progression of CKD [59]. Anemia and resulting tissue hypoxia may increase endothelial injury and stimulate the release of pro-fibrotic cytokines. While anemia is an apparent risk factor for loss of renal function, the loss of RRF in turn increases the likelihood of severe anemia and high EPO requirements once ESRD is reached [60, 61]. The latter phenomenon is probably explained by lower endogenous erythropoietin synthesis in patients without RRF, as evidenced by the correlation of erythropoietin serum levels with RRF observed in pediatric HD patients [34].

Some of the secondary complications of CKD may contribute independently to its progression. *Metabolic acidosis* has been identified as a risk factor for progression in adult and childhood CKD [62, 63]. In a randomized clinical trial, correction of metabolic acidosis slowed CKD progression in adults [64].

In adults, *dyslipidemia* (hypertriglyceridemia and low HDL cholesterol) appears to have a small but significant effect on the relative risk of progression [65]. Hyperlipidemia was also reported to be the risk factor of anuria in children on PD [51]. GFR declined faster in *hypoalbuminemic* patients especially in children with CKD and ESRD, but this may reflect the effect of proteinuria [51, 58, 66].

The role of mineral metabolism in the progression of renal failure is not entirely clear. *Hypocalcemia* and *hyperphosphatemia* were associated with a rapid decline of renal function in children [67, 68]. High serum calcium was also independently associated with a decreased risk of RRF loss in adult dialysis patients [69]. In another study, PD patients with no RRF showed a higher calcium–phosphorus product (Ca × P) [19]. However, it was also reported that after adjustment for baseline renal GFR, there was no significant association between calcium and phosphorus levels and the risk of anuria [70]. It was also reported that *hyperuricemia* and *hypouricemia* are related to RRF loss in adult PD patients [71, 72].

Congestive heart failure was also correlated with faster decline of RRF in adults [50, 69, 73]. In addition, a *peripheral vascular disease* assessed by low ankle-brachial index (ABI) and aortic pulse wave velocity (PWV) was associated with rapid RRF decline in adult PD patients [74–76].

Though RRF is a well-known determinant of patient's water balance as described above, on the contrary, there are reports that water balance affects RRF. In adult patients on PD, *extracellular volume overload* was associated with reduced urine volume [77, 78]. This is consistent with the finding that B-type natriuretic peptide (BNP) is a risk marker for RRF loss in PD patients [79], and volume overload and loss of RRF are supposed to compose a vicious cycle.

Rapid somatic growth and gain in body weight are associated with accelerated deterioration of renal function [42]. Patient age, reflecting body growth, is a general risk factor for progression in children [41, 42, 80]; specifically, adolescents seem to progress more rapidly than prepubertal patients. Accelerated disease progression during *puberty* has been observed in patients with CKD due to diabetes mellitus, posterior urethral valve, reflux nephropathy, and renal hypoplasia [81]. The physiological pubertal rise in blood pressure, an increased metabolic load due to statural growth which cannot be compensated by proportionate renal growth, and vascular or tissue-specific effects of sex steroids are possible mechanisms underlying these associations. On the other hand, administration of recombinant human growth hormone (rhGH), which induces body growth, was not associated with accelerated loss of renal function in children [82].

Interestingly, in adult patients on long-term dialysis, *obesity* is associated with an accelerated decline of RRF [50, 73, 83].

The role of *genetic factors* in determining the rate of renal failure progression is not yet fully understood. Whereas no gender difference has been noted in CKD and ESRD cohorts encompassing the pediatric age range [41, 66], GFR appears to decline more rapidly in adult and adolescent males [34, 58], compatible with an adverse impact of androgens (or a protective effect of female sex steroids) on the conservation of RRF in CKD. However, in children on PD, RRF was not affected by gender [45, 51].

African-American *ethnicity* is a significant risk factor of progression in pediatric CKD patients [41]. Non-white race also predicts rapid loss of RRF in adults on dialysis [69].

Increasing evidence suggests that the individual variability of CKD progression may in part be related to common *genetic and epigenetic variation.* The DD genotype, a common variant of the ACE gene, was found overrepresented in pediatric ESRD as compared to the general population [84]. This was confirmed in children with hypodysplasia, obstructive uropathy, and reflux nephropathy, but not in those with other congenital or hereditary diseases or acquired glomerular disorders [85]. Other studies suggested an association of the DD genotype with declining renal function also in pediatric glomerular diseases with normal renal function [86, 87]. Furthermore, single nucleotide polymorphisms (SNPs) in the transforming growth factor-beta1, KLK1, and vascular endothelial growth factor genes were reported to modify the risk of renal deterioration in reflux nephropathy [80, 88]. SNPs in the D-loop of mitochondrial DNA allele 146 were identified as an independent predictor of kidney survival time [89]. Glutathione-S-transferase-μ1 (GSTM1) null and apolipoprotein L-1 (APOL1) high-risk alleles were also reported to affect CKD progression with hypertension [90, 91]. Moreover, several microRNAs (miR-30d, miR-140-3p, miR-532-3p, miR-194, miR-190, miR-204, miR-206) were downregulated in renal tissues from progressive CKD [92].

Recently, a genome-wide association study (GWAS) identified several genetic variants associated with the decline of renal function in adults with CKD. SNPs in LINC00923 was associated with CKD progression and variants in genes, NAT8B, CASP9, and MUC1, with estimated GFR [93, 94]. The Pediatric Investigation for Genetic Factors Linked with Renal Progression (PediGFR) consortium identified 10 SNPs associated with estimated GFR across three large pediatric CKD cohorts [95].

Specific Risk Factors for Loss of RRF in Patients on Dialysis

RRF decreases with *time on dialysis* [69], and the loss over time is exponential rather than linear [52]. In adult patients on hemodialysis and PD, the decline of RRF was most prominent during the first 3 months after the start of dialysis [37]. Repetitive intravascular volume depletion and hypotensive events are considered important causes of a rapid loss of RRF [73].

The choice of *dialysis modality* has a crucial impact on RRF. There is ample evidence both in adults and in children that RRF is preserved better with PD than with hemodialysis [51, 56, 69, 96, 97]. A more than two times faster decline of

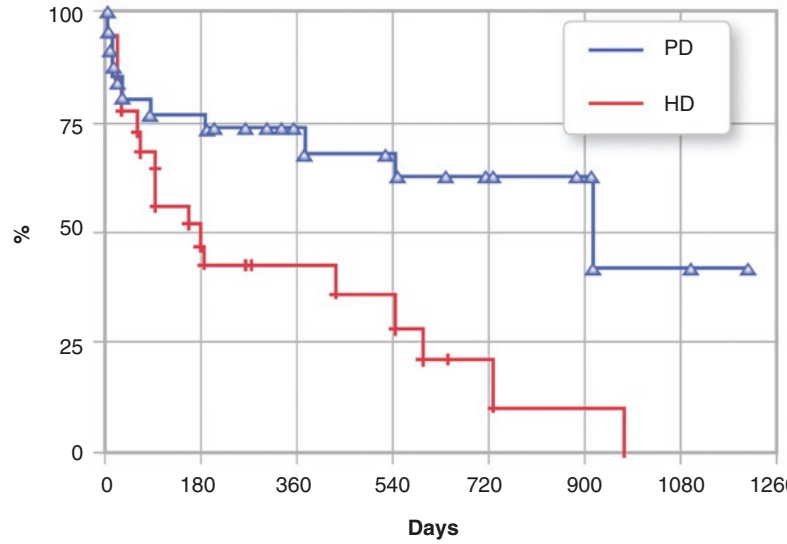

Fig. 11.3 Time to oliguria (daily diuresis <500 mL/m^2) in children with ESRD treated by peritoneal vs. hemodialysis. (Modified from Ref. [98])

RRF was observed in adult patients on HD compared to those on CAPD [69, 96]. In children, a retrospective study revealed that daily urine volume less than 500 mL/m^2 in 50% of patients was reached significantly earlier (within 175 days) after start of HD than after commencement of PD (within 916 days) (Fig. 11.3) [98]. This difference is believed to be mainly due to the rapid removal of large amounts of fluid by intermittent extracorporeal procedures, leading to acute hypotensive episodes, generalized vasoconstriction, tissue hypoperfusion, and lower preglomerular arterial pressure. In addition, the contact of blood with artificial bioincompatible membranes triggers activation of complement system and circulating leukocytes with subsequent release of nephrotoxic inflammatory mediators, which may cause a chronic state of inflammation and acceleration of fibrogenesis at the tissue level [56, 96]. In a study comparing automated PD and hemodiafiltration, automated PD was still associated with a better preservation of RRF than hemodiafiltration despite the use of biocompatible membrane and high hemodynamic stability during the procedure [99].

Though there are controversies [100–102], majority of the studies failed to reveal difference in RRF loss between automated PD and CAPD [51, 103–107]. The tidal variant of APD was reported to preserve RRF better than nontidal modalities [108].

Peritonitis frequency was associated with RRF decline in adult patients on PD [50, 52]. This observation may be explained by hypotensive episodes related to systemic infection and also to the common use of *nephrotoxic antibiotics* such as vancomycin and aminoglycosides. Whereas empirical use of aminoglycosides (usually terminated within 2–3 days) in peritonitis has not been found to affect RRF in adult patients [109, 110], administration of aminoglycoside for at least 3 days was correlated with more rapid decline of RRF [111].

Clinical Management Options to Slow CKD Progression and Preserve RRF on Dialysis

Two management principles show promise to slow down the rate of renal functional loss both in the pre-dialysis stage and when dialysis-dependent renal failure has already occurred: to avoid known and suspected risk factors for progression as much as possible and to apply renoprotective therapies.

Avoidance of Risk Factors

Half of the risk factors listed above are principally modifiable. Most of them are detrimental per se to patient health irrespective of their impact on CKD progression and should be avoided in their own right, even though direct causality has not been universally demonstrated by prospective studies. For example, strict control of hypertension, reduction of proteinuria (especially residual proteinuria during RAS blockade), correction of anemia, metabolic acidosis, hypoalbuminemia, hyperlipidemia, hypocalcemia, hyperphosphatemia, hyperuricemia, congestive heart failure, extracellular volume overload, and obesity; prevention and adequate treatment of UTI; and avoidance of nephrotoxic agents are generally recommended in patients with CKD. In addition, some knowledge of the individual profile of non-remediable risk factors is also important since patients at high risk may benefit particularly from early renoprotective intervention and minimization of remediable risk factors.

In patients in need of dialysis, PD is preferred to hemodialysis under the aspect of preserving RRF. If for some reason hemodialysis is chosen, careful monitoring of the volume status and avoidance of dehydration and hypotensive events, as well as hypertension, volume overload, and congestive heart failure, are crucial to minimize the rate of RRF loss.

Finally, the administration of nephrotoxic drugs such as aminoglycosides should be minimized, and any measures to reduce the rate of peritonitis will impact beneficially on the conservation of RRF.

Blood Pressure Control

Interventional studies aiming at lowering blood pressure in patients with CKD have provided evidence for a causative role of high blood pressure in CKD progression. The randomized controlled ESCAPE trial showed that intensified blood pressure control, with a target 24-h mean arterial pressure below the 50th percentile, confers a substantial long-term benefit on renal function in childhood CKD (Fig. 11.4) [48]. The risk of losing 50% GFR or progressing to ESRD was

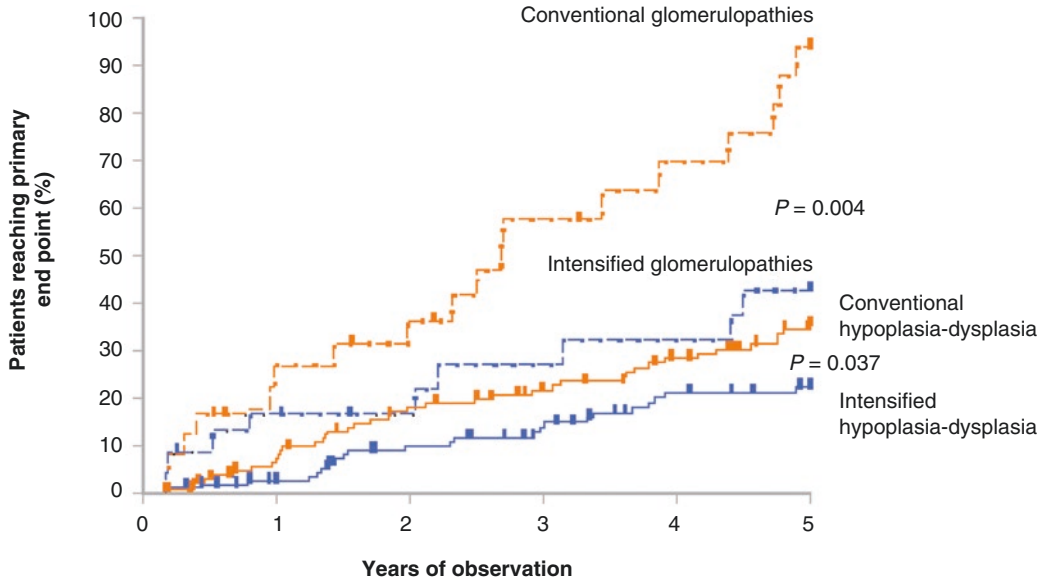

Fig. 11.4 Effect of intensified blood pressure control on renal survival in children with hypo/dysplastic and glomerular disorders receiving fixed-dose ACE inhibition. *Red lines* denote patients randomized to intensified blood pressure target (<50th 24 h MAP percentile) and *blue lines* denote those with conventional target (50–95th 24 h MAP percentile). (Modified from Ref. [48])

reduced by 35% after 5 years in the children managed by strict blood pressure control. The nephroprotective effect was significant both in children with glomerulopathies and in those with renal hypodysplasia.

RAS Inhibition

ACE inhibitors and angiotensin type-2 receptor blockers (ARB) have the potential to slow CKD progression and reduce proteinuria in patients with CKD [35]. In pediatric nephropathies, RAS antagonists reliably lower blood pressure and proteinuria [112], but uncontrolled studies in children with congenital abnormalities of the kidney and the urinary tract have yielded conflicting results as to a specific renoprotective effect of these agents [49, 113]. As in pre-end-stage CKD, there are controversial results on the effect of RAS inhibition on RRF in patients on dialysis [45, 69, 114, 115]. In a large pediatric incident PD cohort, the use of RAS antagonists was associated with a 50% increase in the risk of oligoanuria during prospective observation [45]. In a randomized controlled trial in adult PD patients, a time-dependent effect of ACE inhibition was observed; RRF declined faster and the risk of developing anuria was higher during the first 9 months, whereas RRF declined at a slower pace and anuria occurred less frequently beyond 12 months of treatment [116]. This biphasic effect of ACE inhibition may be explained by hemodynamic mechanisms reducing GFR early during treatment followed by nephroprotective antifibrogenic effects prevailing with long-term administration.

An additional renoprotective effect of add-on ARB was reported in children with CKD who were already treated with ACE inhibitors [117]. In this study, a significant but tolerable elevation of serum potassium was noted, and the benefit was noted in hemolytic uremic syndrome and reflux nephropathy but not in congenital nephrotic syndrome. However, in view of observations in adult patients indicating increased loss of renal function, hypotension, and hyperkalemia with dual blockade [118], close monitoring of these side effects is necessary. In adults, an intensive therapy combining ACE inhibitor, ARB, spironolactone, and statin was reported to slow the progression more effectively [119].

Diuretics

In adults on hemodialysis and PD, loop diuretics help maintain urine output [120–122]. We recently confirmed the beneficial effect of loop diuretics on residual diuresis in a prospective registry study of 400 non-oliguric children who commenced PD [45]. Among the 72 patients receiving furosemide from the start of dialysis, only 10% turned oligoanuric within 30 months as compared to 35% of those who did not receive a diuretic (Fig. 11.5). This effect was independent of age, underlying disease, urine volume at PD start, PD prescription, and co-administration of RAS antagonists. However, this beneficial effect of diuretics on water balance may not accompany better residual renal solute clearance. Studies on adult dialysis patients suggested that renal urea and creatinine clearances were not affected by diuretic administration [121, 123], with some even reporting an adverse effect on solute clearance [54, 55].

Peritoneal Dialysis

In PD, use of more biocompatible PD fluids with markedly reduced content of glucose degradation products (GDP) contributes to preserving the structural and functional integrity of the peritoneal membrane [124, 125]. As GDP are readily absorbed, they may promote not only local but also systemic formation of advanced glycosylation end products (AGE). It has been speculated that the reduced systemic AGE load may be associated with improved preservation of RRF. Results from controlled clinical trials and meta-analysis identified that RRF is better preserved when PD is performed with low-GDP fluids [124, 126–129]. A global cohort study in children also confirmed the beneficial effect of biocompatible PD fluid on RRF [45].

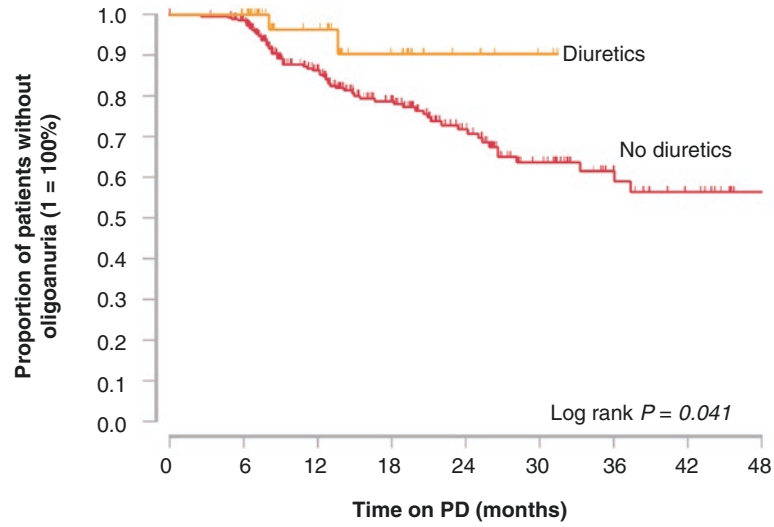

Fig. 11.5 Extended preservation of residual urine output by loop diuretic treatment in children undergoing chronic PD. (Modified from Ref. [45])

Hemodialysis

Not all, but most studies in adult patients on hemodialysis showed that RRF was preserved better with the use of dialyzer membranes made of biocompatible polysulfone material than with cellulose or cuprophane membranes [69, 96, 130, 131]. The protective effect of biocompatible membranes may be related to the attenuated inflammatory response induced upon exposure, characterized by less marked activation of the complement system and circulating leukocytes [96, 132, 133]. It has also been reported that the use of ultrapure water and bicarbonate buffer preserves RRF [5, 134].

In addition, high-flux membranes, hemodiafiltration, and combination of hemodialysis and PD or hemodialysis and hemoperfusion have been reported to improve the preservation of RRF [5, 135–138].

Emerging Therapies

Experimental research supports a role for anti-inflammatory and anti-fibrotic agents in pharmacological nephroprotection. It was reported that mycophenolate mofetil has a protective effect on RRF in adult PD patients [139]. It was also reported that administration of N-acetylcysteine 1200 mg twice daily preserved RRF in adult patients undergoing hemodialysis and PD [140, 141].

Special Conditions

In patients returning to dialysis after failed transplant, continued immunosuppression preserves the residual allograft function for some time [96]. Of course, side effects of the immunosuppressive medications have to be weighed against the benefit of RRF in these patients.

There are unusual situations when more rapid loss of urine volume, or even nephrectomy, is rather preferable because of refractory edema caused by severe proteinuria and hypoalbuminemia. The information described above could help caring for these patients in an opposite way, for example, by administration of NSAIDs.

References

1. González Celedón C, Bitsori M, Tullus K. Progression of chronic renal failure in children with dysplastic kidneys. Pediatr Nephrol. 2007;22(7):1014–20.
2. Wang AY, Lai KN. The importance of residual renal function in dialysis patients. Kidney Int. 2006;69(10):1726–32.

3. Marron B, Remon C, Perez-Fontan M, Quiros P, Ortiz A. Benefits of preserving residual renal function in peritoneal dialysis. Kidney Int. 2008;73(S108):S42–51.
4. Guzzo I, Mancini E, Wafo SK, Rava L, Picca S. Residual renal function and nutrition in young patients on chronic hemodialysis. Pediatr Nephrol. 2009;24(7):1391–7.
5. McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. Kidney Int. 2002;61(1):256–65.
6. Wong J, Sridharan S, Berdeprado J, Vilar E, Viljoen A, Wellsted D, et al. Predicting residual kidney function in hemodialysis patients using serum beta-trace protein and beta2-microglobulin. Kidney Int. 2016;89(5):1090–8.
7. Shafi T, Michels WM, Levey AS, Inker LA, Dekker FW, Krediet RT, et al. Estimating residual kidney function in dialysis patients without urine collection. Kidney Int. 2016;89(5):1099–110.
8. Kim SJ, Sohn YB, Park SW, Jin DK, Paik KH. Serum cystatin C for estimation of residual renal function in children on peritoneal dialysis. Pediatr Nephrol. 2011;26(3):433–40.
9. Montini G, Amici G, Milan S, Mussap M, Naturale M, Ratsch IM, et al. Middle molecule and small protein removal in children on peritoneal dialysis. Kidney Int. 2002;61(3):1153–9.
10. Lowenstein J, Grantham JJ. Residual renal function: a paradigm shift. Kidney Int. 2017;91(3):561–5.
11. Wong J, Kaja Kamal RM, Vilar E, Farrington K. Measuring residual renal function in hemodialysis patients without urine collection. Semin Dial. 2017;30(1):39–49.
12. C-UCPDS Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1996;7(2):198–207.
13. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001;12(10):2158–62.
14. Termorshuizen F, Korevaar J, Dekker F, van Manen J, Boeschoten E, Krediet R. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. Am J Kidney Dis. 2003;41(6):1293–302.
15. Rocco MV, Frankenfield DL, Prowant B, Frederick P, Flanigan MJ, Centers for Medicare & Medicaid Services Peritoneal Dialysis Core Indicators Study Group. Risk factors for early mortality in U.S. peritoneal dialysis patients: impact of residual renal function. Perit Dial Int. 2002;22(3):371–9.
16. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT, et al. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15(4):1061–70.
17. Lee MJ, Park JT, Park KS, Kwon YE, Oh HJ, Yoo TH, et al. Prognostic value of residual urine volume, GFR by 24-hour urine collection, and eGFR in patients receiving dialysis. Clin J Am Soc Nephrol. 2017;12(3):426–34.
18. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK. Are peritoneal dialysis patients with and without residual renal function equivalent for survival study? Insight from a retrospective review of the cause of death. Nephrol Dial Transplant. 2003;18(5):977–82.
19. Wang AY, Lam CW, Wang M, Chan IH, Lui SF, Sanderson JE. Is valvular calcification a part of the missing link between residual kidney function and cardiac hypertrophy in peritoneal dialysis patients? Clin J Am Soc Nephrol. 2009;4(10):1629–36.
20. Shin DH, Lee YK, Oh J, Yoon JW, Rhee SY, Kim EJ, et al. Vascular calcification and cardiac function according to residual renal function in patients on hemodialysis with urination. PLoS One. 2017;12(9):e0185296.
21. Acar B, Yalcinkaya F, Cakar N, Yuksel S, Ozcakar ZB, Uncu N, et al. The outcome for pediatric patients on peritoneal dialysis. J Nephrol. 2008;21(3):394–9.
22. Bakkaloglu SA, Saygili A, Sever L, Noyan A, Akman S, Ekim M, et al. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report. Nephrol Dial Transplant. 2009;24(11):3525–32.
23. Page DE, Knoll GA, Cheung V. The relationship between residual renal function, protein catabolic rate, and phosphate and magnesium levels in peritoneal dialysis patients. Adv Perit Dial. 2002;18:189–91.
24. Li L, Liang W, Ye T, Chen Z, Zuo X, Du X, et al. The association between nutritional markers and biochemical parameters and residual renal function in peritoneal dialysis patients. PLoS One. 2016;11(6):e0156423.
25. Viaene L, Bammens B, Meijers BK, Vanrenterghem Y, Vanderschueren D, Evenepoel P. Residual renal function is an independent determinant of serum FGF-23 levels in dialysis patients. Nephrol Dial Transplant. 2012;27(5):2017–22.
26. Akimoto T, Shiizaki K, Sugase T, Watanabe Y, Yoshizawa H, Otani N, et al. The relationship between the soluble Klotho protein and the residual renal function among peritoneal dialysis patients. Clin Exp Nephrol. 2012;16(3):442–7.
27. Wang A, Woo J, Wang M, Sea M, Sanderson J, Lui S-F, et al. Important differentiation of factors that predict outcome in peritoneal dialysis patients with different degrees of residual renal function. Nephrol Dial Transplant. 2005;20(2):396–403.

28. Dixit MP, Cabansag MR, Piscitelli J, Greifer I, Silverstein DM. Serum beta2-microglobulin and immunoglobulin levels in young hemodialysis patients. Pediatr Nephrol. 1999;13(2):139–42.
29. Chadha V, Blowey DL, Warady BA. Is growth a valid outcome measure of dialysis clearance in children undergoing peritoneal dialysis? Perit Dial Int. 2001;21(Suppl 3):S179–84.
30. Shemin D, Bostom AG, Lambert C, Hill C, Kitsen J, Kliger AS. Residual renal function in a large cohort of peritoneal dialysis patients: change over time, impact on mortality and nutrition. Perit Dial Int. 2000;20(4):439–44.
31. Poulsen CG, Kjaergaard KD, Peters CD, Jespersen B, Jensen JD. Quality of life development during initial hemodialysis therapy and association with loss of residual renal function. Hemodial Int. 2017;21(3):409–21.
32. Park HC, Lee H, Lee JP, Kim DK, Oh KH, Joo KW, et al. Lower residual renal function is a risk factor for depression and impaired health-related quality of life in Korean peritoneal dialysis patients. J Korean Med Sci. 2012;27(1):64–71.
33. Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis. 2010;56(2):348–58.
34. Erkan E, Moritz M, Kaskel F. Impact of residual renal function in children on hemodialysis. Pediatr Nephrol. 2001;16(11):858–61.
35. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139(4):244–52.
36. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, Boguszewska-Baczkowska H, Drozdz D, Kollataj B, et al. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland – a nationwide survey. Nephrol Dial Transplant. 2006;21(3):736–42.
37. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002;62(3):1046–53.
38. Hidaka H, Nakao T. Preservation of residual renal function and factors affecting its decline in patients on peritoneal dialysis. Nephrology (Carlton). 2003;8(4):184–91.
39. Roszkowska-Blaim M, Skrzypczyk P. Risk factors for decline of residual renal function in children treated with peritoneal dialysis. Perit Dial Int. 2016;36(6):669–75.
40. Uchiyama K, Yanai A, Maeda K, Ono K, Honda K, Tsujimoto R, et al. Baseline and time-averaged values predicting residual renal function decline rate in Japanese peritoneal dialysis patients. Ther Apher Dial. 2017;21(6):599–605.
41. Mitsnefes M, Ho P-L, McEnery P. Hypertension and progression of chronic renal insufficiency in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). J Am Soc Nephrol. 2003;14(10):2618–22.
42. Litwin M. Risk factors for renal failure in children with non-glomerular nephropathies. Pediatr Nephrol. 2004;19(2):178–86.
43. Tian JP, Wang H, Tian XK, Du FH, Wang T. The impact of visit-to-visit systolic blood pressure variability on residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. Turk J Med Sci. 2018;48(2):279–85.
44. Neild GH. What do we know about chronic renal failure in young adults? II. Adult outcome of pediatric renal disease. Pediatr Nephrol. 2009;24(10):1921–8.
45. Ha IS, Yap HK, Munarriz RL, Zambrano PH, Flynn JT, Bilge I, et al. Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. Kidney Int. 2015;88(3):605–13.
46. Wingen AM, Fabian-Bach C, Schaefer F, Mehls O. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. Lancet. 1997;349(9059):1117–23.
47. Wong CS, Pierce CB, Cole SR, Warady BA, Mak RH, Benador NM, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. Clin J Am Soc Nephrol. 2009;4(4):812–9.
48. Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361(17):1639–50.
49. Wuehl E, Mehls O, Schaefer F, ESCAPE Trial Group. Long-term dissociation of antiproteinuric and antihypertensive efficacy of ACE inhibition in children with chronic renal failure.COD.OC 16 [Abstract]. Pediatr Nephrol. 2006;21:1505.
50. Singhal MK, Bhaskaran S, Vidgen E, Bargman JM, Vas SI, Oreopoulos DG. Rate of decline of residual renal function in patients on continuous peritoneal dialysis and factors affecting it. Perit Dial Int. 2000;20(4):429–38.
51. Roszkowska-Blaim M, Skrzypczyk P, Jander A, Tkaczyk M, Balasz-Chmielewska I, Zurowska A, et al. The effect of peritoneal dialysis method on residual renal function in children. Adv Perit Dial. 2012;28:112–9.
52. Shin SK, Noh H, Kang SW, Seo BJ, Lee IH, Song HY, et al. Risk factors influencing the decline of residual renal function in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1999;19(2):138–42.
53. de Fijter CW, ter Wee PM, Donker AJ. The influence of automated peritoneal dialysis on the decrease in

residual renal function. Nephrol Dial Transplant. 2000;15(7):1094–6.
54. Liao CT, Shiao CC, Huang JW, Hung KY, Chuang HF, Chen YM, et al. Predictors of faster decline of residual renal function in Taiwanese peritoneal dialysis patients. Perit Dial Int. 2008;28(Suppl 3):S191–5.
55. Szeto CC, Kwan BC, Chow KM, Chung S, Yu V, Cheng PM, et al. Predictors of residual renal function decline in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int. 2015;35(2):180–8.
56. Feber J, Schrer K, Schaefer F, Mkov M, Janda J. Residual renal function in children on haemodialysis and peritoneal dialysis therapy. Pediatr Nephrol. 1994;8(5):579–83.
57. Van Biesen W, Dequidt C, Vanholder R, Lameire N. The impact of healthy start peritoneal dialysis on the evolution of residual renal function and nutrition parameters. Adv Perit Dial. 2002;18:44–8.
58. Furth SL, Cole SR, Fadrowski JJ, Gerson A, Pierce CB, Chandra M, et al. The association of anemia and hypoalbuminemia with accelerated decline in GFR among adolescents with chronic kidney disease. Pediatr Nephrol. 2007;22(2):265–71.
59. Gouva C, Nikolopoulos P, Ioannidis JPA, Siamopoulos K. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int. 2004;66(2):753–60.
60. Wang AY, Wang M, Woo J, Law MC, Chow KM, Li PK, et al. A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. Kidney Int. 2002;62(2):639–47.
61. Borzych-Duzalka D, Bilginer Y, Ha IS, Bak M, Rees L, Cano F, et al. Management of anemia in children receiving chronic peritoneal dialysis. J Am Soc Nephrol. 2013;24(4):665–76.
62. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis. 2005;45(6):978–93.
63. Harambat J, Kunzmann K, Azukaitis K, Bayazit AK, Canpolat N, Doyon A, et al. Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. Kidney Int. 2017;92(6):1507–14.
64. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20(9):2075–84.
65. Chalmers L, Kaskel FJ, Bamgbola O. The role of obesity and its bioclinical correlates in the progression of chronic kidney disease. Adv Chronic Kidney Dis. 2006;13(4):352–64.
66. Soares CM, Diniz JS, Lima EM, Oliveira GR, Canhestro MR, Colosimo EA, et al. Predictive factors of progression to chronic kidney disease stage 5 in a predialysis interdisciplinary programme. Nephrol Dial Transplant. 2009;24(3):848–55.
67. Han KH, Lee SH, Lee HK, Choi HJ, Lee BH, Cho HY, et al. Risk factors for the progression of pediatric chronic kidney disease-a single center study. J Korean Soc Pediatr Nephrol. 2007;11(2):239–46.
68. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, et al. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78(12):1295–304.
69. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol. 2000;11(3):556–64.
70. Noordzij M, Voormolen NM, Boeschoten EW, Dekker FW, Bos WJ, Krediet RT, et al. Disordered mineral metabolism is not a risk factor for loss of residual renal function in dialysis patients. Nephrol Dial Transplant. 2009;24(5):1580–7.
71. Park JT, Kim DK, Chang TI, Kim HW, Chang JH, Park SY, et al. Uric acid is associated with the rate of residual renal function decline in peritoneal dialysis patients. Nephrol Dial Transplant. 2009;24(11):3520–5.
72. Hsieh YP, Yang Y, Chang CC, Kor CT, Wen YK, Chiu PF, et al. U-shaped relationship between uric acid and residual renal function decline in continuous ambulatory peritoneal dialysis patients. Nephrology (Carlton). 2017;22(6):427–35.
73. Liao CT, Chen YM, Shiao CC, Hu FC, Huang JW, Kao TW, et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis. Nephrol Dial Transplant. 2009;24(9):2909–14.
74. Liu JH, Wang SM, Chen CC, Hsieh CL, Lin SY, Chou CY, et al. Relation of ankle-brachial index to the rate of decline of residual renal function in peritoneal dialysis patients. Nephrology (Carlton). 2011;16(2):187–93.
75. Caliskan Y, Ozkok A, Akagun T, Alpay N, Guz G, Polat N, et al. Cardiac biomarkers and noninvasive predictors of atherosclerosis in chronic peritoneal dialysis patients. Kidney Blood Press Res. 2012;35(5):340–8.
76. Tian SL, Tian XK, Han QF, Axelsson J, Wang T. Presence of peripheral arterial disease predicts loss of residual renal function in incident CAPD patients. Perit Dial Int. 2012;32(1):67–72.
77. Davenport A, Sayed RH, Fan S. Is extracellular volume expansion of peritoneal dialysis patients associated with greater urine output? Blood Purif. 2011;32(3):226–31.
78. Tian N, Guo Q, Zhou Q, Cao P, Hong L, Chen M, et al. The impact of fluid overload and variation on residual renal function in peritoneal dialysis patient. PLoS One. 2016;11(4):e0153115.
79. Kawai Y, Tanaka S, Yoshida H, Hara M, Tsujikawa H, Tsuruya K, et al. Association of B-type natriuretic peptide level with residual kidney function in incident peritoneal dialysis patients. Perit Dial Int. 2019;39(2):147–54.

80. Ardissino G, Testa S, Dacc V, Vigan S, Taioli E, Claris-Appiani A, et al. Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy. Data from the Ital Kid Project. Pediatr Nephrol. 2004;19(2):172–7.
81. Lane PH. Puberty and chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(4):372–7.
82. Tonshoff B, Fine RN. Recombinant human growth hormone for children with renal failure. Adv Ren Replace Ther. 1996;3(1):37–47.
83. Drechsler C, de Mutsert R, Grootendorst DC, Boeschoten EW, Krediet RT, le Cessie S, et al. Association of body mass index with decline in residual kidney function after initiation of dialysis. Am J Kidney Dis. 2009;53(6):1014–23.
84. Papp F, Friedman AL, Bereczki C, Haszon I, Kiss E, Endreffy E, et al. Renin-angiotensin gene polymorphism in children with uremia and essential hypertension. Pediatr Nephrol. 2003;18(2):150–4.
85. Hohenfellner K, Wingen AM, Nauroth O, Whl E, Mehls O, Schaefer F. Impact of ACE I/D gene polymorphism on congenital renal malformations. Pediatr Nephrol. 2001;16(4):356–61.
86. Oktem F, Sirin A, Bilge I, Emre S, Agachan B, Ispir T. ACE I/D gene polymorphism in primary FSGS and steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2004;19(4):384–9.
87. Amoroso A, Danek G, Vatta S, Crovella S, Berrino M, Guarrera S, et al. Polymorphisms in angiotensin-converting enzyme gene and severity of renal disease in Henoch-Schoenlein patients. Italian Group of Renal Immunopathology. Nephrol Dial Transplant. 1998;13(12):3184–8.
88. Hussein A, Askar E, Elsaeid M, Schaefer F. Functional polymorphisms in transforming growth factor-beta-1 (TGFbeta-1) and vascular endothelial growth factor (VEGF) genes modify risk of renal parenchymal scarring following childhood urinary tract infection. Nephrol Dial Transplant. 2010;25(3):779–85.
89. Xu J, Guo Z, Bai Y, Zhang J, Cui L, Zhang H, et al. Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with the kidney survival time in chronic kidney disease patients. Ren Fail. 2015;37(1):108–12.
90. Bodonyi-Kovacs G, Ma JZ, Chang J, Lipkowitz MS, Kopp JB, Winkler CA, et al. Combined effects of GSTM1 null allele and APOL1 renal risk alleles in CKD progression in the African American Study of Kidney Disease and Hypertension trial. J Am Soc Nephrol. 2016;27(10):3140–52.
91. Tin A, Grams ME, Estrella M, Lipkowitz M, Greene TH, Kao WH, et al. Patterns of kidney function decline associated with APOL1 genotypes: results from AASK. Clin J Am Soc Nephrol. 2016;11(8):1353–9.
92. Rudnicki M, Perco P, Haene BD, Leierer J, Heinzel A, Muhlberger I, et al. Renal microRNA- and RNA-profiles in progressive chronic kidney disease. Eur J Clin Investig. 2016;46(3):213–26.
93. Parsa A, Kanetsky PA, Xiao R, Gupta J, Mitra N, Limou S, et al. Genome-wide association of CKD progression: the chronic renal insufficiency cohort study. J Am Soc Nephrol. 2017;28(3):923–34.
94. Xu X, Eales JM, Akbarov A, Guo H, Becker L, Talavera D, et al. Molecular insights into genome-wide association studies of chronic kidney disease-defining traits. Nat Commun. 2018;9(1):4800.
95. Wuttke M, Wong CS, Wuhl E, Epting D, Luo L, Hoppmann A, et al. Genetic loci associated with renal function measures and chronic kidney disease in children: the Pediatric Investigation for Genetic Factors Linked with Renal Progression Consortium. Nephrol Dial Transplant. 2016;31(2):262–9.
96. Lang SM, Bergner A, Topfer M, Schiffl H. Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. Perit Dial Int. 2001;21(1):52–7.
97. Misra M, Vonesh E, Van Stone JC, Moore HL, Prowant B, Nolph KD. Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. Kidney Int. 2001;59(2):754–63.
98. Feber J, Scharer K, Schaefer F, Mikova M, Janda J. Residual renal function in children on haemodialysis and peritoneal dialysis therapy. Pediatr Nephrol. 1994;8(5):579–83.
99. Fischbach M, Terzic J, Menouer S, Soulami K, Dangelser C, Helmstetter A, et al. Effects of automated peritoneal dialysis on residual daily urinary volume in children. Adv Perit Dial. 2001;17:269–73.
100. Hiroshige K, Yuu K, Soejima M, Takasugi M, Kuroiwa A. Rapid decline of residual renal function in patients on automated peritoneal dialysis. Perit Dial Int. 1996;16(3):307–15.
101. Hufnagel G, Michel C, Queffeulou G, Skhiri H, Damieri H, Mignon F. The influence of automated peritoneal dialysis on the decrease in residual renal function. Nephrol Dial Transplant. 1999;14(5):1224–8.
102. Michels WM, Verduijn M, Grootendorst DC, le Cessie S, Boeschoten EW, Dekker FW, et al. Decline in residual renal function in automated compared with continuous ambulatory peritoneal dialysis. Clin J Am Soc Nephrol. 2011;6(3):537–42.
103. Bernardo A, Fonseca I, Rodrigues A, Carvalho MJ, Cabrita A. Predictors of residual renal function loss in peritoneal dialysis: is previous renal transplantation a risk factor? Adv Perit Dial. 2009;25:110–4.
104. Holley JL, Aslam N, Bernardini J, Fried L, Piraino B. The influence of demographic factors and modality on loss of residual renal function in incident peritoneal dialysis patients. Perit Dial Int. 2001;21(3):302–5.
105. Dell'Aquila R, Berlingo G, Pellanda MV, Contestabile A. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis: are there differences in outcome? Contrib Nephrol. 2009;163:292–9.

106. Balasubramanian G, McKitty K, Fan SL. Comparing automated peritoneal dialysis with continuous ambulatory peritoneal dialysis: survival and quality of life differences? Nephrol Dial Transplant. 2011;26(5):1702–8.
107. Cnossen TT, Usvyat L, Kotanko P, van der Sande FM, Kooman JP, Carter M, et al. Comparison of outcomes on continuous ambulatory peritoneal dialysis versus automated peritoneal dialysis: results from a USA database. Perit Dial Int. 2011;31(6):679–84.
108. Adachi Y, Nishio A, Ikegami T. Tidal automated peritoneal dialysis preserves residual renal function better than non tidal automated peritoneal dialysis. Adv Perit Dial. 2007;23:98–101.
109. Badve SV, Hawley CM, McDonald SP, Brown FG, Boudville NC, Wiggins KJ, et al. Use of aminoglycosides for peritoneal dialysis-associated peritonitis does not affect residual renal function. Nephrol Dial Transplant. 2012;27(1):381–7.
110. Baker RJ, Senior H, Clemenger M, Brown EA. Empirical aminoglycosides for peritonitis do not affect residual renal function. Am J Kidney Dis. 2003;41(3):670–5.
111. Shemin D, Maaz D, St Pierre D, Kahn SI, Chazan JA. Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. Am J Kidney Dis. 1999;34(1):14–20.
112. Wuhl E, Mehls O, Schaefer F, ESCAPE Trial Group. Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. Kidney Int. 2004;66(2):768–76.
113. Ardissino G, Vigan S, Testa S, Dacc V, Paglialonga F, Leoni A, et al. No clear evidence of ACEi efficacy on the progression of chronic kidney disease in children with hypodysplastic nephropathy – report from the ItalKid Project database. Nephrol Dial Transplant. 2007;22(9):2525–30.
114. Suzuki H, Kanno Y, Sugahara S, Okada H, Nakamoto H. Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am J Kidney Dis. 2004;43(6):1056–64.
115. Mokoli VM, Sumaili EK, Lepira FB, Mbutiwi FIN, Makulo JRR, Bukabau JB, et al. Factors associated with residual urine volume preservation in patients undergoing hemodialysis for end-stage kidney disease in Kinshasa. BMC Nephrol. 2018;19(1):68.
116. Li P, Chow K-M, Wong T, Leung C-B, Szeto C-C. Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. Ann Intern Med. 2003;139(2):105–12.
117. Litwin M, Grenda R, Sladowska J, Antoniewicz J. Add-on therapy with angiotensin II receptor 1 blocker in children with chronic kidney disease already treated with angiotensin-converting enzyme inhibitors. Pediatr Nephrol. 2006;21(11):1716–22.
118. Frimodt-Moller M, Hoj Nielsen A, Strandgaard S, Kamper AL. Feasibility of combined treatment with enalapril and candesartan in advanced chronic kidney disease. Nephrol Dial Transplant. 2010;25(3):842–7.
119. Bianchi S, Bigazzi R, Campese VM. Intensive versus conventional therapy to slow the progression of idiopathic glomerular diseases. Am J Kidney Dis. 2010;55(4):671–81.
120. van Olden RW, van Meyel JJ, Gerlag PG. Acute and long-term effects of therapy with high-dose furosemide in chronic hemodialysis patients. Am J Nephrol. 1992;12(5):351–6.
121. Flinn A, Ledger S, Blake P. Effectiveness of furosemide in patients on peritoneal dialysis. CANNT Js. 2006;16(3):40–4.
122. Bragg-Gresham JL, Fissell RB, Mason NA, Bailie GR, Gillespie BW, Wizemann V, et al. Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). Am J Kidney Dis. 2007;49(3):426–31.
123. Medcalf JF, Harris KP, Walls J. Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. Kidney Int. 2001;59(3):1128–33.
124. Haag-Weber M, Kramer R, Haake R, Islam MS, Prischl F, Haug U, et al. Low-GDP fluid (Gambrosol trio) attenuates decline of residual renal function in PD patients: a prospective randomized study. Nephrol Dial Transplant. 2010;25(7):2288–96.
125. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, et al. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int. 2004;66(1):408–18.
126. Cho Y, Johnson DW, Craig JC, Strippoli GF, Badve SV, Wiggins KJ. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2014;3:CD007554.
127. Wang J, Zhu N, Yuan W. Effect of neutral pH and low-glucose degradation product-containing peritoneal dialysis solution on residual renal function in peritoneal dialysis patients: a meta-analysis. Nephron. 2015;129(3):155–63.
128. Yohanna S, Alkatheeri AM, Brimble SK, McCormick B, Iansavitchous A, Blake PG, et al. Effect of neutral-pH, low-glucose degradation product peritoneal dialysis solutions on residual renal function, urine volume, and ultrafiltration: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2015;10(8):1380–8.
129. Sikaneta T, Wu G, Abdolell M, Ng A, Mahdavi S, Svendrovski A, et al. The trio trial – a randomized controlled clinical trial evaluating the effect of a biocompatible peritoneal dialysis solution on residual renal function. Perit Dial Int. 2016;36(5):526–32.
130. McCarthy JT, Jenson BM, Squillace DP, Williams AW. Improved preservation of residual renal function in chronic hemodialysis patients using polysulfone dialyzers. Am J Kidney Dis. 1997;29(4):576–83.
131. Hartmann J, Fricke H, Schiffl H. Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. Am J Kidney Dis. 1997;30(3):366–73.

132. Schindler R, Boenisch O, Fischer C, Frei U. Effect of the hemodialysis membrane on the inflammatory reaction in vivo. Clin Nephrol. 2000;53(6):452–9.
133. Hakim RM, Wingard RL, Husni L, Parker RA, Parker TF 3rd. The effect of membrane biocompatibility on plasma beta 2-microglobulin levels in chronic hemodialysis patients. J Am Soc Nephrol. 1996;7(3):472–8.
134. Schiffl H, Lang SM, Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. Nephrol Dial Transplant. 2002;17(10):1814–8.
135. Ng TG, Johnson DW, Hawley CM. Is it time to revisit residual renal function in haemodialysis? Nephrology (Carlton). 2007;12(3):209–17.
136. Chandna SM, Farrington K. Residual renal function: considerations on its importance and preservation in dialysis patients. Semin Dial. 2004;17(3):196–201.
137. Lu W, Ren C, Han X, Yang X, Cao Y, Huang B. The protective effect of different dialysis types on residual renal function in patients with maintenance hemodialysis: a systematic review and meta-analysis. Medicine. 2018;97(37):e12325.
138. Ueda A, Nagai K, Hirayama A, Saito C, Yamagata K. Combination therapy with peritoneal dialysis and hemodialysis from the initiation of renal replacement therapy preserves residual renal function and serum albumin. Adv Perit Dial. 2017;33(2017):74–8.
139. Wang X, Zhang X, Lu S, Liu D, Chen G, Dou Y, et al. Protective effect of mycophenolate mofetil on residual renal function in peritoneal dialysis patients: an open label feasibility study. Nephrology (Carlton). 2017;22(12):954–60.
140. Ahmadi F, Abbaszadeh M, Razeghi E, Maziar S, Khoidaki SD, Najafi MT, et al. Effectiveness of N-acetylcysteine for preserving residual renal function in patients undergoing maintenance hemodialysis: multicenter randomized clinical trial. Clin Exp Nephrol. 2017;21(2):342–9.
141. Feldman L, Shani M, Efrati S, Beberashvili I, Yakov-Hai I, Abramov E, et al. N-acetylcysteine improves residual renal function in peritoneal dialysis patients: a pilot study. Perit Dial Int. 2011;31(5):545–50.

Part III

Peritoneal Dialysis

Peritoneal Access in Children Receiving Dialysis

12

Bradley A. Warady and Walter S. Andrews

Peritoneal Dialysis Access

Peritoneal dialysis (PD) is the initial dialytic modality for many children with end-stage kidney disease (ESKD). This is especially true for children who have acquired ESKD during their first decade of life [1]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reveals that of the 9108 courses of dialysis recorded in the dialysis registry between 1992 and 2010, 58% were for PD [2]. The 2018 report of the United States Renal Data System (USRDS) also revealed that PD was the most common initial ESKD treatment modality for children aged 9 years and younger and that 86.1% of those patients <10 kg at dialysis initiation were prescribed PD (Fig. 12.1) [1]. Reasons for the preferential selection of PD in children have included its ability to greatly reduce the need for dietary restrictions, its simplicity of operation, the lack of a need for routine blood access, and the ability of the child on PD to attend school on a regular basis.

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In order for there to be successful PD, there must be a well-functioning peritoneal catheter. Ideally, the catheter provides reliable, rapid dialysate flow rates without leaks or infections. The first description of placement of a chronic indwelling catheter for peritoneal dialysis was in 1968 by Tenckhoff, and the Tenckhoff catheter continues to be the most commonly used PD access [3, 4]. Despite significant improvements in catheter design, however, the catheter has continued to be the Achilles' heel of PD because of catheter-related complications. This chapter will explore the key characteristics of the catheters, the primary surgical techniques for their placement, as well as the most common catheter-related complications in children. It is hoped that this information will result in an increased likelihood of a problem-free PD access for the pediatric patient.

Access Types

The catheters that are commonly used for chronic PD are constructed of soft material, such as silicone rubber or polyurethane. The key elements of the catheters are the unique intraperitoneal configurations (curled or straight), number of Dacron cuffs (one or two), and the subcutaneous tunnel configuration (straight or "swan neck") [5, 6]. If one includes the orientation of the catheter exit site on the abdomen as yet another variable, more than 20 different combinations of catheter characteristics are possible, as documented in the

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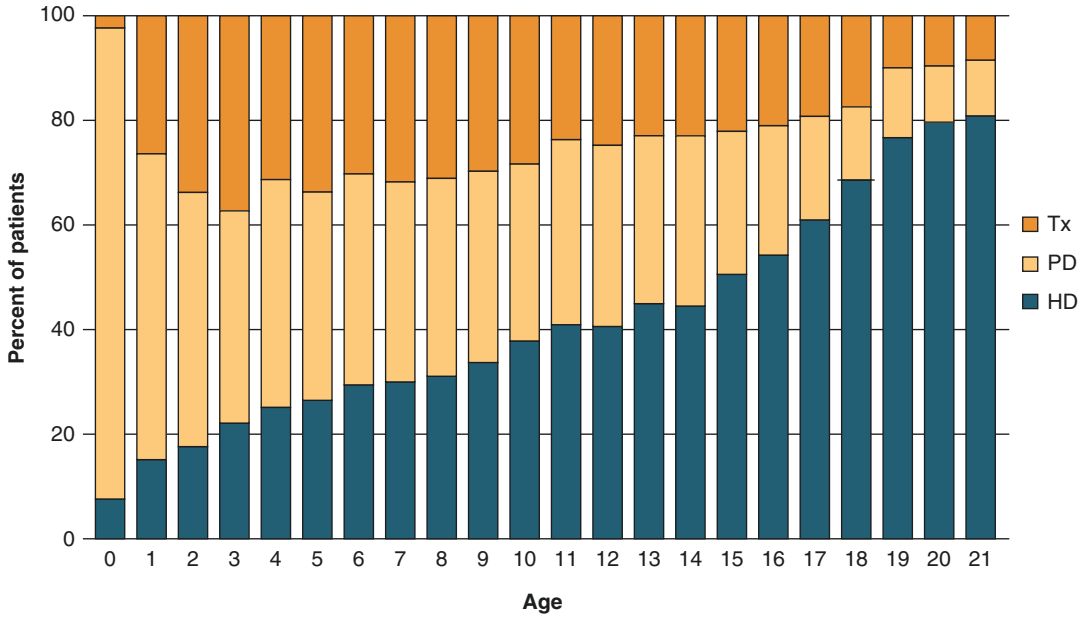

Fig. 12.1 Cross-sectionaltrends in pediatric ESKD modality at initiation by patient age 1996–2016. (Modified from Ref. [1])

Table 12.1 Peritoneal dialysis access characteristics

Catheter	Cuffs	Tunnel	Exit site	N (4391)[a]	% (100.0)
Curled	One	Straight	Lateral	619	14.1
Curled	Two	Swan necked/curved	Down	458	10.4
Curled	Two	Straight	Lateral	315	7.2
Straight	One	Straight	Lateral	313	7.1
Curled	Two	Straight	Down	277	6.3
Curled	One	Straight	Down	267	6.1
Curled	One	Straight	Up	209	4.8
Straight	One	Straight	Up	136	3.1
Presternal	Two	Swan necked/curved	Down	129	2.9
Straight	One	Straight	Unknown	123	2.8
Curled	Two	Swan necked/curved	Lateral	132	3.0
Curled	Two	Swan necked/curved	Unknown	145	3.3
Straight	One	Swan necked/curved	Lateral	104	2.4
Straight	Two	Straight	Lateral	100	2.3
Straight	One	Straight	Down	102	2.3
Curled	One	Straight	Unknown	76	1.7
Curled	One	Swan necked/curved	Down	78	1.8
Curled	One	Swan necked/curved	Lateral	78	1.8
Curled	Two	Straight	Unknown	57	1.3
Straight	Two	Straight	Up	54	1.2
All other combination (<1% each)				618	14.1

[a]Cases with missing elements are excluded

2011 annual report of the NAPRTCS (Table 12.1) [2]. As noted above, the most common catheter with these characteristics used by pediatric patients is the Tenckhoff catheter.

A review of the 2011 NAPRTCS dialysis registry catheter data reveals that most of the catheters that were placed were of the Tenckhoff curled (62.1%) or Tenckhoff straight (25.9%) variety [2]

Table 12.2 Peritoneal dialysis access

	N	%
Peritoneal dialysis courses	4687	100.0
Catheter		
Tenckhoff straight	1213	25.9
Tenckhoff curled	2909	62.1
Toronto Western	26	0.6
Presternal	272	5.8
Other	111	2.4
Unknown/missing	156	3.3
Cuffs		
One	2375	50.7
Two	2124	45.3
Unknown/missing	188	4.0
Tunnel		
Swan neck/curved	1590	33.9
Straight	2895	61.8
Unknown/missing	202	4.3
Exit-site orientation		
Up	564	12.0
Down	1537	32.8
Lateral	1816	38.7
Unknown/missing	770	16.4

(Table 12.2). More recently, the Standardizing Care to Improve Outcomes in Pediatric ESRD (SCOPE) Collaborative showed that of 857 PD catheters, 94.1% were Tenckhoff curled catheters and 5.9% were Tenckhoff straight catheters [7]. The presumed advantages of the curled catheter over the original straight catheter include (1) better separation between the abdominal wall and the bowel, (2) more catheter side holes available for inflow and outflow, (3) less inflow pain, (4) less of a tendency for migration out of the pelvis, (5) less prone to omental wrapping, and (6) potentially less trauma to bowel [8]. However, in contrast to the North American data, the Italian PD registry reflects a predominance of straight catheters, and the adult experience has not revealed any clear difference in functionality [9]. In fact, it should be emphasized that none of the eight adult randomized trials reviewed in the 2017 ISPD Catheter-Related Infection Recommendations which compared straight and coiled PD catheters found differences in the rates of catheter-related infections [10–12]. In addition, two recent studies conducted in adult PD patients revealed a superior outcome with the straight Tenckhoff catheter in terms of catheter survival, whereas in a large pediatric study, use of a swan neck catheter with a curled intraperitoneal segment was a significant risk factor for access revision [12–14]. Finally, neither the NAPRTCS nor the SCOPE data has provided evidence for any association between the intraperitoneal catheter configuration and the development of peritonitis or exit-site/tunnel infection [2, 7].

The next catheter characteristic to consider is the number of Dacron cuffs on the catheter. If a single-cuff catheter is used, it is generally recommended that the cuff be positioned between the rectus sheaths in the rectus muscle, and not in a superficial position. In one series, the incidence of peritonitis was decreased by nearly 37% when the cuff was placed in the rectus sheath compared to a subcutaneous placement of the cuff. When a second cuff was added as a means of securing the catheter's position and potentially helping prevent bacterial migration, there were initial reports of problems with cutaneous extrusion of the second cuff [15, 16]. This was most likely secondary to excess torque being placed on the catheter at the time of placement as a result of the angle between the exit-site and the abdominal wall portion of the catheter. It also proved most likely to occur if the outer cuff was less than 2.0 cm from the exit site, an exceedingly important factor to recognize when placing double-cuff catheters [5, 8]. Cuff extrusion may lead to the cuff being seeded with bacteria and may predispose to the development of an exit-site/tunnel infection. A cuff that has completely extruded still remains a risk factor for an exit-site infection. Thus, cuff extrusion should prompt shaving of the cuff off the catheter [17–19]. While there are very few reports describing the incidence of distal cuff extrusion with double-cuff catheters in children, three series have reported outer cuff extrusion rates of 5.7%, 8%, and 4.8%, respectively [9, 20, 21]. It may be, in part, for this reason that 51% of the catheters in the NAPRTCS database are single cuff [2]. There is, however, some data to suggest that single-cuff catheters are associated with a higher incidence of exit-site/tunnel infections and peritonitis. Lewis et al. compared the incidence of catheter-related infections in children

with single- and double-cuff peritoneal catheters and found a significantly lower incidence of infections in the double-cuff group [22]. A similar conclusion can be drawn from the NAPRTCS 2011 registry data that revealed a significantly lower incidence of peritonitis in association with double-cuff catheters (1/21.6 patient-months) compared to single-cuff catheters (1/16.2 patient-months), although the experience varies in individual centers [2, 21, 23]. In addition, the NAPRTCS data shows a longer time to first peritonitis episode in the double-cuff catheter group [2] . However, the SCOPE Collaborative has failed to show any relationship between the number of catheter cuffs and the development of an exit-site/tunnel infection, and several prospective studies in adults and one quality improvement initiative in children have failed to show a difference in peritonitis rates for single- and double-cuff catheters [5, 7]. Of particular interest, a large retrospective cohort study in adults subsequently suggested that the effect of the number of cuffs may be era related, with the benefit of two cuffs negated by the use of prophylactic antibiotics at the catheter exit site [24]. In turn, despite conflicting data and, most importantly, the lack of the necessary randomized controlled trials, the ISPD has suggested that the use of two cuffs may still be preferable because of non-compliance with the routine application of antibiotics at the catheter exit site [5]. Perhaps in response to this type of data, the NAPRTCS database shows that 52% of catheters in 2002–2011 had two cuffs and, more recently, 73% of the catheters in SCOPE centers had two cuffs [7, 25].

The shape of the extraperitoneal portion of the catheter is variable and can be straight or can have a preformed angle (e.g., "swan neck" configuration), in which there is an inverted U-shaped arc (170–180°) between the deep and the superficial cuffs (Fig. 12.2). The latter configuration was originally described by Twardowski et al. and has been recommended by many pediatric programs as a significant improvement in catheter design [26, 27]. While the cumulative NAPRTCS data reports a swan neck/curved tunnel in only 33.9% of catheters (identical to the results of the North American survey by Washburn et al.), the percentage of catheters in the NAPRTCS data that had the swan neck design increased from 24.7% in 1992–2001 to 53.1% in data collected from 2001–2011 [25, 28]. Likewise, the SCOPE Collaborative and the IPPN reported that 68.6% and 74% of their catheters, respectively, had a swan neck tunnel configuration [7, 29]. The purpose of the catheter arc is to (1) allow the catheter to exit the skin in a downward pointing direction and to (2) allow the distal end of the catheter to enter the peritoneal cavity in an unstressed condition (i.e., without too much torque because of the synthetic material's memory), thereby decreasing the chance for its migration out of the pelvis and the development of early drainage failure. Most studies have found this positive outcome to be true [30–32].

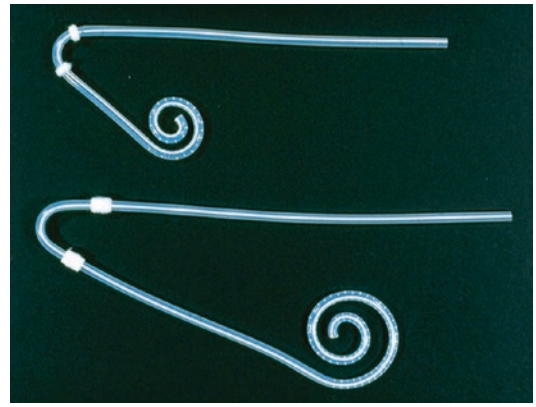

Fig. 12.2 Picture of a Tenckhoff, double-cuff curled catheter with swan neck bend

A modification of this catheter type is the swan neck presternal catheter. The major difference between the swan neck presternal catheter and the standard swan neck catheter is that the presternal catheter has a very long subcutaneous portion and the catheter typically exits over the anterior chest wall. This catheter has been utilized when it is necessary to make the exit site remote from the abdomen, such as in obese patients or patients with incontinence, intestinal stomas, and suprapubic catheters. Crabtree et al. have reported their experience with remote exit sites in adults [33]. They noted a significantly longer time to first exit-site/tunnel infection in the remote exit-site group compared to a standard

exit-site group. However, they also noted a higher incidence of catheter loss from peritonitis in the remote exit-site group. They attributed this to an increased incidence of both an elevated BMI and diabetes in the remote exit-site group. Warchol et al. documented an exit-site infection rate of 1/70.2 patient-months in association with presternal catheter usage in the largest pediatric experience [34]. In a similar manner, locating the catheter exit site on the chest wall of infants with a colostomy has been associated with an acceptable risk of contamination and infrequent peritonitis [35]. However, infants with complex congenital anomalies that require intestinal stomas and a PD catheter exit site that is remote from the stomas often have minimal subcutaneous tissue over the chest which makes cuff erosion/extrusion more likely in that location. One suggested approach to this problem would be to place the two cuffs below the costal margin and then have the catheter exit high on the chest wall [36]. Conversely, a single-cuff catheter may be most desirable.

As mentioned above, a presumed advantage of the swan neck catheter is that it allows a downward pointing exit site which may be associated with a decreased likelihood for the accumulation of dirt and debris within the catheter tunnel prompting the development of a tunnel infection/peritonitis. An upward facing exit site emerged as an independent risk factor for peritonitis in an analysis by Furth et al. of the 1992–1997 NAPRTCS data [37]. The 2011 NAPRTCS data revealed that a straight catheter tunnel was associated with a peritonitis rate of 1/16.2 patient-months, while the rate associated with a swan neck/curved tunnel was only 1/23.9 patient-months [2]. Likewise, the peritonitis rates associated with an upward- and downward-oriented exit site were 1/14.5 patient-months and 1/22.6 patient-months, respectively [2]. In the recent SCOPE analysis of risk factors for peritonitis, the multivariate analysis also revealed that an upward orientation of the exit site was an independent risk factor for peritonitis (RR, 4.2; 95% CI, 1.49 to 11.89; $P < 0.01$) [7]. Finally, while some studies have found the use of the swan neck catheter to be associated with less frequent cuff extrusion, exit-site irritation, and exit-site/tunnel infections, other studies have been unable to confirm the results [38, 39]. In addition, and as mentioned previously, data from the IPPN revealed that the presence of a swan neck tunnel was a significant risk factor for access revision (OR, 1.30; 95% CI, 1.04 to 1.63; $P = 0.02$) [14].

An alternative to the swan neck catheter has been reported by several authors from China [40–42]. They compared the efficacy of using a preformed swan neck catheter to a straight Tenckhoff catheter that was bent into a swan neck configuration (using three surgical incisions) to permit a downward-facing exit site. In all three studies, the performance of the operatively bent Tenckhoff catheter was comparable to the swan neck catheter. The benefit of the latter catheter is related to its significantly lower cost than the swan neck catheter in China.

In summary, the lack of prospective studies in pediatrics designed to evaluate PD catheter characteristics makes it impossible to conclude that one catheter characteristic is superior to another based upon definitive evidence. The NAPRTCS registry data is quite convincing and points out that the time to first peritonitis episode is longer with catheters characterized by two cuffs compared to one, swan neck tunnels compared to straight tunnels, and downward exit sites compared to lateral and upward exit sites. The benefit of this combination of characteristics on decreasing the incidence of peritonitis is significant (Fig. 12.3) [2]. Nevertheless, both the pediatric and adult data highlight the need for additional information on this important topic. Thus, the continued collection of catheter-related data in registries such as the NAPRTCS, SCOPE, and the IPPN, along with the performance of prospective trials, is mandatory if the optimal catheter characteristics are to be determined.

Preoperative Evaluation and Preparation

All patients who are going to undergo PD catheter placement require careful preoperative evaluation. One factor that has been repeatedly cited in

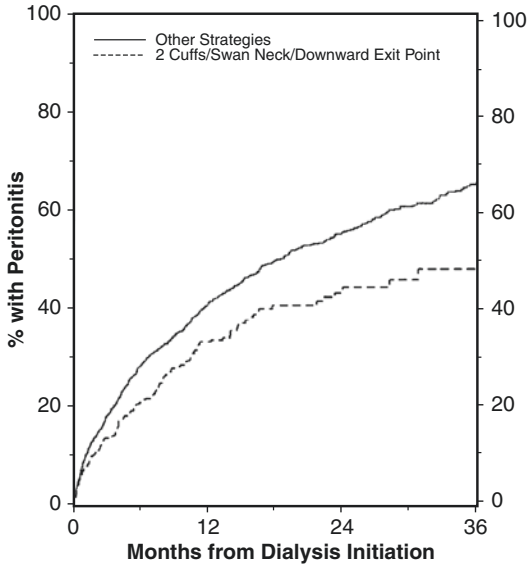

Fig. 12.3 Comparison between catheter with downward-facing exit site, swan neck, and two cuffs versus all other strategies and the time to first episode of peritonitis. (Source: Adapted from Ref. [2])

the literature as being associated with an increased risk for post-placement PD catheter migration is constipation [43]. Constipation is common in patients with chronic kidney disease (CKD) and must be addressed preoperatively with the use of either laxatives or an enema. If an enema is used, attention to its phosphorus content is imperative.

A careful preoperative physical examination is required to determine if the patient has any evidence of a hernia. In children who receive PD, the incidence of hernias is inversely proportional to age, with an overall frequency of 8.0–57.0% [44–47]. The highest frequency of inguinal hernias occurs within the first year of life; they are often bilateral and all require surgical correction. Umbilical hernias can worsen in the PD patient as a result of the increase in intra-abdominal pressure generated by the dialysis fluid. As a result, some have advocated peritoneography or laparoscopic inspection for hernias at the time of catheter placement [45]. If detected, the hernias can then be fixed at the same time the PD catheter is inserted [48–50]. Forehand knowledge of the need for hernia repair will allow the surgeon to allot the appropriate operative time to perform this additional procedure.

A critical portion of the catheter placement procedure is deciding upon the most appropriate location of the exit site. In babies, the exit site of the catheter needs to be outside of the diaper area to help prevent contamination. In older children, it should be either above or below the beltline. The location of the exit site should be discussed with the patient and parents in the preoperative setting. The presence of a vesicostomy, ureterostomy, colostomy, or gastrostomy will also influence the exit-site location. As noted previously, the exit site must be planned so that it is either on the opposite side of the abdomen from any stoma site or, if this is not possible, the catheter may need to exit on the chest in order to increase the distance between the stoma and the exit site. Placement of the exit site on the chest wall with a downward orientation has successfully limited the number of infections in such high-risk situations in children and adults [5, 34, 35, 50, 51]. As younger and generally more complex babies are now surviving, the need for peritoneal dialysis in the setting of multiple stomas is becoming much more common and mandates particular attention to this catheter-related issue [36].

Preoperative showering and the use of chlorhexidine wipes for several days prior to the operative procedure may help decrease the risk of postoperative infection [52]. Preoperative antibiotic administration within 60 minutes prior to PD catheter placement has also been shown, in several studies, to decrease the incidence of peritonitis after insertion of a PD catheter in both children and adults [10, 11, 53, 54]. Interestingly, these studies have shown that any class of antibiotic will be beneficial [5, 10, 53, 55, 56]. Currently, we utilize a first- or second-generation cephalosporin to provide antistaphylococcal coverage, unless the patient is known to already be colonized with *methicillin-resistant Staphylococcus aureus* (MRSA). In the presence of MRSA, we recommend the prophylactic use of clindamycin. This recommendation comes from the pediatric and adult guidelines of the International Society for Peritoneal Dialysis (ISPD) [10, 53, 57].

Routine prophylaxis with vancomycin is not recommended in order to try to avoid the development of vancomycin-resistant organisms, despite the finding in an adult experience of superior results with prophylactic vancomycin versus a cephalosporin [57]. If the child has a lower gastrointestinal stoma, we often add a single dose of an aminoglycoside antibiotic.

Some programs, including our own, will also screen the patient for *S. aureus* nasal carriage prior to PD catheter placement. If positive, a course of intranasal mupirocin (twice daily for 5 days) is recommended [58]. This approach has also recently been recommended by the ISPD [10].

Omentectomy

The data recommending the performance of an omentectomy/omentopexy at the time of catheter placement to prevent PD catheter occlusion is compelling [59]. If an omentectomy is performed, the incidence of catheter occlusion is about 5% compared to an occlusion rate of 10–22.7% in patients without an omentectomy [49, 60]. A survey conducted by the Pediatric Peritoneal Dialysis Study Consortium (PPDSC) found that an omentectomy was routinely performed in 53% of pediatric centers at the time of catheter placement, similar to the 59% figure derived from a survey of North American surgeons [28, 61]. An omentectomy was performed with the insertion of 82.4% of catheters in the Italian PD registry [4]. In a single-center study of 101 pediatric PD patients who underwent reoperation for infection or catheter malfunction, the lack of an omentectomy was a significant risk factor for catheter revision [62]. In practical terms, the omentectomy does not have to be complete. The remnant amount needs to be such that it cannot reach to the catheter once the catheter is positioned in the pelvis.

One group of investigators, however, interpreted their own data related to the issue of omentectomy somewhat differently [60]. Even though they noted a 20% decrease in the incidence of catheter blockage with omentectomy, they calculated that 11 omentectomies would be required to prevent two omental PD catheter blockages. Therefore, they felt that nine patients would undergo an unnecessary omentectomy. In their hands, a secondary omentectomy was not difficult, resulting in their conclusion that omentectomies should only be carried out after a blockage occurs.

An omentopexy can be considered as an alternative to omentectomy [63]. Whereas the objection to omentectomy is the potential for bleeding and the obvious need to extract the omentum from the abdomen, an omentopexy decreases the chances of either of these complications and accomplishes the same desired outcome.

In our center, we believe that either an omentectomy or, more recently, an omentopexy is a fairly simple procedure that can be carried out at the initial operation with little morbidity and should be strongly considered in all cases.

Fibrin Sealant

Fibrin glue has been used in a variety of surgical specialties for its ability to be an effective sealant. The use of fibrin glue in PD has been reported to be both effective in treating established leaks and, when used at the time of catheter implantation, may help prevent the development of peritoneal leaks around catheters that are used soon after being placed [64–66]. Our experience with fibrin glue would support both of these assertions. Typically, 5 cc fibrin glue is applied around the internal cuff and down the tunnel between the inner and outer cuffs prior to closing of the catheter insertion incision.

Surgical Technique

Since Moncrief and Popovich first reported on the use of continuous ambulatory peritoneal dialysis (CAPD), there have been a number of modifications of the technique for implantation of the PD catheter [28, 67, 68]. The complica-

tions of dialysate leakage, dislocation of the catheter, erosion/extrusion of the cuffs, exit-site/tunnel infections, and peritonitis have in one way or another influenced the surgical technique. The two most common PD catheter insertion techniques are the open and laparoscopic techniques. Other approaches include blind placement using the Tenckhoff trocar, blind placement using a guide wire (Seldinger technique), and the mini-trocar peritoneoscopy placement technique [5].

To date, there is no conclusive evidence to suggest that a laparoscopic approach is superior to the open approach [69]. However, over the last few years, several authors have reviewed their experience and concluded that a laparoscopic approach does offer some advantages over the open approach [70–72]. Crabtree et al. have reported a 96% 5-year primary catheter survival without revision and a 99% assisted 5-year catheter survival using a laparoscopic approach [5]. In a prior review of the literature, there was evidence presented on the incidence of PD catheter flow dysfunction and its relationship to the insertion technique: percutaneous needle/guide wire, 10.5–11.2%; open surgical placement, 10.4–17.1%; and laparoscopic, 6–6.9% [70]. The low incidence of catheter flow problems in the laparoscopic group was attributed to a combination of rectus sheath tunneling of the catheter (allowing for positioning of the catheter in the pelvis), along with managing the omentum with either omentopexy or omentectomy. Crabtree et al. have also found that the laparoscopic approach was not necessarily contraindicated when there has been previous surgery or peritonitis [73]. Another author codified their laparoscopic approach as the three-in-one procedure (PD catheter placement, omentectomy, and repair of any hernias). In their series, they described a statistically significant longer catheter life, decreased need for reoperations, and no incidence of omental blockage [74]. At our institution, we currently use the laparoscopic technique as our preferred method for catheter insertion.

Laparoscopic Technique

With the use of laparoscopy, placement of a PD catheter can be performed under direct vision [75]. Additional advantages of the laparoscopic technique are that it allows the use of much smaller peritoneal incisions, thereby decreasing the chance for dialysate leakage, and it makes it possible to conduct a thorough examination of the abdomen. If any pathology is identified that would potentially interfere with catheter performance (adhesions, inguinal hernias), the problem(s) can be corrected at the time of catheter placement. We currently use a modification of the technique first described by Daschner et al. [76] and more recently by Crabtree et al. [70].

The catheter insertion site is chosen with consideration of the patient's size, the need for the catheter to exit in a downward direction, and the presence of any stomas. Consideration must also be given to the fact that small children may need a gastrostomy in the future. If there are no plans for a gastrostomy at the time of PD catheter placement or later, we prefer to place the catheter on the left side of the abdomen so that it is away from the future transplant incision. The exit site of the catheter in our hands is typically positioned above the beltline or diaper area. However, in very large children, it may be necessary to locate the catheter below the beltline so that the catheter will reach into the pelvis. The catheter entrance site is marked, usually just lateral and below the umbilicus, over the rectus sheath. An appropriate-sized catheter is then picked by having the inner cuff of the catheter over the entrance site and the bottom of the curl at the symphysis pubis. The exit site is then located and marked so that the catheter's exit site orientation will be downgoing.

Under general anesthesia, a vertical incision is made in the umbilicus, and the umbilical fascia is sharply incised. Using blunt dissection, the peritoneum is entered and a 5 mm port is placed. A 5 mm laparoscope is then inserted and the abdomen is insufflated. A 3 mm instrument is then inserted through a stab wound at the marked catheter exit site. The abdomen is then inspected

for any adhesions or inguinal hernias. If adhesions are noted, they are lysed at this time, and any inguinal hernias are repaired laparoscopically at the end of the case. The omentum is then assessed and, if necessary, removed. We feel that a complete omentectomy is not necessary as long as the omentum is prevented from entering the pelvis. We remove the omentum by inserting a 3 mm scope via the 3 mm stab wound, and the omentum is pulled out via the umbilicus and excised with electrocautery. The omentum can also be plicated using different techniques [5].

A 2 cm transverse incision is then made at the previously marked entrance site for the PD catheter and carried down to the anterior rectus sheath. The anterior sheath is opened for a distance of 3 mm, and a 5 mm port is inserted through the rectus muscle down to the posterior rectus sheath and then tunneled under direct vision via the umbilical camera for a distance of between 3 and 7 cm (depending on the size of the patient), and then the tip of the port is popped into the abdomen above the bladder.

A guide wire is inserted into the abdomen via the entrance site port. The port is then removed and a 20 French sheath is inserted into the abdomen over the guide wire (Fig. 12.4). The PD catheter is then inserted deep into the pelvis behind the bladder (uterus) under direct vision. The pneumoperitoneum is maintained by pushing the proximal cuff of the PD catheter into the sheath and clamping the end of catheter, thereby preventing gas loss. Once the catheter has been positioned into the pelvis, the sheath is removed (Fig. 12.5). As the sheath is being removed, the inner cuff is positioned to lie between the anterior and posterior portions of the rectus sheath. The inner cuff is then fixed to the anterior rectus sheath with a purse string suture of 3-0 PDS. A second purse string suture of 3-0 PDS is then placed around the fascial exit site of the catheter. Care is taken to make sure that the innermost portion of the cuff does not project into the peritoneum (Fig. 12.6). The camera and all ports are then removed, and the umbilicus is repaired, including repair of any umbilical hernia.

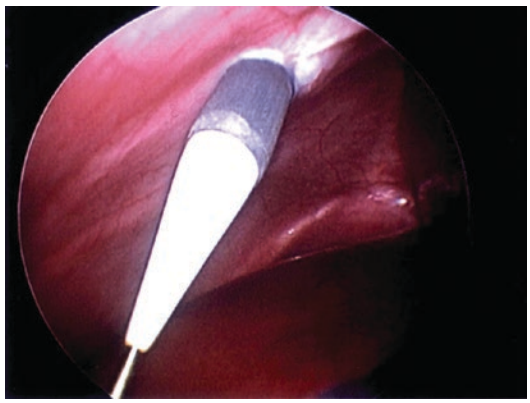

Fig. 12.4 A laparoscopic view of the 20 French peelaway sheath being inserted into the peritoneum over a guide wire. (From Chapter 45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

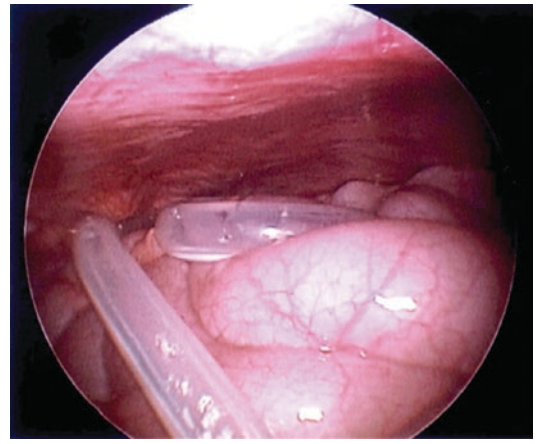

Fig. 12.5 A laparoscopic view of the PD catheter which lies positioned in the pelvis. The catheter is sitting between the bowel and the anterior abdominal wall. (From Chapter 45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

At the previously marked catheter exit site, a deep subcutaneous tunnel is created between the catheter exit site and the catheter entrance site using either the previous 20 French sheath dilator or a tendon passer. The end of the catheter is then pulled through the tunnel, positioning the outer cuff so that it is approximately 2.0 cm from the exit site and the end of the catheter is exiting the skin in a downward fashion. Shorter distances between the exit site and outer cuff pre-

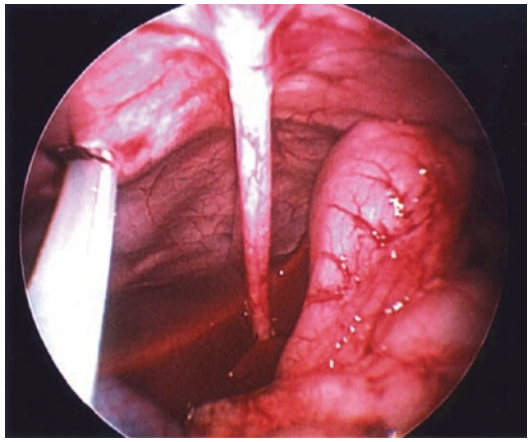

Fig. 12.6 A laparoscopic view of the PD catheter (*left*) showing it leaving the peritoneal cavity. Note that the inner cuff is not visible within the peritoneal cavity. (From Chapter 45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

dispose to cuff extrusion, while greater distances lead to formation of a deep sinus tract, granulation tissue formation, and an increased risk of a tunnel infection [48]. At this point, fibrin sealant is injected around the catheter entrance site and down the subcutaneous tunnel and around the second cuff. We feel that this helps insure a leak-free closure. The entrance site of the catheter is then closed in two layers. The exit site of the catheter is dressed, and the catheter is secured to prevent local trauma, but no fixation suture is used at the exit site. The use of a fixation suture is contraindicated because it can contribute to both an exit-site/tunnel infection and poor exit-site healing [5, 53].

Open Technique

Catheter location and length are determined using the same methods as noted with the laparoscopic approach. The most frequent open technique utilizes a transverse incision over the mid portion of the rectus muscle lateral to the umbilicus. The rectus muscle is split in the direction of its fibers and the posterior sheath is then opened longitudinally. An omentectomy is then carried out under direct vision. The PD catheter is threaded over a stiffening wire to allow its placement deep in the pelvis, a few degrees off the midline to help prevent obstruction to flow in the setting of a full rectum. The posterior sheath is closed and the inner cuff is fixed to the posterior sheath as part of this closure. The inner cuff is positioned within the rectus muscle, and the anterior sheath is then closed tightly around the catheter with a second purse string suture around the cuff of the catheter at the level that it exits the anterior rectus sheath. The catheter is then tunneled out to the skin, and the outer cuff is situated 2.0 cm from the catheter exit site, as described above. Fibrin glue is also applied using the same technique as with the laparoscopic approach. An insertion through the rectus sheath is generally deemed preferable to the midline because of the thinness of the abdominal wall in children and a decreased propensity for postoperative leakage [48]. However, the few prospective trials on incision location that have been conducted in adults have not demonstrated a superiority of the rectus sheath versus the midline approach [5].

One advantage of the open technique is the ability to directly visualize placement of the catheter into the pelvis. This can be beneficial in those patients who have previously undergone pelvic surgery. In addition, the open technique allows for an omentectomy to be easily performed at the same time the PD catheter is placed. The major problem with this technique is the necessity for a significant incision in the peritoneum. In turn, for optimal dialysis performance and a decreased likelihood of postoperative leakage of dialysis fluid, this technique ideally requires a 2-week rest period between the time of catheter insertion and the initiation of dialysis [5, 58, 77]. This delay allows for healing of the peritoneal incision and for incorporation of the cuff into the peritoneum and posterior sheath.

Postimplantation Care

The exit site of the catheter, since it is not occlusive, is a potential site of infection after PD catheter placement. In an attempt to address this

issue, Moncrief previously suggested that the external portion of the catheter should initially remain buried beneath the skin in a subcutaneous pocket for 4–6 weeks in order for both cuffs to become incorporated into the tissues [78]. After this time period, an exit site is created over the subcutaneous pocket, and the catheter is exteriorized. The patient is able to proceed to full-volume PD without the need for a break-in period. While successful in its application as evidenced by an approximate 90% immediate function rate after externalization, prospective trials comparing initial exteriorization of the catheter versus implantation and subcutaneous burying of the catheter for 6 weeks did not demonstrate a significant difference in the rate of either peritonitis or exit-site/tunnel infections or on long-term catheter survival [5, 8, 79–83]. Twardowski et al., on the other hand, merely recommended that initially, the exit site should only be covered with several layers of sterile gauze and should be kept dry [84, 85]. Some oozing from the exit site is common and the gauze can wick this away from the skin.

An occlusive dressing should *not* be used. Occlusive dressings tend to trap fluid at the exit site predisposing to bacterial growth and subsequent infection. Trauma to the exit site, usually from repeated catheter motion, needs to be minimized. Therefore, the catheter must be securely fixed with a dressing, and dressing changes should not routinely occur more often than once per week until the exit site is healed. Ideally, specially trained staff should conduct the dressing changes, which allows a consistent aseptic technique to be followed and which decreases the risk for bacterial colonization [53, 86, 87]. Submersion of the exit site should be avoided to prevent colonization with waterborne organisms. This is the approach used in our program, one that has helped prevent the development of early exit-site/tunnel infections as a complication of catheter implantation in virtually all cases [86].

Timing of Catheter Use

Some controversy exists as to whether the catheter should be used immediately after placement or whether a timed period (e.g., rest period) should elapse prior to its use to facilitate healing and help prevent the development of complications such as leakage and infection. The 1998 ISPD catheter guidelines recommended a dialysis-free period of 10–15 days after catheter insertion, while the 2005 European guidelines recommended at least a 2-week waiting period, whenever possible [8, 58]. These recommendations were supported by a study conducted by Patel et al. in which immediate versus delayed (an average of 20 days) catheter use was compared [88]. The authors noted an increased incidence of dialysate leakage in the immediate use group, but a disconcerting increase in exit-site/tunnel infections and peritonitis in the delayed catheter use group. In a retrospective review of NAPRTCS data, Rahim et al. found that early (<14 days) versus late onset of usage was associated with an increased risk of leakage, but there was no difference in the risk of infection [77]. The Italian PD registry did not reveal any difference in the incidence of leakage or catheter survival when comparing catheters used early (<7 days) versus late [4]. Most recently, Crabtree et al. recommended a break-in period of at least 2 weeks to decrease the risk of mechanical complications, and Keswani et al. and the SCOPE Collaborative found that dialysis initiation at less than 14 days following PD catheter insertion was significantly associated with the development of peritonitis within 60 days of PD catheter placement [5, 89]. Accordingly, while there is little evidence upon which to generate a definitive recommendation, observational data and expert opinion suggest that delayed PD initiation should be encouraged whenever possible. Of course, when early usage is necessary, efforts should be made to minimize any increase in intraperitoneal pressure by using small exchange volumes, possibly in the supine position with a cycling device [90, 91]. In addition, Imani et al. noted that the risk of postimplantation leaks in infants was greatest in the first 3 days, suggesting that if it was not possible to wait a full 2 weeks to use a catheter, a delay of at least 3 days should be targeted [50].

In contrast to regular PD initiation, many centers do initiate a PD catheter flushing procedure following catheter placement until reg-

ular PD is being conducted. The primary reason for flushing is to prevent fibrin or blood clot from obstructing the catheter. While a variety of different schedules exist, a commonly practiced approach is to flush the catheter with a fill volume of 10–20 ml/kg on a weekly basis until regular dialysis is initiated [92]. If substantial blood is noted in the effluent immediately after the insertion, it is advisable to flush the catheter within 24 hours of the surgical procedure.

Chronic Exit-Site Care

The goal of chronic exit-site care is to prevent the development of exit-site/tunnel infections. The SCOPE Collaborative has evaluated the frequency of exit-site infections in more than 700 children on PD and found a rate of 0.25 exit-site infections per dialysis year [93]. As suggested by Twardowski and Prowant, exit-site care consists of assessment of the exit site, cleansing the exit site, immobilizing the catheter, and protecting the exit site and tunnel from trauma [84, 94]. SCOPE has also emphasized the importance of hand hygiene and of regularly evaluating the exit site using standardized criteria [95]. In adults, it is recommended that exit-site care occur at least twice weekly, and always after a shower [10]. Cleansing agents that have been used include soap and water, povidone-iodine, chlorhexidine, and electrolytic chloroxidizing solutions. To date, no one cleansing agent has been shown to be superior to the others. In addition to the direct exit-site care, data in children and adults support the use of prophylactic antibiotic agents to decrease the incidence of *S. aureus* carriage in patients [53]. The application of either mupirocin or gentamicin creams to the catheter exit site has been efficacious in decreasing exit-site/tunnel infections, the latter agent in particular against Gram-negative infections [96–101]. Alternating mupirocin and gentamicin has been found to be associated with an increased risk for fungal peritonitis vs. gentamicin alone [102].

Mechanical Complications

Mechanical complications are generally felt to be the second most common reason (after infection) for PD catheter failure. In an analysis of 452 PD catheter revisions in children, Borzych-Duzalka et al. found that mechanical malfunction was the reason for revision in 60% of cases and access dysfunction secondary to mechanical causes doubled the risk of technique failure compared with infectious causes [14]. The mechanical complications include obstruction of the catheter by omentum, migration of the catheter out of the pelvis, and blockage of the catheter by fibrin or clots. The issue of obstruction by omentum has been previously reviewed and, as mentioned above, usually can be prevented by conducting a partial omentectomy or omentopexy at the time of catheter insertion [63, 103]. When omental blockage does occur, laparoscopic removal of the involved omentum can be easily accomplished. Migration of the catheter out of the pelvis can lead to poor dialysate inflow or outflow, as well as increased pain with dialysis. One approach to repositioning the catheter is through the use of interventional radiology techniques, in which a guide wire is used to move the catheter back to a workable position in the abdomen. Using this technique, Savader et al. reported that they were able to obtain a durable patency rate of 50% in those patients who experienced early catheter malposition (less than 30 days) and a durable patency rate of 82% with late malpositions (greater than 30 days) [104]. The complication rate was low (3%), with only a single episode of peritonitis. The risk for migration of the catheter can be lessened by the addition of rectus tunneling at the time of catheter insertion. Also, if there are recurrent problems with catheter migration, the catheter can be secured laparoscopically with a suture in the pelvis [63].

Our center has used a laparoscopic approach to non-functioning PD catheters. In patients who have had no previous abdominal procedures besides the peritoneal catheter placement, we create a pneumoperitoneum by insufflating through the malpositioned PD catheter. Once a pneumoperitoneum is achieved, a 3 mm port is placed in the left upper

quadrant, and a 3 mm laparoscope is inserted. A stab wound is then made in the right upper quadrant and a 3 mm grasper is inserted. The catheter can then be manipulated under direct vision and repositioned back into the pelvis. Any adhesions that are encountered during the repositioning of the catheter are lysed at the same time, and any obstructing omentum can be removed via the port or stab site. This technique avoids a large incision in the peritoneum, thus allowing a rapid return to dialysis.

For catheters that are occluded by fibrin or blood clot, tissue plasminogen activator (tPA) has been shown to be very effective in unblocking these catheters. Two milligrams of TPA is reconstituted in 40 cm^3 of normal saline and is instilled in the catheter for 1 h. This has resulted in the restoration of patency in 57% of catheters [105–107].

Exit-Site Infection, Tunnel Infection, and Peritonitis

Catheter exit-site/tunnel infections and peritonitis are a significant cause of catheter failure. The Italian PD registry documented catheter infections as the most common catheter-related complication, with a prevalence of 73.2% and an incidence of 1 episode/27.4 patient-months [4]. As noted above, the SCOPE Collaborative recently found an annualized overall exit-site infection rate of 0.25 (equivalent to 1 episode/48 patient-months), with 69% of the infections involving the exit site alone, 23% involving only the catheter tunnel, and 8% involving both locations [93]. The goal in all cases should be the prevention of infection by following published recommendations regarding catheter insertion and care and by regular exit-site monitoring with a scoring system [53]. If, however, an infection does occur, medical management is typically successful [10, 53, 108]. Oral antibiotics that may be used for the treatment of exit-site/tunnel infections in children are described in Table 12.3 [53]. Daily exit-site care is also recommended when an infection is present [10]. In situations in which oral antibiotic therapy of an exit-site infection is unsuccessful or when it has been accompanied by a tunnel infection, intravenous or intraperitoneal antibiotic therapy should be considered.

Table 12.3 Oral antibiotics used in exit-site and tunnel infections

Antibiotic	Recommended dose	Dose frequency	Per-dose maximum
Amoxicillin	10–20 mg/kg/day	Daily	1,000 mg
Cephalexin	10–20 mg/kg/day	Daily or 2 times daily	1,000 mg
Ciprofloxacin	10–15 mg/kg/day	Daily	500 mg
Clarithromycin	7.5 mg/kg/day	Daily or 2 times daily	500 mg
Clindamycin	30 mg/kg/day	3 times daily	600 mg
Dicloxacillin		4 times daily	500 mg
<40 kg	12–50 mg/kg/day		
>40 kg	125–500 mg/dose		
Erythromycin (as base)	30–50 mg/kg/day	3 or 4 times daily	500 mg
Fluconazole	6 mg/kg/day	Every 24–48 h	400 mg
Levofloxacin	10 mg/kg	Every 48 h	Day 1 500 mg. then 250 mg
Linezolid			600 mg
<5 years	10 mg/kg/dose	3 times daily	
5–11 years	10mg/kg/dose	2 times daily	
≥12 years	600 mg/dose	2 times daily	
Metronidazole	30 mg/kg/day	3 times daily	500 mg
Rifampin[a]	10–20 mg/kg/day	2 times daily	600 mg
Trimethoprim-sulfamethoxazole (based on TMP)	5–10 mg/kg/day	Daily	80 mg

Used with permission from Warady et al. [53]

[a]Should not be used as monotherapy, or used routinely in areas in which tuberculosis is endemic

Surgical salvage of the catheter by unroofing/cuff shaving has been conducted [5, 18, 19, 109, 110]. Cuff shaving involves removing (or shaving off) the infected subcutaneous cuff and then rerouting the catheter to a different exit site remote from the infected site . Wu et al. described a technique in which the authors were able to preserve the intraperitoneal portion of the dialysis catheter and simply excise the external infected portion of the catheter [110]. This was accomplished by cutting down on the entrance site of the catheter into the peritoneum. At this point, the catheter is divided just above the internal cuff, and a new external portion with a new external cuff is then glued in place and passed out to the skin via a separate tunnel. The infected external portion of the catheter is then removed. They reported 26 catheter revisions in 23 patients with 100% resolution of the infection without interruption of peritoneal dialysis. To date, we have not had to utilize this technique, but it is intriguing to consider it for those patients in whom interruption of PD would be extraordinarily difficult.

The more standard surgical intervention for infection would be complete removal of the catheter when there is refractory peritonitis, fungal peritonitis, or a refractory catheter exit-site/tunnel infection [5, 53]. Preservation of the peritoneum should always take precedence over preservation of the catheter. In those patients in whom the infection is caused by a Gram-positive organism and the dialysate white blood cell count is $<100/mm^3$, catheter removal and replacement can occur as a single procedure under antibiotic coverage [111–113]. In contrast, fungal peritonitis and Gram-negative infections mandate that there is at least a 2–3-week interval between removal and reinsertion.

PD Catheter Care Post-Kidney Transplantation

If the PD catheter is not removed at the time of kidney transplantation, it is recommended that dressing care occur weekly during the post-transplant period. In most cases, catheters are removed within 4 weeks following successful kidney transplantation. It is not necessary to obtain routine PD cultures. While two studies noted an absence of catheter infections after transplantation if the PD catheters were left in place but not used, one of the studies did find an increased incidence of catheter infections after the first post-transplant month [114, 115]. They also noted that the majority of complications that would require the use of the catheter occurred within the first month. For this reason, they advocate and we agree that the peritoneal catheter can be safely left in place for 1 month, after which time it should be removed if it is no longer needed.

Complications with PD Catheter Removal

An interesting short report by Korzets et al. makes the case that the removal of a PD catheter can be associated with significant complications [116]. In their series of 40 catheter removals, 10 (25%) of the procedures were associated with complications, and 8 of these required further surgical intervention. Half of their complications were related to bleeding. Their usual technique was to remove the PD catheter under local anesthesia, which they felt contributed significantly to their complication rate. They also make a strong case against using traction as the removal technique because of the complications of a retained cuff and subsequent infection. The surgeon removing the catheter must be aware of the device type and implant procedure and recognize that the more complex the catheter design, the more difficult the removal. In summary, the removal of a PD catheter is a real operation that should be done in the operating room with anesthesia, and it requires strict attention to detail to prevent annoying but potentially significant complications that could require a return to the operating room.

Conclusion

The peritoneal catheter is the lifeline for the patient receiving peritoneal dialysis. Attention to detail is, in turn, necessary for everything from the selection of the best location for the exit site to the prophylactic measures used to prevent

infectious complications. The establishment of a catheter "team" with a select group of participating surgeons and the regular evaluation of treatment results are initiatives designed to optimize the function of this important component of PD.

References

1. Saran R, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2019;73(3 suppl 1):Svii–Sxxii. S1–S772
2. NAPRTCS 2011 Annual Dialysis Report.
3. Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. ASAIO Trans. 1968;14:181–7.
4. Rinaldi S, Sera F, Verrina E, et al. Chronic peritoneal dialysis catheters in children: a fifteen-year experience of the Italian Registry of Pediatric Chronic Peritoneal Dialysis. Perit Dial Int. 2004;24(5):481–6.
5. Crabtree JH, Shrestha BM, Chow KM, Figueiredo AE, Povlsen JV, Wilkie M, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. Perit Dial Int. 2019;39(5):414–36.
6. Twardowski ZJ. Peritoneal access: the past, present, and the future. Contrib Nephrol. 2006;150:195–201.
7. Sethna CB, Bryant K, Munshi R, Warady BA, Richardson T, Lawlor J, et al. Risk factors for and outcomes of catheter-associated peritonitis in children: the SCOPE collaborative. Clin J Am Soc Nephrol. 2016;11(9):1590–6.
8. Gokal R, Alexander S, Ash S, et al. Peritoneal catheters and exit-site practices toward optimum peritoneal access: 1998 update. (Official report from the International Society for Peritoneal Dialysis). Perit Dial Int. 1998;18(1):11–33.
9. Rinaldi S, Sera F, Verrina E, et al. The Italian Registry of Pediatric Chronic Peritoneal Dialysis: a ten-year experience with chronic peritoneal dialysis catheters. Perit Dial Int. 1998;18:71–4.
10. Szeto CC, Li PK, Johnson DW, Bernardini J, Dong J, Figueiredo AE, et al. ISPD catheter-related infection recommendations: 2017 update. Perit Dial Int. 2017;37(2):141–54.
11. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Catheter-related interventions to prevent peritonitis in peritoneal dialysis: a systematic review of randomized, controlled trials. J Am Soc Nephrol. 2004;15(10):2735–46.
12. Hagen SM, Lafranca JA, JN IJ, Dor FJ. A systematic review and meta-analysis of the influence of peritoneal dialysis catheter type on complication rate and catheter survival. Kidney Int. 2014;85(4):920–32.
13. Chow KM, Wong SSM, Ng JKC, Cheng YL, Leung CB, Pang WF, et al. Straight versus coiled peritoneal Dialysis catheters: a randomized controlled trial. Am J Kidney Dis. 2020;75(1):39–44.
14. Borzych-Duzalka D, Aki TF, Azocar M, White C, Harvey E, Mir S, et al. Peritoneal Dialysis access revision in children: causes, interventions, and outcomes. Clin J Am Soc Nephrol. 2017;12(1):105–12.
15. Alexander SR, Tank ES. Surgical aspects of continuous ambulatory peritoneal dialysis in infants, children and adolescents. J Urol. 1982;127(3):501–4.
16. Vigneau A, Hardy B, Balfe JA. Chronic peritoneal catheter in children: one or two Dacron cuffs? (Letter). Perit Dial Bull. 1981;1:151.
17. Scalamogna A, De Vecchi A, Maccario M, Castelnovo C, Ponticelli C. Cuff-shaving procedure. A rescue treatment for exit-site infection unresponsive to medical therapy. Nephrol Dial Transplant. 1995;10(12):2325–7.
18. Yoshino A, Honda M, Ikeda M, et al. Merit of the cuff-shaving procedure in children with chronic infection. Pediatr Nephrol. 2004;19(11):1267–72.
19. Crabtree JH, Burchette RJ. Surgical salvage of peritoneal dialysis catheters from chronic exit-site and tunnel infections. Am J Surg. 2005;190(1):4–8.
20. Stone MM, Fonkalsrud EW, Salusky IB, Takiff H, Hall T, Fine RN. Surgical management of peritoneal dialysis catheters in children: five-year experience with 1,800 patient-month follow-up. J Pediatr Surg. 1986;21(12):1177–81.
21. Donmez O, Durmaz O, Ediz B, Cigerdelen N, Kocak S. Catheter-related complications in children on chronic peritoneal dialysis. Adv Perit Dial. 2005;21:200–3.
22. Lewis MA, Smith T, Postlethwaite RJ, Webb NJ. A comparison of double-cuffed with single-cuffed Tenckhoff catheters in the prevention of infection in pediatric patients. Adv Perit Dial. 1997;13:274–6.
23. Neu AM, Miller MR, Lawlor SJ, Richardson T, Martz K, Rosenberg C, Newland J, McAfee N, Begin B, Warady BA. Design of the standardizing care to improve outcomes in pediatric end stage renal disease collaborative. Peidatr Nephrol. 2014;29(9):1477–84.
24. Nessim SJ, Bargman JM, Jassal SV. Relationship between double-cuff versus single-cuff peritoneal dialysis catheters and risk of peritonitis. Nephrol Dialysis Transplant. 2010;25(7):2310–4.
25. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol (Berlin, Germany). 2017;32(12):2319–30.
26. Twardowski ZJ, Prowant BF, Nichols WK, Nolph KD, Khanna R. Six-year experience with swan neck catheters. Perit Dial Int. 1992;12(4):384–9.
27. Auron A, Simon S, Andrews W, et al. Prevention of peritonitis in children receiving peritoneal dialysis. Pediatr Nephrol. 2007;22(4):578–85.
28. Washburn KK, Currier H, Salter KJ, Brandt ML. Surgical technique for peritoneal dialysis catheter placement in the pediatric patient: a North American survey. Adv Perit Dial. 2004;20:218–21.

29. Warady BA, Feneberg R, Verrina E, et al. Peritonitis in children who receive long-term peritoneal dialysis: a prospective evaluation of therapeutic guidelines. J Am Soc Nephrol. 2007;18(7):2172–9.
30. Gadallah MF, Mignone J, Torres C, Ramdeen G, Pervez A. The role of peritoneal dialysis catheter configuration in preventing catheter tip migration. Adv Perit Dial. 2000;16:47–50.
31. Lye WC, Kour NW, van der Straaten JC, Leong SO, Lee EJ. A prospective randomized comparison of the Swan neck, coiled, and straight Tenckhoff catheters in patients on CAPD. Perit Dial Int. 1996;16(Suppl 1):S333–5.
32. Moreiras P, Cuina L, Goyanes G, Lavoratti G, Gonzalez L. Mechanical complications in chronic peritoneal dialysis. Clin Nephrol. 1999;52(2):124–30.
33. Crabtree JH, Burchette RJ. Comparative analysis of two-piece extended peritoneal dialysis catheters with remote exit-site locations and conventional abdominal catheters. Perit Dial Int. 2010;30(1):46–55.
34. Warchol S, Ziolkowska H, Roszkowska-Blaim M. Exit-site infection in children on peritoneal dialysis: comparison of two types of peritoneal catheters. Perit Dial Int. 2003;23(2):169–73.
35. Chadha V, Jones LL, Ramirez ZD, Warady BA. Chest wall peritoneal dialysis catheter placement in infants with a colostomy. Adv Perit Dial. 2000;16:318–20.
36. Ta A, Saxena S, Badru F, Lee ASE, et al. Laparoscopic peritoneal Dialysis catheter placement with chest wall exit site for neonate with stoma. Perit Dial Int. 2019;39(5):405–8.
37. Furth SL, Donaldson LA, Sullivan EK, Watkins SL. Peritoneal dialysis catheter infections and peritonitis in children: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 2000;15(3–4):179–82.
38. Eklund BH, Honkanen EO, Kala AR, Kyllonen LE. Peritoneal dialysis access: prospective randomized comparison of the Swan neck and Tenckhoff catheters. Perit Dial Int. 1995;15(8):353–6.
39. Lo W, Lui S, Li F, et al. A prospective randomized study on three different peritoneal dialysis catheters. Perit Dial Int. 2003;23:S127–31.
40. Yip T, Lui SL, Tse KC, et al. A prospective randomized study comparing Tenckhoff catheters inserted using the triple incision method with standard swan neck catheters. Perit Dial Int. 2010;30(1):56–62.
41. Xie JY, Chen N, Ren H, Huang XM, Zhu P. Prospective studies on applications of a two-cuff Swan neck catheter and a Tenckhoff catheter to Chinese CAPD patients. Clin Nephrol. 2009;72(5):373–9.
42. Li CL, Cui TG, Gan HB, Cheung K, Lio WI, Kuok UI. A randomized trial comparing conventional swan-neck straight-tip catheters to straight-tip catheters with an artificial subcutaneous swan neck. Perit Dial Int. 2009;29(3):278–84.
43. Flanigan M, Gokal R. Peritoneal catheters and exit-site practices toward optimum peritoneal access: a review of current developments. Perit Dial Int. 2005;25(2):132–9.
44. Hooman N, Esfahani ST, Mohkam M, Derakhshan A, Gheissari A, Vazirian S, et al. The outcome of Iranian children on continuous ambulatory peritoneal dialysis: the first report of Iranian National Registry. Arch Iran Med. 2009;12(1):24–8.
45. Stringel G, McBride W, Weiss R. Laparoscopic placement of peritoneal dialysis catheters in children. J Pediatr Surg. 2008;43(5):857–60.
46. Laakkonen H, Holtta T, Lonnqvist T, Holmberg C, Ronnholm K. Peritoneal dialysis in children under two years of age. Nephrol Dialysis Transplant. 2008;23(5):1747–53.
47. Lessin MS, Luks FI, Brem AS, Wesselhoeft CW Jr. Primary laparoscopic placement of peritoneal dialysis catheters in children and young adults. Surg Endosc. 1999;13(11):1165–7.
48. Brandt M, Brewer E. Peritoneal dialysis access in children. Dordrecht: Kluwer Academic Publishers; 2004.
49. Conlin MJ, Tank ES. Minimizing surgical problems of peritoneal dialysis in children. J Urol. 1995;154(2 Pt 2):917–9.
50. Imani PD, Carpenter JL, Bell CS, Brandt ML, Braun MC, Swartz SJ. Peritoneal dialysis catheter outcomes in infants initiating peritoneal dialysis for end-stage renal disease. BMC Nephrol. 2018;19(1):231.
51. Twardowski ZJ. Presternal peritoneal catheter. Adv Ren Replace Ther. 2002;9(2):125–32.
52. Leaper D, Burman-Roy S, Palanca A, Cullen K, Worster D, Gautam-Aitken E, et al. Prevention and treatment of surgical site infection: summary of NICE guidance. BMJ. 2008;337:a1924.
53. Warady BA, Bakkaloglu S, Newland J, Cantwell M, Verrina E, Neu A, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
54. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Antimicrobial agents to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. Am J Kidney Dis. 2004;44(4):591–603.
55. Harvey EA. Peritoneal access in children. Perit Dial Int. 2001;21(Suppl 3):S218–22.
56. Bonifati C, Pansini F, Torres DD, Navaneethan SD, Craig JC, Strippoli GF. Antimicrobial agents and catheter-related interventions to prevent peritonitis in peritoneal dialysis: using evidence in the context of clinical practice. Int J Artif Organs. 2006;29(1):41–9.
57. Gadallah MF, Ramdeen G, Mignone J, Patel D, Mitchell L, Tatro S. Role of preoperative antibiotic prophylaxis in preventing postoperative peritonitis in newly placed peritoneal dialysis catheters. Am J Kidney Dis. 2000;36(5):1014–9.
58. Dombros N, Dratwa M, Feriani M, et al. European best practice guidelines for peritoneal dialysis.

3 peritoneal access. Nephrol Dial Transplant. 2005;20(Suppl 9):ix8–12.
59. Reissman P, Lyass S, Shiloni E, Rivkind A, Berlatzky Y. Placement of a peritoneal dialysis catheter with routine omentectomy – does it prevent obstruction of the catheter? Eur J Surg. 1998;164(9):703–7.
60. Lewis M, Webb N, Smith T, Roberts D. Routine omentectomy is not required in children undergoing chronic peritoneal dialysis. Adv Perit Dial. 1995;11:293–5.
61. Neu AM, Kohaut EC, Warady BA. Current approach to peritoneal access in North American children: a report of the Pediatric Peritoneal Dialysis Study Consortium. Adv Perit Dial. 1995;11:289–92.
62. Phan J, Stanford S, Zaritsky JJ, DeUgarte DA. Risk factors for morbidity and mortality in pediatric patients with peritoneal dialysis catheters. J Pediatr Surg. 2013;48(1):197–202.
63. Cao W, Tu C, Jai T, Liu C, et al. Prophylactic laparoscopic omentectomy: a new technique for peritoneal dialysis catheter placement. Ren Fail. 2019;41(1):113–1.
64. Sojo E, Bisigniano L, Turconi A, et al. Is fibrin glue useful in preventing dialysate leakage in children on CAPD? Preliminary results of a prospective randomized study. Adv Perit Dial. 1997;13:277–80.
65. Sojo ET, Grosman MD, Monteverde ML, Bailez MM, Delgado N. Fibrin glue is useful in preventing early dialysate leakage in children on chronic peritoneal dialysis. Perit Dial Int. 2004;24(2):186–90.
66. Rusthoven E, van de Kar NA, Monnens LA, Schroder CH. Fibrin glue used successfully in peritoneal dialysis catheter leakage in children. Perit Dial Int. 2004;24(3):287–9.
67. Popovich R, Moncrief J, Decherd JF, et al. The definition of a novel wearable/portable equilibrium peritoneal dialysis technique. Trans Am Soc Artif Intern Organs. 1976;5:64.
68. Gadallah MF, Pervez A, el-Shahawy MA, et al. Peritoneoscopic versus surgical placement of peritoneal dialysis catheters: a prospective randomized study on outcome. Am J Kidney Dis. 1999;33(1):118–22.
69. Htay H, Johnson DW. Catheter type, placement, and insertion techniques for preventing catheter-related infections in maintenance peritoneal Dialysis patients: summary of a Cochrane review. AJKD. 2019;74(ISS 5):703–5.
70. Crabtree JH, Burchette RJ. Effective use of laparoscopy for long-term peritoneal dialysis access. Am J Surg. 2009;198(1):135–41.
71. Copeland DR, Blaszak RT, Tolleson JS, et al. Laparoscopic Tenckhoff catheter placement in children using a securing suture in the pelvis: comparison to the open approach. J Pediatr Surg. 2008;43(12):2256–9.
72. Maio R, Figueiredo N, Costa P. Laparoscopic placement of Tenckhoff catheters for peritoneal dialysis: a safe, effective, and reproducible procedure. Perit Dial Int. 2008;28(2):170–3.
73. Crabtree JH, Burchette RJ. Effect of prior abdominal surgery, peritonitis, and adhesions on catheter function and long-term outcome on peritoneal dialysis. Am Surg. 2009;75(2):140–7.
74. Wong YS, Pang KKY, Ma ALT, et al. A standardized technique of laparoscopic placement of peritoneal dialysis catheter with omentectomy and closure of patent processus vaginalis: a 3-in-1 minimally invasive surgical approach in children. J Pediatr Surg. https://doi.org/10.1016/j.jpedsurg.2019.09.033.
75. Wang JY, Chen FM, Huang TJ, et al. Laparoscopic assisted placement of peritoneal dialysis catheters for selected patients with previous abdominal operation. J Investig Surg. 2005;18(2):59–62.
76. Daschner M, Gfrorer S, Zachariou Z, Mehls O, Schaefer F. Laparoscopic Tenckhoff catheter implantation in children. Perit Dial Int. 2002;22(1):22–6.
77. Rahim KA, Seidel K, McDonald RA. Risk factors for catheter-related complications in pediatric peritoneal dialysis. Pediatr Nephrol. 2004;19(9):1021–8.
78. Moncrief JW, Popovich RP. Moncrief-Popovich catheter: implantation technique and clinical results. Perit Dial Int. 1994;14(Suppl 3):S56–8.
79. Danielsson A, Blohme L, Tranaeus A, Hylander B. A prospective randomized study of the effect of a subcutaneously "buried" peritoneal dialysis catheter technique versus standard technique on the incidence of peritonitis and exit-site infection. Perit Dial Int. 2002;22(2):211–9.
80. Esson ML, Quinn MJ, Hudson EL, Teitelbaum I. Subcutaneously tunnelled peritoneal dialysis catheters with delayed externalization: long-term follow-up. Adv Perit Dial. 2000;16:123–8.
81. Brown PA, McCormick BB, Knoll G, Su Y, Doucette S, Fergusson D, et al. Complications and catheter survival with prolonged embedding of peritoneal dialysis catheters. Nephrol Dialysis Transplant. 2008;23(7):2299–303.
82. Crabtree JH, Burchette RJ. Peritoneal dialysis catheter embedment: surgical considerations, expectations, and complications. Am J Surg. 2013;206(4):464–71.
83. Brum S, Rodrigues A, Rocha S, Carvalho MJ, Nogueira C, Magalhaes C, et al. Moncrief-Popovich technique is an advantageous method of peritoneal dialysis catheter implantation. Nephrol Dialysis Transplant. 2010;25(9):3070–5.
84. Twardowski ZJ, Prowant BF. Exit-site healing post catheter implantation. Perit Dial Int. 1996;16(Suppl 3):S51–70.
85. Twardowski ZJ, Prowant BF. Exit-site study methods and results. Perit Dial Int. 1996;16(Suppl 3):S6–31.
86. Jones LL, Tweedy L, Warady BA. The impact of exit-site care and catheter design on the incidence of catheter-related infections. Adv Perit Dial. 1995;11:302–5.
87. Prowant BF, Warady BA, Nolph KD. Peritoneal dialysis catheter exit-site care: results of an international survey. Perit Dial Int. 1993;13(2):149–54.

88. Patel UD, Mottes TA, Flynn JT. Delayed compared with immediate use of peritoneal catheter in pediatric peritoneal dialysis. Adv Perit Dial. 2001;17:253–9.
89. Keswani M, Redpath Mahon AC, Richardson T, Rodean J, Couloures O, Martin A, et al. Risk factors for early onset peritonitis: the SCOPE collaborative. Pediatr Nephrol (Berlin, Germany). 2019;34(8):1387–94.
90. Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24(9):1633–42.
91. Dejardin A, Robert A, Goffin E. Intraperitoneal pressure in PD patients: relationship to intraperitoneal volume, body size and PD-related complications. Nephrology Dialysis Transplant. 2007;22(5):1437–44.
92. Cho Y, Boudville N, Palmer SC, Chow JSF, Hawley CM, Jose MD, et al. Practice of peritoneal Dialysis catheter Flushing in Australia and New Zealand: multi-center cross-sectional survey. Perit Dial Int. 2018;38(2):98–103.
93. Swartz SJ, Neu A, Skversky Mason A, Richardson T, Rodean J, Lawlor J, et al. Exit site and tunnel infections in children on chronic peritoneal dialysis: findings from the Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) collaborative. Pediatr Nephrol (Berlin, Germany). 2018;33(6):1029–35.
94. Twardowski ZJ, Prowant BF. Classification of normal and diseased exit sites. Perit Dial Int. 1996;16(Suppl 3):S32–50.
95. Neu AM, Richardson T, Lawlor J, Stuart J, Newland J, McAfee N, et al. Implementation of standardized follow-up care significantly reduces peritonitis in children on chronic peritoneal dialysis. Kidney Int. 2016;89(6):1346–54.
96. Chua AN, Goldstein SL, Bell D, Brewer ED. Topical mupirocin/sodium hypochlorite reduces peritonitis and exit-site infection rates in children. Clin J Am Soc Nephrol. 2009;4(12):1939–43.
97. Wong S, Chu K, Cheuk A. Prophylaxis against gram-positive organisms causing exit-site infection and peritonitis in continuous ambulatory peritoneal dialysis patients by applying mupirocin ointment at the catheter exit-site. Perit Dial Int. 2003;23:153–8.
98. Bernardini J, Bender F, Florio T, et al. Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. J Am Soc Nephrol. 2005;16(2):539–45.
99. Freitas C, Rodrigues A, Carvalho MJ, Cabrita A. Exit site infections: systematic microbiologic and quality control are needed. Adv Perit Dial. 2009;25:26–31.
100. Mahaldar A, Weisz M, Kathuria P. Comparison of gentamicin and mupirocin in the prevention of exit-site infection and peritonitis in peritoneal dialysis. Adv Perit Dial. 2009;25:56–9.
101. Xu G, Tu W, Xu C. Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. Nephrol Dial Transplant. 2010;25(2):587–92.
102. Wong PN, Tong GM, Wong YY, Lo KY, Chan SF, Lo MW, et al. Alternating mupirocin/gentamicin is associated with increased risk of fungal peritonitis as compared with gentamicin alone – results of a randomized open-label controlled trial. Perit Dial Int. 2016;36(3):340–6.
103. Cribbs RK, Greenbaum LA, Heiss KF. Risk factors for early peritoneal dialysis catheter failure in children. J Pediatr Surg. 2010;45(3):585–9.
104. Savader SJ, Lund G, Scheel PJ, et al. Guide wire directed manipulation of malfunctioning peritoneal dialysis catheters: a critical analysis. J Vasc Interv Radiol. 1997;8(6):957–63.
105. Shea M, Hmiel SP, Beck AM. Use of tissue plasminogen activator for thrombolysis in occluded peritoneal dialysis catheters in children. Adv Perit Dial. 2001;17:249–52.
106. Sakarcan A, Stallworth JR. Tissue plasminogen activator for occluded peritoneal dialysis catheter. Pediatr Nephrol. 2002;17(3):155–6.
107. Krishnan RG, Moghal NE. Tissue plasminogen activator for blocked peritoneal dialysis catheters. Pediatr Nephrol. 2006;21(2):300.
108. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment [published correction appears in Perit Dial Int. 2018 Jul-Aug;38(4):313]. Perit Dial Int. 2016;36(5):481–508.
109. Macchini F, Testa S, Valade A, et al. Conservative surgical management of catheter infections in children on peritoneal dialysis. Pediatr Surg Int. 2009;25(8):703–7.
110. Wu YM, Tsai MK, Chao SH, Tsai TJ, Chang KJ, Lee PH. Surgical management of refractory exit-site/tunnel infection of Tenckhoff catheter: technical innovations of partial replantation. Perit Dial Int. 1999;19(5):451–4.
111. Swartz RD, Messana JM. Simultaneous catheter removal and replacement in peritoneal dialysis infections: update and current recommendations. Adv Perit Dial. 1999;15:205–8.
112. Schroder CH, Severijnen RS, de Jong MC, Monnens LA. Chronic tunnel infections in children: removal and replacement of the continuous ambulatory peritoneal dialysis catheter in a single operation. Perit Dial Int. 1993;13(3):198–200.
113. Majkowski NL, Mendley SR. Simultaneous removal and replacement of infected peritoneal dialysis catheters. Am J Kidney Dis. 1997;29(5):706–11.
114. Andreetta B, Verrina E, Sorino P, et al. Complications linked to chronic peritoneal dialysis in children after kidney transplantation: experience of the Italian Registry of Pediatric Chronic Peritoneal Dialysis. Perit Dial Int. 1996;16(Suppl 1):S570–3.
115. Arbeiter K, Pichler A, Muerwald G, et al. Timing of peritoneal dialysis catheter removal after pediatric renal transplantation. Perit Dial Int. 2001;21(5):467–70.
116. Korzets Z, Hasdan G, Bulkan G, Klein E, Bernheim J, Shpitz B. Early postoperative complications of removal of Tenckhoff peritoneal dialysis catheter. Perit Dial Int. 2000;20(6):789–91.

Technical Aspects and Prescription of Peritoneal Dialysis in Children

13

Enrico Eugenio Verrina and Lyndsay A. Harshman

Introduction

Since 1978, when continuous ambulatory peritoneal dialysis (CAPD) was first introduced for the treatment of pediatric patients with end-stage renal disease (ESRD) (see also Chap. 1), a series of technological improvements have been incorporated into the peritoneal dialysis (PD) procedure. Important improvements have been achieved in the safety and ease of use of the mechanical devices employed in the dialysis procedure, as well as in the dialytic efficacy and biocompatibility of the PD solutions. The availability of automated dialysis delivery systems called "cyclers" provides great prescription flexibility and the ability to monitor therapy results, thereby facilitating improved patient adherence to the dialysis prescription. Unlike CAPD, in which treatment is truly continuous for 24 h of each day, in automated peritoneal dialysis (APD), treatment is usually limited to only a portion of the 24 h, usually overnight. Both CAPD and APD are currently widely used in children around the world.

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In this chapter, we describe the most recently developed and currently available equipment for the various forms of PD and provide information on how this equipment can be used to deliver the desired PD therapy for pediatric patients of all ages and sizes. Particular attention is paid to the technical developments that have proven to be most useful in fulfilling the specific clinical needs of the pediatric patient population.

Update on PD Connection Technology

The PD solution container is connected to the patient's PD catheter by a length of plastic tubing called a transfer set. Over the years, a number of transfer sets and associated devices have been developed in an attempt to reduce the possibility of bacterial contamination while making either the catheter-to-transfer set or the transfer set-to-container connections.

Catheter-to-Transfer Set Connectors

A special Luer-lock catheter adapter made of titanium exists and can be utilized to prevent cracking of the plastic connector or accidental disconnection – problems that had unfortunately frequently occurred with the earlier generations of plastic plug-in-style connectors. Titanium

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transfer sets are available and have a relatively light weight with resistance to degradation from electrolyte-containing PD solutions. More recently, catheter-to-transfer set connectors made of more durable plastics have also been developed and can be considered as an alternative to titanium. These more durable plastics may be a suitable option for acute PD catheter sets that will not transition to chronic use as well as in the extremely low birth weight (ELBW) infant given the lighter weight relative to titanium.

Transfer Set-to-Container Connection

The original transfer set-to-container connecting system had a spike-and-port design, which was later improved by the addition of external sleeves to reduce the risk of contamination. However, spiking the dialysis solution container may be difficult for many patients/caregivers. Failure to mate the spike with the port correctly can result in contamination and increased risk for subsequent peritonitis. This has led to the development of a screw-type or Luer-lock connecting system, resulting in easier insertion and a lower chance of accidental dislodgement.

Transfer Sets

The ideal transfer set should be characterized by:

- Ease of connecting maneuvers
- The least number of connections at risk for touch contamination
- Small dimension (patient acceptability)
- No breaking components or glue
- No online disinfectant solution or, if present, no risk of its infusion into the peritoneal cavity

Several types of transfer set have been developed over the years.

Straight Transfer Set (the Standard Oreopoulos System)

When introduced by Oreopoulos [1], this transfer set made the connection considerably easier and reduced the incidence of peritonitis in CAPD patients. One significant limitation of this system was that the PD fluid was infused into the abdominal cavity immediately after the connection which increased the risk for potential bacterial contamination. Furthermore, the patient had to carry the bag and transfer set until the following exchange.

The Y-Set

The Y-set [2] was developed to free the patient from the need to remain attached to the empty bag between exchanges and allow a flush-before-fill phase after the connection. The priming of the tubing with a small amount of fresh dialysis solution, followed by the discharge of the spent dialysate into the drainage bag, together with the injection of a disinfectant solution into the Y-set lumen after the exchange to sterilize it, was able to dramatically lower peritonitis rates [3]. Precautions were still required to flush the antiseptic solution completely before instilling fresh dialysis solution.

A further evolution of the Y-set was represented by the double bag system [4], where the Y-set is already attached to the dialysis solution bag and to an empty bag, eliminating the spiking procedure. The Y-set is connected to an adapter tubing during the exchange and is discarded after each use. The patient flushes the system after breaking color-coded frangible seals, drains the dialysate effluent, and then fills the peritoneal cavity with the dialysis solution. With this system, the patient has to wear only a small adapter tubing, without any antiseptic solution inside, between the exchanges.

In the absence of a disinfectant inside the transfer set after the exchange, touch contamination at disconnection may lead to significant growth of bacteria before the following exchange.

Here, the flush-before-fill procedure could fail to completely wash out the contaminating microorganisms, especially those with high adhesiveness to the plastic of the devices (e.g., *Staphylococcus aureus*, *Pseudomonas* sp.). For this reason, at the end of the exchange, the transfer set is closed with a disinfectant-containing cap (MiniCap®, Baxter Healthcare Corporation, McGraw Park, Illinois, USA). The povidone-iodine contained in the disconnect caps of these sets has the potential to be a contributing factor to thyroid function changes such as hypothyroidism. Patients most at risk to be potentially affected are primarily infants and children with small peritoneal dialysate fill volumes, where high dialysate concentrations of iodine may result [5]. In such patients, thyroid function should be monitored. In order to minimize iodine exposure, the contents of the peritoneal cavity should be drained prior to the initiation of the subsequent fill cycle whenever possible.

In another connecting device, disconnection takes place without opening the system (A.N.D.Y. Plus®, Fresenius Medical Care, Bad Homburg, Germany), since the line is clamped very close to the catheter and then broken; the plastic clamp perfectly fits the line causing complete occlusion.

Another device developed to increase the safety and ease of the line connection is represented by a connector that has a rotating gear with a fixed position for any phase of the exchange (Dianectan®, Laboratoire Aguettant, Lyon, France); in this system, when the cap is positioned, the catheter has already been automatically closed.

In a further development, a polyolefin-made plasticizer-free system (stay•safe®, Fresenius) may reduce potentially harmful exposure to phthalate esters [6].

The development of safe and simple-to-use connecting devices has contributed to simplifying and shortening patient and caregiver training, with an associated reduction in peritonitis episodes due to touch contamination both in adult [7, 8] and in pediatric patients [9] (see also Chap. 16).

Peritoneal Dialysis Prescription

The strategic process of determining a PD prescription for pediatric patients with ESRD requires a tailored treatment schedule to meet the needs of each individual child, according to a series of parameters including age, body size, associated nonrenal diseases, residual renal function (RRF), clinical condition(s), blood pressure, nutritional status, and peritoneal membrane (PM) transport characteristics [10, 11]. At the same time, potential negative effects of chronic PD on the patient's metabolism and on the anatomical and functional integrity of the PM should be taken into account. Finally, the socioemotional burden of PD treatment should be minimized to allow for a satisfactory level of psychological and social rehabilitation for the patient and his/her family

The selection of chronic PD modality and treatment prescription should be based on knowledge of PM physiology in parallel with an accurate assessment of individual patient PM transport characteristics. Therefore, a basic description of the PD system and of the driving forces of solute and water exchange will be briefly presented, and the issue of PM function tests will be addressed.

The Peritoneal Dialysis System

The PD system has three major components: the peritoneal microcirculation; the PM; and the dialysis fluid [12].

Peritoneal Microcirculation

Peritoneal capillary blood flow has been reported to vary between 50 and 150 mL/min in adults [13]. Blood flow through the peritoneal membrane is usually preserved to allow solute removal even in moderately hypotensive subjects [14]. Peritoneal blood vessel density decreases with age, from the highest levels in infancy; thus, solute removal rates decrease proportionately [15]. In addition to blood flow, the peritoneum has

an active lymphatic system, which includes specialized structures (*lacunae*) located on the undersurface of the diaphragm.

Peritoneal Membrane

The PM lines the inner surface of the abdominal and pelvic walls (parietal peritoneum), covers the intraperitoneal organs, forms both the visceral mesentery and the omentum, and connects loops of the bowel (visceral peritoneum) [16].

The PM is the barrier that solutes and water must cross during dialysis. It is a complex structure composed of:

- *The capillary wall*. Peritoneal capillaries are mainly of the continuous type, with less than 2% of fenestrated capillaries [17]. Peritoneal capillary endothelial cells are linked to each other by tight junctions and surrounded by a basement membrane. Healthy endothelium thus plays a central role in the control of PM vascular permeability [18].
- *The interstitium*. The PM interstitium is composed of extracellular matrix, containing a limited number of cells (fibroblasts, mononuclear cells) and lymphatic vessels. Hyaluronan, a major component of the extracellular matrix, has been reported to be an important determinant of the resistance to fluid and solute transport [19].
- *The layer of mesothelial cells.* These cells have a system of tight and gap junctions, microvillus projections at the free surface, and several organelles in their cytoplasm. Mesothelial cells have been reported to participate in glucose transport and regulation of water and solute fluxes through tight junction modulation, but their actual role as a rate-limiting barrier to PM transport is still debated [20, 21].

Dialysis Fluid Compartment

Both the composition of the PD solution and the modalities of its delivery influence the peritoneal exchange. PD solutions contain an osmotic agent to produce the osmotic gradient required to obtain ultrafiltration (UF), a buffer to correct the patient's metabolic acidosis, along with balanced concentrations of calcium, magnesium, and electrolytes. Dialysis fluid is infused into the peritoneal cavity in an amount that is scaled to the patient's body size and clinical conditions.

Driving Forces of Solute and Water Exchange

The driving forces of solute and water exchange across the PM, between the dialysis solution and the capillary blood and surrounding tissues, are represented by diffusive transport, UF, and convective mass transfer [21].

Diffusive Transport

Diffusion consists of passive solute exchange between two solutions (blood and dialysis fluid) separated by a semipermeable membrane. Main factors affecting the rate of solute diffusion are represented by:

- *The solute concentration gradient between blood and dialysate*. Because blood flow through the PM is relatively stable and apparently well preserved even in unstable patients who are moderately hypotensive, the concentration gradient is best maintained by replacing the dialysis fluid in the abdomen as often as is feasible.
- *The molecular weight (MW) of the solute.* Since diffusion is a size-selective process, small molecules (urea, creatinine) diffuse more rapidly than larger molecules (vitamin B_{12}, "middle molecules," higher-MW proteins). Low-MW compounds such as urea are preferentially removed by diffusion. Each compound is characterized by a specific PM permeability coefficient. Phosphate transport is lower than that of urea and creatinine since its molecules are surrounded by an aqueous layer which increases their effective MW. Moreover, phosphate transport is influenced by active transmembrane transporters.

- *The effective surface area and permeability of the PM.* The PM is a dynamic dialysis membrane [11], and it is the functional and not the anatomic peritoneal surface area that is important in peritoneal exchange. The peritoneal vascular exchange surface area is determined by the peritoneal vascular mesenteric perfusion and the density of the functional pores of the perfused capillaries available for dialytic exchange [22, 23]. This area can be estimated by means of the so-called three-pore permeability model [24]. According to this model, the peritoneum is characterized as a heteroporous three-pore membrane with few (~1–2%) water-exclusive ultrasmall pores (aquaporins, radius 2–4 Å), a small percentage (~5%) of large pores (radius 200–300 Å), and a majority (~90–95%) of small pores (radius 40–60 Å). Hydrophilic small solute transport occurs primarily by diffusion across the small pores, while the movement of proteins and other macromolecules occurs across the large pores and is driven by hydrostatic forces. Fluid transport can occur across all three pathways and is determined by crystalloid and colloid osmotic pressures. The total membrane pore area that is engaged in exchanges is dynamically affected by different factors; for example, fill volume (with a progressive increase in functional PM area recruitment taking place until the fill volume approximates 1400 mL/m^2 body surface area in children 2 years of age and older), patient posture (with positive recruitment occurring in the supine position), and PD fluid composition [25–28]. The impact of dialysate volume is felt to rest on the principle of geometry of diffusion [29], which simply states that the larger the dialysate exchange volume, the longer the transperitoneal concentration gradient will persist to drive diffusion. The permeability of the tissue between the capillary lumen and the peritoneal space can be altered by illness – increasing during acute peritonitis or progressively decreasing with peritoneal fibrosis.
- *Residual peritoneal volume from previous exchanges.* The concentration gradient and hence diffusive transport are also impacted by the presence of a residual peritoneal volume from previous exchanges. Small solutes in the residual fluid will likely have equilibrated with serum; this will lead to a time "zero" solute concentration that is much greater than zero, despite the fact that the instilled dialysate concentration of a solute was zero. This will impact fluid flux and solute transport. Residual peritoneal volume can be substantial and of clinical relevance in children [30].

Ultrafiltration

UF is the bulk movement of water along with permeable solutes across the PM. In the PD system, the driving force for UF is primarily represented by the osmotic pressure, which can be the result of either crystalloid (i.e., generated by diffusible solutes such as glucose in the dialysis fluid) or colloid (i.e., generated by nondiffusible solutes such as icodextrin in the dialysis fluid and albumin in plasma). The effects of the hydrostatic pressure gradient resulting from the difference between intravascular pressure and intraperitoneal pressure (IPP) are usually of minor importance in PD unless exceedingly high levels of IPP are reached [31]. Other factors that can affect UF are membrane surface area and hydraulic permeability. The flux of water (J_F) across the membrane can be expressed by the following equation [32]:

$$J_F = K_f \left(\left[P_c + s_f \right] - \left[p_c + P_f \right] \right)$$

where K_f is the peritoneal membrane permeability coefficient, P_c is the hydraulic pressure in the capillary, s_f is the osmotic pressure of the peritoneal fluid, p_c is the oncotic pressure in the capillary, and P_f is the hydraulic pressure of the fluid under flux.

In the course of the PD dwell, fluid is lost from the peritoneal cavity both directly into the surrounding tissues and via lymphatic vessels and capillaries. Net UF results from the balance between osmotic UF and peritoneal fluid absorption. High peritoneal fluid absorption can be clinically important in some patients in whom net UF can be substantially reduced and the absorption

of macromolecules into the lymphatics increased. Lymphatic absorption has been estimated to account for 20% of net fluid absorption from a PD exchange [33]. Fluid is believed to move primarily into interstices in the peritoneal cavity and to be driven by intraperitoneal hydraulic pressure [34]. The limited data on lymphatic absorption in children are conflicting [33, 35].

The peritoneal fluid absorption rate can be determined when a PD exchange is modeled using the three-pore model. In one pediatric study, the absorption rate increased with body size in absolute terms but decreased when normalized to body size. The decrease was slight when scaled to body surface area (BSA) but marked when scaled to body weight (BW) [36].

Glucose is the most frequently used osmotic agent in standard PD solutions. It exerts its crystalloid osmotic effect through aquaporins, and its absorption from the dialysate to the plasma leads to a time-dependent dissipation of the osmotic gradient. In some patients, the rate of glucose absorption makes glucose unsuitable for maintenance of UF during a long dwell [37]. Conversely, PD solutions containing a polymer of glucose with an average MW of 16,200 Dalton (Icodextrin® Baxter, Deerfield, IL) exert a more sustained colloid osmotic effect through the small pores and have been shown to maintain UF over a prolonged exchange dwell time [38–40].

Convective Mass Transfer

Convective mass transfer occurs when water moves from capillaries to peritoneal cavity down a pressure gradient, "dragging" dissolved molecules along with it ("solvent drag"). The convective transport of a solute depends on the amount of fluid removed by UF and on membrane permeability. Permeability of a membrane to a given solute can be expressed by the sieving coefficient and calculated by dividing the concentration of solute in the ultrafiltrate by its concentration in plasma water (in the absence of a concentration gradient). The sieving of sodium reflects aquaporin function and thus free water transport [41]. During PD exchanges, the contribution of convection to solute removal is limited for small molecules but significant for high-MW compounds such as the "middle molecular weight" uremic toxins [42, 43].

Peritoneal Membrane Function Tests

Peritoneal solute and fluid transport may vary considerably from patient to patient and in the same patient during different phases of PD treatment, as a consequence of the recurrence and/or severity of peritonitis episodes, or of the exposure of the PM to PD solutions and materials. Moreover, inherited genetic variants could affect the transport capacity of the PM through the regulation of specific mediators [44]. Therefore, PM transport characteristics should be assessed at the beginning of chronic PD (usually, 1 month after the start of dialysis treatment) and then monitored two to four times per year. Additional monitoring may be required in case of recurrent or particularly severe peritonitis episodes or following other clinical events that may cause changes in PM transport capacity [42, 45]. In this way, intraindividual changes in the functional status of PM can be detected, and adjustments in PD prescription can be made.

PM function tests represent the first step in the process of tailoring the PD prescription to individual patient needs and characteristics. The application of these tests to the pediatric patient population has long been hampered by a lack of standardization of dialysis mechanics during the test. Appropriate scaling for body size plays a central role in this standardization and for the calculation of PM function parameters. While in infants the peritoneal surface area per unit BW is twice that of adults, the relationship between BSA and PM surface area is constant and age independent. In early pediatric transport studies, standardization of exchange volumes by BW contributed to the false perception of differences in peritoneal permeability between children and adults, with an enhanced transport function in the youngest patients. Further analysis revealed that the apparent enhanced solute transfer in children

was due to faster solute concentration equilibration with blood associated with the use of relatively small dwell volumes scaled on BW [46]. On the contrary, scaling the exchange volume by BSA maintains the relationship between dialysate volume and PM surface area across populations and makes comparison of peritoneal transport properties between patients of different body sizes possible [47, 48]. BSA can be calculated by means of mathematical formulas from the patient's weight and height (see Section "Monitoring PD Adequacy in the Clinical Setting"). An exchange volume of 1100 mL/m^2 BSA approximates the standard 2000 mL exchange volume applied to adult patients.

Mass Transfer Area Coefficient

Diffusive permeability of the PM can be expressed by means of the mass transfer area coefficient (MTAC), which describes the maximal clearance theoretically achievable at a constantly maximal gradient for diffusion, that is, when dialysate solute concentration is zero. MTAC is independent of dialysate glucose concentration. Determination of MTAC helps to model both long and short PD dwells and to individualize the dialysis prescription and can be performed with the help of computer technology that gives reliable results in pediatric patients. Comparison of MTAC values obtained in patients of different age and body size is possible when exchange volume has been standardized to BSA [30, 49]. A small but significantly greater solute transport capacity has been reported in infants, as a consequence of higher peritoneal permeability or larger effective surface area of the PM [30].

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) remains the most widely employed means of characterizing PM transport capacity in adult and pediatric patients [30, 45, 50, 51]. The PET measures the rate at which solutes, usually creatinine (Cr), urea, and glucose, come to equilibration between the blood and the dialysate. PET results provide the clinician with data to adapt the dwell time to the individual PM function characteristics and provide the opportunity to evaluate prescription changes over time during the PD treatment. To reach a satisfactory level of reproducibility of PET results, a standard PET in children can be performed with a dwell volume of 1100 mL/m^2 BSA using a 2.5% dextrose PD solution. In pediatric patients, comparable results have been obtained by using 2.5% dextrose [30] or 2.27% anhydrous glucose PD solutions. Dialysate-to-plasma (D/P) ratios of Cr and urea and dialysate glucose concentration to initial dialysate glucose concentration at time 0 (D/D$_0$) are calculated at 2 and 4 h of the test. A blood sample is obtained at time 2 h. If dialysate Cr concentration is determined colorimetrically (and not enzymatically), it must be corrected for the interference of the high glucose levels in the dialysate by the formula:

$$\text{Corrected Cr}\left(\text{mg/dL}\right) = \text{measured Cr}\left(\text{mg/dL}\right) - \text{correction factor} \times \text{dialysate glucose}\left(\text{mg/dL}\right)$$

The correction factor should be determined in the laboratory of each dialysis center, by dividing measured Cr of a fresh, unused PD solution by the measured glucose concentration. Small solute concentrations in plasma should be expressed per volume of plasma water (aqueous concentration) instead of per volume of whole plasma by dividing solute concentrations measured in whole plasma by 0.90 [52].

PET can be also performed by using a 4.25% dextrose or 3.86% anhydrous glucose PD solution to obtain more accurate information on UF capacity and assess sodium sieving, or the maximum dip in dialysate over plasma sodium concentration, which typically occurs during the initial 30–90 min of the dwell [53, 54]. In this way, free water transport capacity through the aquaporins can be evaluated, and UF failure can be more easily detected [11].

Cr and urea D/P ratios and dialysate glucose D/D$_0$ calculated at 2 and 4 h of the PET can be compared to the results from a large pediatric

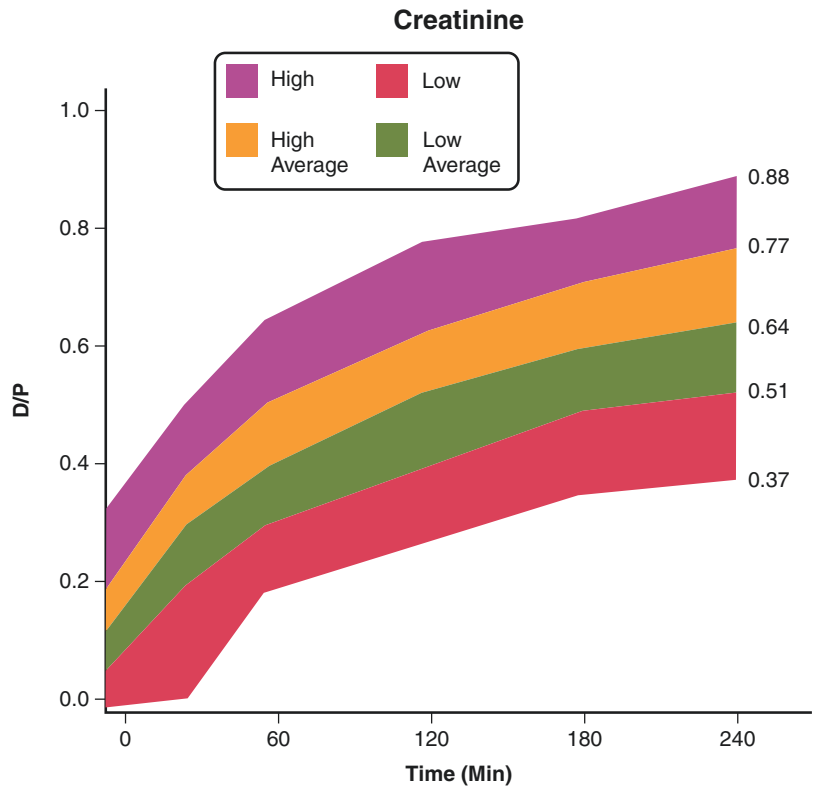

Fig. 13.1 Peritoneal equilibration test results for creatinine. *Colored* areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population. (Modified from Ref. [30])

study in which the same PET procedure was adopted (Figs. 13.1 and 13.2) [30]. Thus, patients will be characterized as having a high, high average, low average, or low solute transport capacity (Table 13.1). Similarly to what is reported in adult patients, the high transporter status may be associated with poor treatment outcome and has been identified as a significant risk factor for inadequate weight control, poor statural growth [55], and low-turnover bone disease [56]. Studies comparing PET parameters obtained with PD solutions of different osmolality did not show any effect of the dialysate glucose concentration on the D/P creatinine or the categorization into a transport group [53, 54]. Conversely, the preceding dwell composition and duration can influence small solute transport and net UF significantly. Higher D/P creatinine ratio was reported after a long dwell with icodextrin compared with a dwell with 2.27% glucose, even when a rinsing procedure with glucose was performed before the PET [11, 54]. Therefore, the same PD solution should be used for the PET and for the dwell of the preceding night.

Warady and Jennings reported that the PET results obtained at 2 and 4 h, based on either creatinine or glucose transport in 20 children who had been on PD for a period of 7 months or less, provided identical characterization of PM transport capacity for the same solute [57]. The authors proposed the use in pediatric patients of a simplified, 2-h PET procedure, the so-called short PET, as already described in adult patients [58]. Since the short PET is more convenient for patients, families, and nursing staff and is associated with cost savings, the adoption of this procedure may help in performing the evaluation of PM transport characteristics on a more routine basis among pediatric PD centers [59, 60].

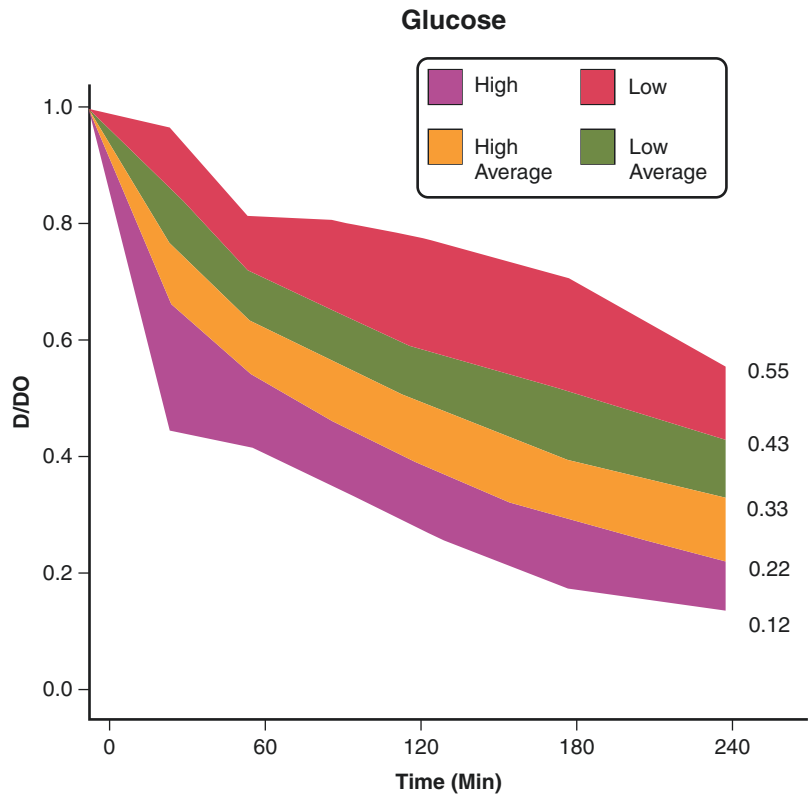

Fig. 13.2 Peritoneal equilibration test results for glucose. Colored areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population. (Modified from Ref. [30])

Table 13.1 Classification of peritoneal transport capacity according to the results of urea and creatinine dialysate-to-plasma ratio (D/P) and of dialysate glucose/initial dialysate glucose concentration ratio (D/D_0) at 4 h dwell of a peritoneal equilibration test performed with 1100 mL/m^2 body surface area of a 2.5% dextrose dialysis solution [30]

Category of peritoneal transport	D/P urea	D/P creatinine	D/D_0 glucose
High	0.91–0.94	0.77–0.88	0.12–0.21
High average	0.82–0.90	0.64–0.76	0.22–0.32
Low average	0.74–0.81	0.51–0.63	0.33–0.42
Low	0.54–0.73	0.37–0.50	0.43–0.55

The four categories of peritoneal transport are bordered by the maximal, mean +1 standard deviation (SD), mean, mean −1 SD, and minimal values for the study population of pediatric patients (Data adapted from Ref. [30], used with permission)

Standard Permeability Analysis

Standard permeability analysis (SPA) and the PD capacity test (see below) are two other PM function tests that have given reliable results in adult and pediatric patients but are less frequently employed than the PET in the clinical setting and are mainly performed for research purposes. SPA can be considered an adaptation of PET, where polydisperse dextran-70 is added to the PD solution in order to obtain the simultaneous measurement of transcapillary UF, the marker's clearance rate (to assess lymphatic reabsorption), and intraperitoneal volume (IPV) [61, 62].

Personal Dialysis Capacity Test

The personal dialysis capacity (PDC) test [24] is based on the three-pore model of solute and fluid transport across the peritoneum. The PDC test describes the PM transport characteristics by functional parameters, which are calculated from data obtained from several exchanges of different duration and performed with PD solutions of different glucose concentration over a day. The PDC protocol includes five exchanges to be performed in 24 h using different dwell times and

two glucose solutions for patients on CAPD; a simplified protocol for patients on APD is also available [36]. The effective peritoneal surface area, final rate of fluid reabsorption, and large pore flow are calculated in this model [63]. The PDC test has been successfully employed in children to model individual PM function [36]. In one pediatric study, D/P or D/D_0 ratios derived from PET analysis were used to estimate effective peritoneal surface area by using a specific computer program [25].

Prescription of Peritoneal Fill Volume

As previously described, scaling IPV by patient BSA has become a standard in pediatric PD prescription and allows an accurate assessment of membrane transport capacity [23, 42, 45]. IPV and patient posture dynamically affect the recruitment of effective PM area available for PD exchange, which corresponds to the unrestricted pore area over diffusion distance as determined using the three-pore model [24, 25]. Raising IPV from 800 to 1400 mL/m^2 BSA leads to maximization of peritoneal vascular surface area [25]. On the other hand, a too large IPV may cause patient discomfort, pain, dyspnea, hydrothorax, hernia, emesis, gastroesophageal reflux, and loss of UF due to increased lymphatic drainage. These complications may lead to reduced patient compliance to the PD regimen prescription and are primarily related to an elevated IPP [11]. Hydrostatic IPP is a reproducible patient-characteristic parameter, and its measurement helps evaluate fill volume tolerance in the individual patient [31]. In the supine position, a fill volume leading to an IPP of 14 cm H_2O in children above 2 years of age, and of 8–10 cm H_2O in infants, is considered the maximum tolerable IPV, above which abdominal pain and a decrease in respiratory vital capacity may occur, and a higher risk of hernia and leakage is reported [23]. Increasing IPV above this peak volume can result in reduced PD efficiency. An IPV of 1400 mL/m^2 BSA seems to be suitable to ensure optimal recruitment of vascular pore area in children; however, this should be considered as a maximal limit, the safety of which has not been validated in children. In infants, the target fill volume is generally 600–800 mL/m^2 BSA until 2 years of age [45, 64]. In many cases fill volume prescription is based more on individual patient's tolerance than on a theoretically optimal exchange volume [11].

In clinical practice, peritoneal fill volume can be increased in steps toward the maximum limit of 1400 mL/m^2 BSA (or 800 mL/m^{2}BSA in infants) for a night exchange, while the patient is lying down, according to clinical tolerance and IPP measurement, in order to ensure as high recruitment of vascular pore area as possible and achieve adequate solute removal and UF [23]. Bedside measurement of IPP, i.e., of an objective parameter of abdominal filling, can be performed following the procedure described by Fischbach et al. [31]. Measured IPP levels can be compared with age-dependent normal values in children above 2 years of age [65].

Prescription of Dwell Time

Dwell duration is an important determinant of PD efficacy and should always be determined according to the individual patient's transport status [23, 42, 45]. Short exchanges lead to satisfactory clearance of small solutes (like urea) and UF, which can be further enhanced by increasing dialysate glucose concentration. High transporter patients benefit from short exchanges, due to the dissipation of the osmotic gradient by fast glucose absorption. Infants usually require shorter dialysis cycles than do older children to maintain the osmotic gradient and achieve adequate fluid removal. Long exchanges favor the removal of solute of relatively higher MW, such as Cr and phosphate. Phosphate clearance is clinically important owing to the contribution of hyperphosphatemia to metabolic bone disease and cardiovascular morbidity. It should be considered that while performing a PET, the time needed to obtain a D/P for phosphate of 0.50–0.60 is three to four times longer than it is for urea [11, 31, 66]. On the other hand, a long dwell time exchange can be associated with the risk of

impaired UF or dialysate reabsorption while using glucose-based solutions. An icodextrin-based solution is more appropriate for such long dwells (see also Chap. 14) [67].

A potentially useful way to individualize dwell duration in pediatric patients on APD according to peritoneal transport capacity is the calculation of the so-called APEX time. While performing a PET, APEX time corresponds to the point at which D/P urea and D/D_0 glucose equilibration curves cross and should represent the optimal length of APD cycles.

The abovementioned prescription principles should be applied to the delivery of different PD regimens, which will be described in the following section.

Peritoneal Dialysis Methods and Regimens

Chronic PD can be performed either manually (CAPD = continuous ambulatory PD) or utilizing an automatic dispenser of PD solution, commonly called a "cycler" (APD = automated PD). The PD regimen can be continuous, with dialysis solution present in the peritoneal cavity evenly throughout 24 h, or intermittent, with an empty abdomen for part of the day, usually during daytime (Fig. 13.3). Continuous regimens allow complete equilibration of small solutes as well as removal of middle-sized molecules. The presence of a large volume of dialysate in the abdomen during the day can be associated with patient discomfort, the occurrence of abdominal hernias (especially in infants and young children), and problems of body image (especially in adolescents). Moreover, continuous absorption of glucose from the dialysate compromises appetite and aggravates uremic dyslipidemia.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD represents a continuous regimen of manual PD in which dialysis solution is present in the peritoneal cavity continuously, 7 days per week (Fig. 13.3). The short interruptions at the time of the 3–5 daily exchanges do not disqualify the regimen as continuous if they do not exceed 10% of total dialysis time [68].

In the CAPD exchange, a double-bag PD solution container with a Y-set disconnect system is currently employed. CAPD solution, as well as the solutions for any other form of PD, is usually warmed to body temperature prior to inflow, to avoid uncomfortable lowering of the body temperature and shivering. Drainage of spent dialysate and inflow of fresh dialysis solution are performed manually, relying on gravity to move fluid into and out of the abdomen. CAPD products fulfill the requirements of ease of use and a simple interface that should be characteristic of a home-based, self-care treatment. CAPD has the undoubted advantage of a limited cost of the equipment.

As described, the prescription of the fill volume per exchange should be scaled for BSA rather than BW. According to the guidelines of the European Committee on adequacy of the pediatric PD prescription [42], the initial fill volume can be 600–800 mL/m^2 during the day and 800–1000 mL/m^2 overnight. If an increase in the dialysis dose is indicated, the fill volume can be gradually increased according to patient tolerance and to IPP measurements [31]. When there is inadequate UF overnight due to rapid glucose absorption, an icodextrin-based PD solution can be employed for the prolonged nighttime exchange.

CAPD is usually effective in patients who still have RRF, while it may provide inadequate solute and fluid removal in children with poor RRF and in infants when their high nutritional requirements are achieved by liquid formula [69]. In all CAPD patients, RRF should be closely monitored, together with the UF capacity and the patient's dry BW. Patients with a low-average or high-average peritoneal transport status as per the PET [30] can be maintained on CAPD, with close monitoring of the dialysis adequacy indices. A limitation of CAPD is that in order to further enhance the delivered dialysis dose there is no other means than increasing the number of exchanges. If increasing the number of exchanges

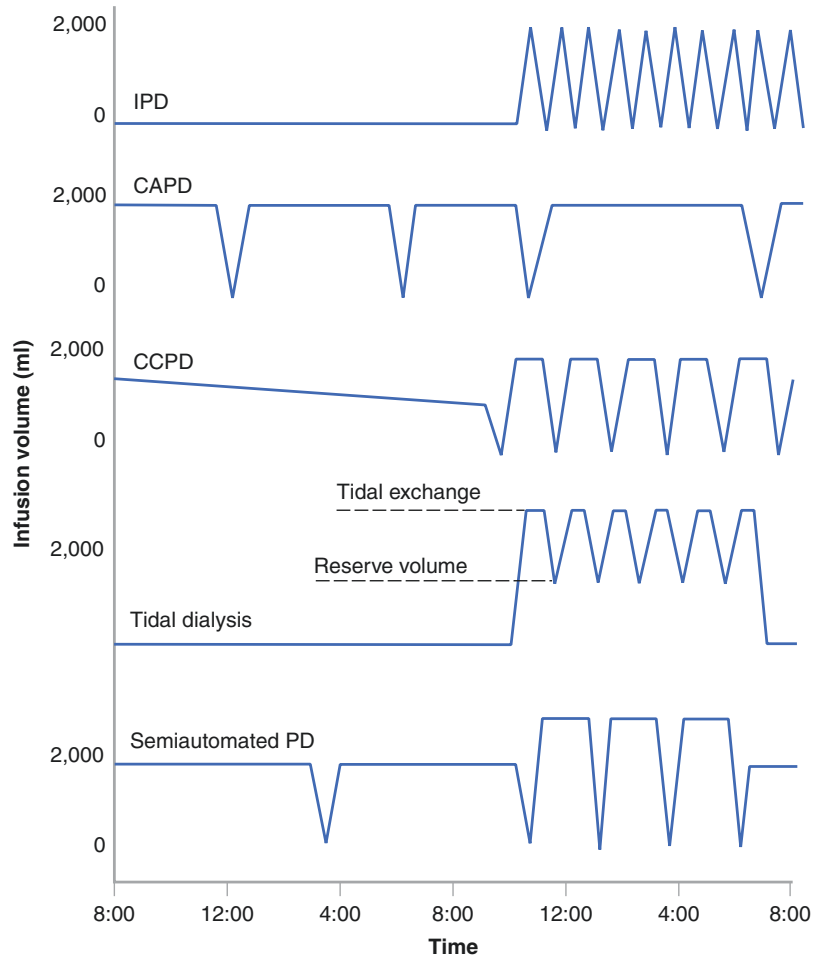

Fig. 13.3 Schematic representation of various peritoneal dialysis (PD) regimens based on a standard fill volume of 2000 mL of dialysis fluid. *IPD* nightly intermittent PD, *CAPD* continuous ambulatory PD, *CCPD* continuous cyclic PD

to obtain adequate UF and solute removal represents an excessive burden upon the patient and the family, a shift of the patient to an APD modality should be considered.

Automated Peritoneal Dialysis (APD)

APD represents the PD modality of choice for children and has largely replaced CAPD in the treatment of this category of patients, at least in those countries where its use is not limited by cost constraints [70–73]. Financial and technical problems still represent a limitation to the use of APD for many units in developing countries. The preference for APD as the dialytic modality of choice for children with ESRD has largely been a lifestyle choice; indeed, nighttime APD treatment enables children to attend school full-time and reduces the impact of dialysis treatment on the way of life of the patients and of their families [74]. Therefore, APD can ensure a higher level of psychological and social rehabilitation of children with ESRD when compared to other forms of chronic dialysis. The option of an empty abdomen during the day, or a half-volume daytime dwell, has the potential to reduce the interference with nutritional intake and minimize the incidence of abdominal hernias. At the same time, performing the nighttime exchanges in the lying position allows the use of larger fill volumes. Sequential measurements of IPP in children showed that in the supine position, an IPV up to 1400 mL/m^2 BSA was not associated with an unsafe increase of IPP. However, such a high fill volume is infrequently prescribed, due to prob-

lems of patient tolerance [75, 76]. Increasing the nocturnal fill volume allows more effective contact between dialysate and the PM, with the recruitment of a larger functional peritoneal surface area (i.e., the area available for the diffusive transport of solutes) and a higher permeability × surface area product, frequently referred to as solute diffusive transport coefficient (KoA) [77]. In addition, the small solute KoA has been reported to be higher in the supine position than during the ambulatory upright position. Another important reason for using APD in pediatric patients is that with the range of treatment options which are available through this modality, the dialytic prescription can be tailored to the individual patient's age, body size, clinical condition, growth-related metabolic needs, and PM transport status. APD is the preferred PD modality also in the treatment of infants: 71% and 85% of infants initiating chronic PD in Europe (between 1991 and 2013) and in the United States (between 1990 and 2014), respectively, started on APD [78, 79]. The flexibility of exchange frequency provided by the cycler allows frequent exchanges with short dwell times in anuric infants who require high ultrafiltration rates, or longer dwell times in infants with polyuric renal failure [11, 64].

Mathematical modeling software programs have been developed to calculate kinetic parameters to mathematically simulate the results of the APD regimens and to rapidly find the best personalized dialysis schedule, thus avoiding long trials for the patient [80]. Such programs are based on specific kinetic models and the individual patient's peritoneal function test. Two of these software programs have been validated and applied to pediatric patients [36, 49, 81]. Both of these software programs have a user-friendly interface, a mathematical model describing the PD system, and a specific individual peritoneal function test as data entry. The accuracy of these mathematical models in predicting the results of different APD schedules is greater for solute removal than for UF, owing to inability of kinetic modeling to account for changes in residual dialysate volume, the marked variability of UF in different exchanges and on different days, even in the same patient, the large variability of daily fluid intake, and the confounding effects of residual diuresis in non-anuric patients [82, 83]. A certain amount of error is almost always a component of modeling biologic systems as well; moreover, since mathematical modeling refers to perfect and virtually uneventful APD sessions (no alarms, no delay in the drain and fill phases), the simulations may at times be too "optimistic." However, computer-assisted kinetic models can be regarded as useful tools for the calculation and normalization of kinetic indices and for mathematical simulation of the various APD regimens. They can help determine the optimal dose of dialysis for each patient, but in the individual patient, direct measurement of solute clearances and UF remains necessary.

Finally, the choice of the proper APD regimen through which the individual dialytic prescription could best be accomplished is currently based not only on patient clinical and metabolic conditions and peritoneal transport but also on lifestyle considerations.

A description of the main characteristics of the various APD regimens will follow.

Nightly Intermittent Peritoneal Dialysis (NIPD)

NIPD is an intermittent PD modality consisting of a number of short nocturnal cycles performed every night by an automated cycling machine in the patient's home, without a daytime dialysate dwell (Fig. 13.3). The presence of a dry peritoneal cavity during the day is the crucial feature distinguishing NIPD from other models of APD. The reasons why children with ESRD represent a patient group that may likely benefit most from a "dry" day have been already discussed and are summarized in Table 13.2. The reduced exposure of the PM to glucose and glucose degradation products, together with the reduced deposition of advanced glycosylation end products (AGE), has been reported to be beneficial for long-term PM preservation [84]. The prescription of a small fill volume during the daytime is frequently adopted in an attempt to lessen

Table 13.2 Advantages and limitations of nightly intermittent peritoneal dialysis

Advantages	Limitations
No glucose absorption during the daytime	Not recommended in patients with poor residual renal function
Daytime normal intraperitoneal pressure	Inadequate small solute clearance in patients with low and low-average transport
Preservation of body image (for adolescents mainly)	Inadequate middle-sized molecule clearance
Reduced loss of proteins and amino acids Better preservation of the peritoneal membrane integrity	No flush of the catheter and lines at the start of the night session (increased risk of infection)

the risk of peritoneal infection due to touch contamination through the preventive effect of a "drain before fill" phase with the flush of the peritoneal catheter and of the lines at the start of the night APD session [85].

The major limitation of NIPD may be that the absence of a daytime dwell reduces solute clearance compared to continuous PD modalities; the negative impact on the clearance of middle molecules is even more pronounced. The evaluation of peritoneal transport status is mandatory while selecting patients for NIPD. NIPD is primarily indicated in patients characterized by a high transport PM, who show rapid equilibration of solute concentrations and adequate UF only with rapid exchanges and/or patients with significant RRF. NIPD may be not suitable for children with low and low-average peritoneal transport or for anuric patients. This frequently represents the initial mode of PD employed in children with RRF [42]. A typical initial prescription can be formulated as follows:

- Nine to 12 hours of total treatment time.
- A fill volume of 800–1000 mL/m^2 exchanged five to ten times (young infants frequently require more cycles); an exchange dwell time of approximately 1 h represents a typical choice for the initial APD prescription in pediatric patients [11].
- Dialysis solution should contain 1.36% (1.5% dextrose) glucose or higher concentrations depending upon UF requirements. Solutions with different concentrations can be mixed by the cycler to titrate tonicity of the infused solution according to the patient's individual needs.

In the course of treatment, the NIPD regimen can evolve according to clearance and UF requirements, which are mainly dictated by the decline of urine volume. In particular, the importance of the control of fluid balance on patient outcome should be emphasized [83, 86, 87]. An increase of the efficiency of NIPD can be obtained by:

- Maximizing the dwell volume, according to patient tolerance and IPP limits [23, 25, 31].
- Increasing the number of exchanges in patients with high and high-average PM transport capacity. This should be done up to a point, beyond which clearance and UF decrease since the non-dialytic time, corresponding to the fill and drain phases, becomes more important than the benefit of further increasing dialysate volume.
- Increasing the total treatment time, as the patient's compliance and social life allow. The number of exchanges can be kept constant in patients with low and low-average PM transport capacity.
- Increasing dialysate tonicity in order to enhance UF rate. Since solutions from dialysate bags are proportionally mixed by the cycler (provided they are positioned at the same level), the tonicity of the dialysate can be titrated by choosing different tonicity for the various bags; the most common glucose concentrations used are 1.5%, 2% (obtained from equal mixing of the other two concentrations), and 2.5% [86].

If a sufficient increase of solute and water removal is not achieved with these adjustments of the NIPD schedule, the patient may be at risk for inadequate treatment and would benefit from consideration of a different APD regimen.

Continuous Cyclic Peritoneal Dialysis (CCPD)

CCPD, just like CAPD, represents a continuous regimen of PD (Fig. 13.3). In the morning, at the end of the overnight PD session, the patient disconnects from the cycler, leaving in the abdomen a fresh exchange of dialysis solution, ranging in volume from 50% (more frequently in children) to 100% of the night fill volume. In the classic form of CCPD, this daytime exchange is drained at bedtime when the cycler is reconnected, so that patient involvement is reduced, as with NIPD, to one session for preparation of the equipment and solutions and a very short period for disconnection. The long daytime dwell makes a very significant contribution to solute removal and to UF; moreover, clearance of middle-sized uremic toxins that is poorly influenced by short cycles of APD with high-flow regimens is much more dependent on total dialysis time and favorably influenced by prolonged exchanges [88]. Since complete saturation of the dialysate with small solutes over a long dwell exchange is often achieved, daytime clearance is also dependent on the net UF (convective transport), that in turn can be influenced by the choice of the osmotic agent, the fill volume (which results in various IPPs), and the membrane transport status[1] [89].

A continuous PD regimen is recommended when RRF has become negligible and/or the desired targets of solute and fluid removal cannot be achieved any longer by a NIPD regimen. Consideration of PM transport characteristics is also important for the choice of the optimal schedule of CCPD [90, 91]. Patients with high-average transport rates often do best on CCPD (Table 13.1).

During a long daytime dwell, glucose is largely absorbed, while a sustained net UF can be achieved with the use of the icodextrin-based PD solution (ICO). Available data on the use of this alternative osmotic agent in pediatric patients show that over a 12–14-h dwell, net UF obtained with ICO is similar to that obtained with a 3.86% (4.25% dextrose) glucose solution, and significantly greater than that reached with a 1.36% (1.5% dextrose) glucose solution both in adult and pediatric patients [92, 93]. The evaluation of the intraperitoneal volume-to-time curve during a 14-h dwell with icodextrin solution in children showed a gradual increase in net UF [38]. From the results of the mathematical modeling of the UF profile obtained with icodextrin solution, and based on the kinetic parameters of 396 adult patients, no separation between the PET transport categories was found [94]. By comparing the results of two 4-h PETs, performed in nine pediatric patients using 3.86% (4.25%) glucose and 7.5% icodextrin as a test solution, Rusthoven et al. [40] found that the two solutions had different effects on the change in IPP. During the PET performed with a 3.86% (4.25%) glucose solution, the increase in IPP was positively correlated with transcapillary UF and inversely correlated with patients' BSA; conversely, while by using an icodextrin solution, IPP demonstrated minimal rise during the 4-h dwell, and no correlation was found with fluid kinetics or patient BSA.

If a further increase in solute clearance is required, and/or net UF is still insufficient for a patient's clinical needs, as is often seen in patients with a low-average transport status treated with CCPD, more than one diurnal exchange can be used. With this optimized APD schedule (continuous optimal peritoneal dialysis, COPD), an exchange of the dialysate is performed at midday or after school, using the cycler in a disconnectable manner (Fig. 13.3), and the length of each dwell is optimized according to the patient's peritoneal transport rate and the type of osmotic agent employed [42, 88]. This modality requires more patient participation but allows the patient to achieve small solute dialysate-to-plasma equilibration during both of the two daytime exchanges.

[1]It should be noted that reliance on membrane transport assessments based on mass transfer of urea or creatinine ignores the difficulty and importance of phosphate clearance. Phosphate PD clearance is usually insufficient to obtain a satisfactory control of hyperphosphatemia, and there is a continued need for dietary restriction and phosphate binder administration. Phosphate removal by PD can be improved by increasing dwell time [89] and by optimizing exchange duration through the calculation of the so-called phosphate purification dwell time (PPT) from a PET [66].

Tidal Peritoneal Dialysis (TPD)

TPD is an automated PD technique in which an initial infusion of solution into the peritoneal cavity is followed, after a usually short dwell time, by drainage of only a portion of the dialysate, leaving an intra-abdominal reserve volume (Fig. 13.3). The tidal drain volume is replaced with fresh dialysis fluid to restore the initial IPV with each cycle. At the end of the dialysis session (sometimes also once in the middle of the session), the whole dialysate volume is drained. The amount of ultrafiltrate expected to be generated during each cycle must be estimated and added to the drain volume. Otherwise, the intra-abdominal volume will become progressively larger, thus affecting the efficiency of dialysis and the patient's comfort.

TPD can be performed for the following indications:

- Increasing clearances as a result of the continuous contact between dialysate and PM, with a sustained diffusion of solutes
- Improving the efficiency of the dialysis technique by reducing inflow and outflow dead times (during which the peritoneal cavity is almost empty), particularly at high dialysate flow rates
- Avoiding repeated cycler alarms of low flow rate due to peritoneal catheter malfunction
- Reducing pain during the last part of the drain cycle

The major determinants of TPD efficiency are the total volume of delivered PD fluid and the individual peritoneal transport rate. Only high transport patients can reach adequate solute clearances with nightly performed TPD (NTPD), while high-average transport patients would benefit from one or more daytime dwells, thus undergoing continuous TPD (CTPD).

The results of studies on pediatric patients showed that TPD efficiency was equal to or higher than standard APD but required larger total session dialysate volumes [95, 96].

Optimization of TPD may be obtained by adapting the tidal volume to the individual drainage profile, thus reducing the fill and drain dead times to the minimum [97]. The peritoneal catheter drainage profile can be accurately evaluated by looking at the information on peritoneal fluid drainage during each cycle of an APD session recorded by the software of the new cyclers. Catheter drainage does not demonstrate a linear behavior, since a high flow rate is only maintained until a critical IPV is reached. After this critical point (also called the breakpoint), the flow rate drops, and the final part of the drainage can take more than twice the time of the previous segment. During this slow-flow portion of drainage, the peritoneal cavity is almost empty, and solute clearance is significantly reduced [76, 98]. Since the critical IPV is an individual characteristic, tailoring the tidal volume to the drainage profile of each patient reduces idle time, thus improving the overall efficiency of the system. This optimization would be particularly indicated in patients without an optimally functioning catheter.

Adapted APD

The need to combine adequate ultrafiltration and solute removal, especially in anuric children and infants with a mostly liquid diet, has led to the development of a new approach combining short dwells with a relatively small volume of PD fluid to maximize UF with long dwells using a larger fill volume to enhance solute removal [99]. This APD schedule is called adapted APD and is performed by means of new-generation cyclers that can deliver short exchanges with small fill volume in the first part of the APD session, followed by longer exchanges with larger fill volume. With the use of adapted APD, a significant increase of urea, creatinine, sodium, and phosphate removal combined with improved UF was obtained in a randomized, prospective crossover trial conducted in adult patients [99]. An additional crossover trial in adults and a pilot study in children suggest that sodium and fluid removal are increased by adapted APD, leading to improved blood pressure control when compared with conventional PD [100].

Such results were achieved applying the same total amount of glucose (and glucose exposure) and dialysate volume during the same total dialysis time (and treatment costs) than in the standard APD session. PET results and IPP measurement data can be used to define dwell time and fill volume, respectively [101].

Concluding Remarks

For each regimen of chronic PD delivered to pediatric patients with ESRD, the dialysis prescription should be adjusted and monitored following the guidelines of the European Pediatric Dialysis Working Group [42] and the 2006 update of the NKF-KDOQI clinical practice recommendations for pediatric PD adequacy [45]. In the absence of definitive results from large randomized controlled studies on the correlation between solute removal and clinical outcome in pediatric patients treated with PD, current clinical opinion supports the recommendation that the target delivered solute clearance should meet or exceed adult standards. In patients with RRF, the contribution of renal and peritoneal clearance can be added for practical reasons. Regular assessment of the prescribed PD schedule should be performed, taking into account not only targets of small solute depuration but all the parameters involved in the definition of adequacy of dialysis treatment in childhood, such as adequate growth, blood pressure control, and nutritional status; avoidance of hypovolemia and sodium depletion; and adequate psychomotor development [42, 45, 55]. These issues will be specifically addressed later in this chapter and elsewhere in this text.

Peritonitis in APD Patients

Some peculiar aspects of the diagnosis and management of peritonitis in APD patients deserve a brief discussion owing to the clinical relevance of this complication, which significantly affects PD treatment among pediatric patients. (For an in-depth discussion of this topic, please also see Chap. 16). A number of factors can make the diagnosis of peritonitis more difficult in APD than in CAPD: (1) peritoneal effluent is not readily available for inspection, owing to the use of a nontransparent effluent bag or effluent drained directly to a household outlet; (2) the shorter dwell times and the high volume and continuous flow of the dialysis fluid would result in lower white blood cell (WBC) number and less effluent cloudiness; and (3) the abdomen is frequently (although not necessarily) dry during the day. For these reasons, the presence of a cloudy effluent, which is an early sign of peritonitis, may be missed initially. Similarly, the dialysate WBC count may be lower than the value currently considered indicative of peritoneal infection. Moreover, short dwell times and a large dilution factor of the dialysate may increase the possibility of a false-negative culture [102]. In view of these issues, the use of a reactive test strip (Combur^2 Test® LN, Roche) which is sensitive to granulocyte peroxidase, can be helpful for the early diagnosis of peritonitis. In some centers, when a positive Strip-Test of the drained fluid from the daytime dwell or from the first APD cycle is observed, and no other signs and/or symptoms of peritonitis are present, the patient is instructed to obtain a fluid sample for culture and to program the cycler so as to leave an amount of dialysate equal to at least 50% of the night fill volume at the end of the night APD session and for at least a 4-h dwell. Then, a new sample for WBC count and culture is obtained from the effluent of this dwell, and laboratory diagnosis in the usual manner is conducted. When the positivity of the Strip-Test performed at the beginning of night APD session is associated with at least one other sign or symptom of peritonitis (such as abdominal pain or fever), an effluent sample is immediately obtained for culture, and an empiric regimen of intraperitoneal antibiotic therapy is started. In general, during peritonitis the daytime dwell that contains antibiotics should be a full exchange as long as antibiotic treatment is continued.

Evaluation of the Adequacy of Peritoneal Dialysis Treatment

Historically, the first studies on the correlation between the delivered dialysis dose and the adequacy of dialysis treatment were performed in hemodialysis patients and were mainly based on urea kinetic modeling. Therefore, the concept of "adequate" dialysis was initially adopted to define a minimum hemodialysis dose, below which a clinically unacceptable rate of negative outcomes might occur. The most frequently used outcome measures were represented by patient hospitalization, morbidity, and mortality. As a consequence, the influence of small solute clearance on the outcome of PD patients was a major focus of interest during the 1990s. The results of observational studies in adult patients treated with CAPD suggested that better patient survival and lower morbidity and mortality were associated with higher clearances of low-MW molecules, such as urea and creatinine [103, 104]. Small solute clearance was considered the key criterion of PD adequacy in the clinical practice guidelines developed in year 2000 by the Kidney Disease Outcomes Quality Initiative (KDOQI), which defined dialysis adequacy by certain minimum urea and creatinine clearance values [105]. In the following years, a reanalysis of the data from the original CANUSA study as well as the results of prospective randomized interventional trials did not demonstrate any clear advantage for patient survival by further increasing peritoneal small solute clearances beyond a minimal "adequate" level but showed that RRF is a much stronger predictor of survival than peritoneal clearance [106–108]. Failure of increased PD dose to significantly improve patient outcomes could be due to higher IPP associated with larger exchange volume, failure to increase clearance of middle molecules, and increased exposure of the PM to glucose-based dialysis fluids [109]. Moreover, some recommendations for higher clearance proved difficult to be fully applicable in clinical practice, especially among pediatric patients.

In children, even more than in adults, adequacy of PD treatment cannot be exclusively defined by targets of solute and fluid removal. Clinical assessment of adequacy of PD treatment should also take into consideration a comprehensive series of clinical, metabolic, and psychosocial aspects, the most important of which are listed in Table 13.3.

Table 13.3 Clinical, metabolic, and psychosocial aspects that should be taken into consideration in the assessment of the adequacy of chronic peritoneal dialysis treatment in pediatric patients

Hydration status
Nutritional status
Dietary intake of energy, proteins, salts, and trace elements
Electrolyte and acid-base balance
Calcium phosphate homeostasis
Control of anemia
Blood pressure control
Growth and mental development
Level of psychosocial rehabilitation

Clearance of Small Solutes

In the literature, there are no definitive outcome data indicating that any measure of dialysis adequacy is predictive of well-being, morbidity, or mortality in pediatric patients on chronic PD. Therefore, the 2006 KDOQI guidelines [45] simply stated that by clinical judgment the target delivered small solute clearance in children should meet or exceed adult standards.

A minimal delivered dose of small solute clearance should correspond to a Kt/V_{urea} of no less than 1.8 per week. Data from pediatric and adult studies found the serum albumin level to be a predictor of patient survival and a Kt/V_{urea} of 1.8 or greater in adult PD patients has been associated with better serum albumin values [45, 110]. This target should be intended as total clearance (i.e., the arithmetical sum of peritoneal clearance and renal clearance) or peritoneal clearance alone in patients without RRF (defined as a renal Kt/V_{urea} of less than 0.1 per week). Even if peritoneal clearance and renal clearance have a different impact on patient outcome [106–109], they can be added to determine total clearance in clinical practice. The term *delivered* refers to the

actual dose the patient is receiving based on direct measurement, not to an estimated value obtained by using a kinetic modeling program. Solute clearance should be measured within the first month after the start of chronic PD treatment and at least once in every 6 months thereafter in a clinically stable patient. More frequent measurements should be conducted when:

- Dialysis clearance may have been compromised (e.g., 1 month after the resolution of a peritonitis episode).
- There is a rapid loss of RRF.
- There is clinical evidence of inadequate dialysis.

In any case, if a patient is not doing well and no other cause of the worsening of his clinical conditions than kidney failure can be identified, a trial of increased dialysis dose is indicated [45].

The 2006 KDOQI guidelines [45] recommended the use of Kt/V_{urea} as a surrogate for adequate dialysis, at least in CAPD patients. Historically, both Kt/V_{urea} and creatinine clearance (CrCl) have been employed to evaluate PD clearance. It has been proposed that the ratio of these two parameters should be 1:30 [11, 42]. A discrepancy between urea and creatinine-based PD adequacy parameters has historically been reported in adults [111, 112] and in children [42].

In APD patients, for whom targets of CrCl have recently been published, the relationship between CrCl and Kt/V_{urea} is much more variable than in patients on CAPD [11, 113]. Indeed, urea clearance is mostly related to dialysate volume and number of exchanges, while CrCl is predominantly affected by the duration of the dwell time (i.e., the duration of contact of the peritoneum with dialysate, which is currently called "contact time") and by RRF. The finding of adequate values of Kt/V_{urea} associated with inadequate values of CrCl can be related to a hyperpermeable PM state, or a too low IPV, since both of these conditions are associated with a greater removal of urea than creatinine [11, 55, 113]. Finally, scaling of Kt/V_{urea} to BW and CrCl to body surface area may differently influence values obtained in the calculation of these parameters in infants and small children as a result of a higher ratio of BSA/weight [42]. The 2006 KDOQI recommendations stated that the determination of dialysis and urine Kt/V_{urea} alone for follow-up was preferred mainly due to the simplicity of its calculation and the observation that studies on adult PD patients have not provided evidence of a benefit in terms of patient outcome when expressing clearance in any manner other than Kt/V_{urea} [45, 112].

Since Kt/V_{urea} is scaled for urea distribution volume (V), which is assumed to equal total body water (TBW), accurate estimation of TBW is a critical component of dialysis dose measurement. The gold-standard isotope dilution technique to determine TBW is laborious, costly, and not widely available; therefore, anthropometric prediction equations based on height and weight are commonly used to estimate TBW. Equations derived from healthy children [114] systematically overestimate TBW in pediatric patients receiving PD. In this patient population, anthropometric TBW prediction equations have been developed and validated by comparison with the determination of TBW by means of a heavy water (H_2O^{18} or D_2O) dilution technique [115]. These formulae are based on an anthropometric parameter called *height times weight*, which correlates linearly with TBW when both values are log-transformed and are as follows:

$$\text{Boys}: \text{TBW} = 0.10 \times \left(\text{HtWt}\right)^{0.68} - 0.37 \times \text{weight}$$

$$\text{Girls}: \text{TBW} = 0.14 \times \left(\text{HtWt}\right)^{0.65} - 0.35 \times \text{weight}$$

Hyperphosphatemia and elevated calcium times phosphorus product are associated with calcifying large-vessel arteriopathy, which develops even in young patients with childhood-onset ESRD [116, 117]. Schmitt and coworkers [118] raised the issue whether dialytic phosphate removal might provide a more reliable direct measure of dialysis efficacy than urea and creatinine clearance. By studying peritoneal phosphate kinetics and daily dialytic and renal phosphate elimination in 35 pediatric patients receiving chronic APD, these authors found that the peritoneal transport state defined by the creatinine equilibration pattern is poorly predictive of daily

phosphate clearances; this finding suggests that a specific evaluation of the D/P phosphate ratio should be done to define an individual's phosphate transport category. The efficacy of phosphate elimination by means of a standard APD regimen is limited and independently predicted by total fluid turnover, the number of cycles, 2-hour D/P phosphate, dwell time, and achieved ultrafiltration [118].

In summary, numerical targets of small solute clearance, as defined by currently available guidelines, should be interpreted cautiously and in the context of patient clinical assessment. Neither K_t/V_{urea} nor CrCl are the perfect indices to predict outcome in PD patients; however, they provide complementary measurements of dialysis dose. Indeed, these targets should be included as a part of global patient care. Failure to achieve them should not be considered an indication to abandon PD if all other aspects of patient care are successfully addressed by PD treatment.

Clearance of Middle-Sized Molecules

Failure to achieve adequate clearance of the so-called middle-sized molecules (from 300 to 5000 daltons of MW) is one of the possible explanations for the failure of increased dialysis dose to improve patient survival [109]. Small solute and middle-sized molecule clearances respond differently to changes in the PD prescription, since the former is mainly determined by the frequency of exchanges and total volume of dialysate, while the latter depends more on the dialysate/PM contact time [119, 120]. The transport rate of middle-sized molecules is much slower than that of small solutes and more dependent on the convective component of transmembrane solute movement [121]. In practice, the removal of middle-sized molecules and low-MW proteins, such as β_2-microglobulin and leptin, mainly depends on RRF [122, 123]. Moreover, an increase in the restriction coefficient for macromolecules was reported in relation to time on chronic PD, which is associated with increased size selectivity and reduced peritoneal permeability for higher-MW solutes [62]. Hence, particular attention should be paid to middle molecule clearance, especially in children on NIPD and in all PD patients as RRF is declining. In these cases, a continuous PD regimen (CCPD or CAPD) should be adopted even if small solute clearance is above the target without the longer dwell [45]. Increased β_2-microglobulin and leptin clearance have been reported in patients receiving a long dwell with icodextrin solution [124].

Fluid Balance

Systematic adjustment of the PD prescription should be planned in order to achieve and maintain fluid balance and normal blood pressure. PD has been considered an optimal approach to reach this therapeutic result thanks to its continuous nature, which avoids fluctuations of the total body volume and offers better hemodynamic stability than intermittent therapies. Nevertheless, PD population surveys show a high prevalence of hypertension and cardiovascular mortality with inadequacy of UF as a significant predictor of mortality in anuric adult PD patients [87, 125]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [126] showed that 57% of nearly 4000 pediatric patients on dialysis had blood pressure (BP) values higher than their age-, sex-, and height-specific 95th percentile; moreover, 20% of patients had blood pressure values at or above the 95th percentile while receiving antihypertensive medication. In Europe, systolic or diastolic BP higher than the 95th percentile was reported in 35.5% of 851 pediatric PD patients, irrespective of the use of antihypertensive medications [127]. As reported by the International Pediatric Peritoneal Dialysis Network (IPPN), 48% of 507 pediatric PD patients treated in 55 centers had echocardiographic evidence of left ventricular hypertrophy (LVH) [128]. Hypertension and cardiac impairment were most frequently found in the younger and nephrectomized PD patients [129]. Even if the cause of hypertension is multifactorial, volume overload is likely to play an important etiologic role in a relevant percentage

of patients on PD therapy [45, 130]. Chronic fluid overload represents an important clinical problem in pediatric PD patients, especially when RRF is decreasing.

Routine monitoring of volume status and daily UF volume, along with periodic assessment of residual urine output, are therefore essential in the process of attaining adequate fluid balance on PD [42, 45]. In the absence of validated, readily applicable indicators of volume status, the assessment of patient target weight mainly relies on clinical judgment and assessment of vital signs. In clinical practice, the desirable target weight of a patient on chronic PD can be reasonably approximated as that weight at which the patient is edema-free and has a blood pressure within the limits of the normal range for age and gender, with minimal need for antihypertensive medications. Since fluctuations in patient weight secondary to growth and to changes in nutritional status may occur, repeated evaluations of target weight at regular intervals are mandatory in all patients.

In order to increase the efficacy of the PD prescription to attain an adequate UF rate, a series of factors that can affect the maintenance of patient fluid balance should be considered, together with the related recommended interventions:

PM transport characteristics. PM transport characteristics affect net fluid removal at a given dwell time by determining the osmotic gradient time curve of each individual patient. As already mentioned, a modification of the standard PET utilizing 4.25% dextrose solution can be employed to better evaluate the UF kinetics and the maximum dip in D/P sodium, which reflects the sodium-free water transport [82, 83]. For instance, if the patient has a fast transport, as a result of either a large peritoneal surface area or a too low prescribed fill volume, improved UF will be obtained by increasing the fill volume as tolerated and/or by shortening the dwell time. In patients with decreased sodium-free water transport and no dip in D/P sodium after 1–2 h of the dwell, there will be no benefit from the use of a high dialysate glucose concentration; in these cases, a long exchange with an icodextrin PD fluid (daytime dwell on APD; nighttime dwell on CAPD) may enhance their UF capacity [11]. La Milia and colleagues [131] suggested calculation of the exact volume of free water transport by measuring the amount of sodium transported through the small pores over a 1-h dwell; since the total ultrafiltered volume is known, subtracting the small pore transport from the total transport will give the amount of water transported through the water channels. Smit and coworkers [132] added to this method the use of a volume marker, so that free water transport could be calculated at each time point. From both studies, the contribution of free water transport appeared to be about 40–50% in the first hour of an exchange performed with an hypertonic PD solution [132].

Peritoneal surface area available for the exchanges. An extremely limited vascular surface area might be the consequence of postinfectious or postsurgical adhesions, peritoneal fibrosis, or peritoneal sclerosis.

Dwell time and PD solution tonicity. These two parameters are interrelated and should be considered jointly. For instance, low dialysate dextrose concentration and prolonged dwell time will inevitably lead to inadequate fluid removal in high transport patients [83]. An increase of dextrose tonicity is associated with enhanced UF, but the osmotic gradient dissipates over time; therefore, adjusted concentration dextrose solutions are indicated for short dwells, while for the nighttime dwell in CAPD and the daytime dwell in APD, icodextrin solution may be more appropriate. A potentially useful rule of thumb to define the optimal dwell duration in children on APD according to peritoneal transport characteristics is the so-called APEX time during a PET. As already mentioned, this is the time point at which the D/P urea and the D/D_0 glucose equilibration curves cross. APD cycle length should be equivalent to the APEX time [66].

Lymphatic absorption. A high effective lymphatic absorption rate may be the conse-

quence of a marked elevation in IPP [133]. A reduction of the fill volume may help reverse the propensity for fluid reabsorption by decreasing IPP.

Mechanical complications. Low drained dialysate volumes can be the consequence of peritoneal catheter malfunction, leading to incomplete dialysate drainage, especially after prolonged dwells on CAPD and CCPD, or dialysate leakage through the catheter tunnel or from the peritoneal cavity to the pleural space.

Fluid and sodium intake. Dietary counseling on sodium and fluid restriction should take into account renal and/or dialysis-related sodium losses, since sodium depletion may result in hypotension and impaired growth, especially in infants. Compliance with dietary recommendations should be regularly assessed.

Residual diuresis. The use of loop diuretics can be considered with caution in children with RRF (see the following paragraph).

In summary, practical strategies to alter PD prescriptions with the aim of improving the UF rate can include:

- *During short dwells of APD*: Increase the number of cycles and/or overall treatment time and/or glucose concentration; however, every effort should be made to employ the lowest possible dextrose concentration required to achieve the desired UF rate.
- *During prolonged dwells*: Utilize icodextrin solution; if needed, replace single long exchange with two or more exchanges.

The Role of Residual Renal Function in Treatment Adequacy

Prospective randomized trials of dialysis adequacy and observational studies in adult patients confirmed that RRF is a much stronger predictor of patient survival than peritoneal clearance [106–108, 134, 135]. In pediatric populations, no data from large-scale trials on the correlation between RRF and patient outcome are currently available. However, a single-center observational study on pediatric PD patients [136] reported that growth velocity was higher in a group of children with RRF than in children without RRF, even if the same mean total solute clearance was achieved in the two groups. In a nationwide analysis on the incidence of arterial hypertension among children undergoing chronic dialysis in Poland [137], residual urine output was higher in normotensive patients. Furthermore, when reviewing cardiovascular risk in a group of 59 pediatric PD patients, residual diuresis was negatively correlated with diastolic dysfunction [138]. In the IPPN data, oliguria (diuresis <0.5 L/m2 BSA per day) was associated with LVH [128].

The rate of RRF decline in pediatric patients on PD was reported to be slower than in patients on HD, and high urine volume at start of chronic PD is predictive of sustained diuresis [139, 140]. It is still not clear if there is any difference in the rate of preservation of RRF between patients on CAPD and patients on APD [141, 142]. A single-center, retrospective study of 30 children treated with CAPD or APD showed a better preservation of RRF in CAPD patients whose primary renal disease was a glomerulopathy or a familial or hereditary renal disease [143].

The PD prescription should be aimed to preserve RRF as long as possible, by gradually increasing the dialysis dose in steps, accurately targeting UF rate to maintain the patient's dry BW, and using the lowest possible dialysate glucose concentration required to achieve the desired UF volume [45, 140]. Loop diuretics can be used to increase urinary water and salt excretion without detriment to renal function in the peritoneal dialysis patient [144].

Efforts to preserve RRF also involve the prevention of such nephrotoxic insults as the following [45]:

- Exposure to nephrotoxic medications; in particular, aminoglycoside antibiotics should be employed in the treatment of PD-related peritonitis only when taking into account their

nephrotoxicity, as well as ototoxicity and vestibular toxicity.
- Exposure to radiocontrast agents.
- Extracellular fluid volume depletion.
- Urinary tract obstruction and infection.

The use of angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB) to preserve RRF has been studied in adult patients on chronic PD [145, 146]. A systematic review and meta-analysis of randomized controlled trials on this issue showed that there are only limited data supporting the efficacy of these medications in slowing the decline of RRF [147]. Experience on the effect of these agents on RRF in children on chronic dialysis is still limited; while this issue is worth investigating further, close monitoring for the occurrence of hyperkalemia is recommended, especially in anuric patients in whom peritoneal potassium excretion may be adversely affected [148] and if dual blockade is employed [149].

In summary, interventions that may contribute to the preservation of RRF in the course of chronic PD treatment should be adopted whenever possible [45]. At the same time, RRF should be routinely measured by means of an accurate 24-h urine collection, and PD prescription should be adjusted accordingly and in a timely fashion, in order to prevent inadequate treatment.

Clinical Evaluation of PD Treatment Adequacy

Large-scale, prospective outcome studies in children treated with chronic PD are lacking owing to the small number of patients per center, the relatively short period of time on dialysis prior to renal transplantation, and the, fortunately, low patient mortality rate. Nevertheless, some pediatric studies have effectively addressed the issue of the correlation between PD dose and selected clinical aspects.

Growth is a potentially valuable outcome measure specific to pediatrics and can be used to evaluate the efficacy of PD depuration. Multivariate analysis of the data of a multicenter study [55] showed a weak positive correlation of height standard deviation score (SDS) with dialytic creatinine clearance and a negative correlation with peritoneal transport status, since children with high transport on PET had a lower change in height SDS. Accelerated height velocity was reported in 62% of the patients who met or exceeded DOQI target clearances [150]. Chada et al. [136] suggest that growth correlates with renal solute clearance but not with peritoneal clearance. Similar to adult studies, these data may confirm that peritoneal and residual renal small solute clearances are not equivalent. IPPN data showed that among children who initiated chronic PD at <24 months of age, length SDS, adjusted for age and length at study entry, age at PD start, and region of residence did not change significantly with time; however, growth was significantly better in patients receiving biocompatible PD fluid and in those receiving rhGH for at least 6 months [151].

Nutrition is an issue of particular interest in pediatric PD, since it can significantly affect growth and development of children. Children on CPD commonly suffer from protein and calorie malnutrition with loss of muscle mass and protein stores, and this condition is associated with increased morbidity and mortality [152]. Compared with normal healthy children, pediatric patients receiving chronic PD have significantly lower energy intake, as well as diminished height, weight, triceps skinfold thickness, and mid-arm muscle circumference [152, 153]. In these patients, dietary protein intake is inconsistently correlated with delivered Kt/V_{urea} [154–156]. However, the relationship between Kt/V_{urea} and the normalized protein equivalent of nitrogen appearance (nPNA) has often been criticized as merely being the result of mathematical coupling [157]. Finally, a higher Kt/V_{urea} was associated with a lower serum albumin level in children, suggesting that enhancing PD dose may reach a point of no further benefit (i.e., a Kt/V_{urea} value of more than 2.75/week), owing to an increased loss of albumin in the peritoneal effluents [158].

A study of 18 children on PD showed that increasing weekly Kt/V_{urea} and CrCl was positively correlated with cardiac function and

inversely with left ventricular mass [159]. In an already mentioned study on the assessment of cardiovascular risk conducted in 59 pediatric PD patients, Kt/V_{urea} was a significant predictor of carotid intima-media thickness [138].

Monitoring PD Adequacy in the Clinical Setting

Regular assessment of the delivered dialysis dose can be performed following the NKF-DOQI clinical practice guidelines [45], with some adaptations to specific problems of childhood, and the European guidelines on adequacy of the pediatric PD prescription [42]. This assessment is fundamentally based on the direct measurement of dialytic and renal clearance, through a 24-h collection of dialysate and urine. For practical reasons, peritoneal and renal clearance can be added to determine total clearance, even if they have a different impact on patient's outcome. All dialysate discharged during 24 h should be accurately collected, including the daytime exchange(s) if present, total volume precisely measured, and a sample obtained after mixing effluent thoroughly. The same attention should be paid to performance of a complete 24-h urine collection. Urine collection requires a preservative, such as thymol, to be added to the collection or refrigeration to inhibit the growth of bacteria that can degrade urea; dialysate does not require refrigeration or preservative.

Weekly peritoneal Kt/V_{urea} can be calculated with the following formula [160]:

$$(24-\text{hour D/P urea} \times 24-\text{hour dialysate volume} \times 7)/V$$

where D/P represents the dialysate-to-plasma urea concentration ratio and V the distribution volume of urea that is assumed to equal TBW, which can be calculated from the already reported formulas [115].

In patients with RRF, renal Kt/V_{urea} corresponds to

$$\left(\text{mL/min urea clearance} \times 1{,}440\,\text{min/day} \times 7\right)/\left(1{,}000\,\text{mL} \times V\right).$$

CrCl calculation is normalized to BSA, which can be calculated from weight and height by the the use of the Gehan and George formula [161]:

$$\text{BSA}\left(\text{m}^2\right) = 0.0235 \times \left(\text{height,cm}\right)^{0.42246} \times \left(\text{weight,kg}\right)^{0.51456}$$

The following formula can be employed to calculate dialytic CrCl per week [160]:

$$\left(24-\text{hour D/P Cr} \times 24-\text{hour dialysate volume} \times 7 \times 1.73\,\text{m}^2\right)/\text{BSA}\left(\text{m}^2\right)$$

Residual renal clearance is better expressed as the average of CrCl and urea clearance, each of which can be calculated by the standard formula:

$$\text{Solute clearance}\left(\text{mL/min}\right) = \frac{\left(24-\text{h urine Volume in mL} \times \text{urine solute concentration}\right)}{\left(1440\,\text{min/day} \times \text{serum solute concentration}\right)}$$

This calculation is then normalized to patient's BSA.

PD dose assessment should be coupled with an evaluation of nutritional status, including anthropometric measurements (skinfold thickness, mid-arm circumference), a 3-day dietary record (to be evaluated by a renal dietitian), and the determination of normalized protein equiva-

lent of nitrogen appearance (nPNA), taking dialysate protein losses into account.

Body composition of children on PD can be evaluated by means of bioelectrical impedance analysis (BIA). Specific equations to predict fat-free mass (FFM) and TBW from BIA data have been provided and are as follows [162]:

$$\mathrm{FFM}\left[\mathrm{kg}\right] = 0.65 \times \left(\mathrm{height}^2 / \mathrm{impedance}\right)\left[\mathrm{ohms}/\mathrm{cm}^2\right] + 0.68 \times \mathrm{age}\left(\mathrm{years}\right) + 0.15$$

$$\mathrm{TBW}\left[\mathrm{L}\right] = 0.144 \times \left(\mathrm{impedance} / \mathrm{height}^2\right)\left[\mathrm{ohms}/\mathrm{cm}^2\right] + 40 \times \mathrm{weight}\left[\mathrm{kg}\right] + 1.99.$$

The first measurement of PD dose can be obtained as early as 1 week after the patient is stabilized on a defined PD prescription. Subsequently, PD dose measurements can be completed every 3 months and in the event of any significant change in clinical status and/or in the amount of residual diuresis. A PET can be performed 1 month after chronic PD initiation and then repeated every 12 months or earlier in case of unexpected changes in delivered PD dose or if any clinical condition that could permanently affect the peritoneal transport properties occurs, such as recurrent or persistent peritonitis.

In the clinical setting, routine clinical and biochemical outcome evaluations in pediatric patients on stable chronic PD can be organized according to the following timetable.

Every Month
- Clinical and physical examination
- Height/length
- Weight
- Head circumference (in infants and toddlers)
- Blood pressure
- Blood urea nitrogen and creatinine
- Sodium, potassium, acid-base status
- Hemoglobin/hematocrit
- Serum albumin, serum calcium, phosphorus, and magnesium
- Daily urine volume and UF

Every 3 Months
- Serum ferritin
- Serum iron
- Total iron binding capacity
- Alkaline phosphatase
- Parathyroid hormone
- 25-Hydroxyvitamin D
- Kt/V_{urea} and CrCl from a 24-h dialysate and urine collection

Every 12 Months
- Ambulatory blood pressure monitoring
- Echocardiography
- Hand and wrist x-ray for bone age
- Neurodevelopment assessment (every 6 months in children <2 years of age)
- Peritoneal equilibration test

In the course of PD treatment, attention should be paid by the patient's parents, dialysis nurses, and physicians to potential manifestations of inadequate dialysis. In practice, the signs and/or symptoms that should be regularly recorded and evaluated are the following:

- Clinical manifestations of overt uremia (uremic pericarditis, pleuritis)
- Clinical and/or biochemical signs of malnutrition
- Hypertension/hypervolemia
- Hyperkalemic episodes
- Hyperphosphatemia and/or excessive calcium times phosphorus product
- Kt/V_{urea} and/or CrCl values below the minimal recommended targets
- Clues of patient and family noncompliance.

It should be stressed again that numerical targets of small solute removal must be interpreted cautiously and in the context of patient clinical assessment; failure to reach these targets should be regarded as a warning sign for treatment failure, requiring careful reevaluation of each constituent of the therapeutic program. The contribution of RRF to the adequacy of PD treat-

ment is extremely important and tends to deteriorate with time on chronic dialysis, albeit at a slower rate in PD than in HD patients. Therefore, RRF should be regularly measured, although this may be difficult to do accurately in young children, requiring good cooperation by caregivers. While RRF is declining, adaptation of the PD prescription by increasing dialysis should be performed in a timely manner in order to anticipate and prevent the occurrence of the abovementioned signs and/or symptoms of inadequate treatment.

Machines for Automated Peritoneal Dialysis

The rapid evolution that APD has experienced has been closely linked to the development of new automatic machines, which are referred to as cyclers, which have been also adapted for pediatric needs.

Characteristics of Cyclers for Automated Peritoneal Dialysis

Advances in the fields of electronics and computer technology generated substantial modifications of the old cyclers employed for high-flow intermittent PD (IPD), to machines that are now smaller, lighter, more user-friendly, less expensive, and increasingly reliable. Since APD is performed by the patient or caregiver at home, the most important requirements that cyclers should fulfill are the following:

- Small size, light weight, and easy portability, which have been obtained by means of component miniaturization
- Simple interface with unequivocal messages and/or symbols (touch screen)
- Safe, accurate, and reliable functioning in the patient's home setting

Patient satisfaction should therefore be one of the leading design criteria for an APD machine [163]. At the same time, the technology incorporated in the cycler should be so advanced as to allow one to:

- Individualize the dialytic prescription.
- Measure the delivered dialysis dose and net UF.
- Monitor patient adherence to the prescribed treatment schedule.
- Detect excessive IPP.
- Detect peritoneal catheter malfunction.
- Fulfill the basic requirements of safety according to local and global standards.

Moreover, the overall cost of treatment must be contained, although proportionate to the expected level of patient well-being and rehabilitation.

Some of the technical options incorporated in modern cyclers for APD are:

- Online warming of dialysate.
- Pressure monitors to assess IPP.
- Gravity-assisted roller or diaphragm pumps to infuse and/or drain the dialysate; the pumps do not operate directly on the peritoneal cavity but on the heater and drain bag.
- Cassette receptacles for the tubing set, to simplify the procedure and minimize operator errors and risk of contamination, thus facilitating a quick and safe connection.
- Bar code readers to match the prescription with the PD solution selected by the patient.
- Automated connecting devices to facilitate the connection between the bags and the tubing manifold.
- Ad hoc connectors to perform one exchange of dialysate during the day.
- Newer generations of cyclers are incorporating voice-led instructions for ease of training and improved caregiver troubleshooting at home. Furthermore, there is a significant potential for integration of cycler data to the electronic medical record (see "Registration and Transmission of Treatment Data") with current advances in cycler technology.

The machine interface is typically characterized by an easy and clear display with unequivo-

cal messages, through which trained personnel and patients can easily set up the prescribed dialysis schedule. Usually, there are various levels of access to code protected programs so that scheduled changes can be programmed only by the operator. The access to the prescription and control level of the cycler is usually protected by a password that is known only by authorized personnel, while data of the ongoing treatment can be easily visualized on the display of the cycler.

The miniaturization of most components allows full portability by means of both reduced dimension and light weight.

In particular, cyclers to be used for the treatment of children should have a specific pediatric mode designed to:

- Accurately deliver even a small volume of dialysate (as low as 60 ml per exchange in the newer cyclers), with the possibility of very small increments.
- Have a low recirculation volume set (20 mL or less) for low fill volume PD regimens.
- Allow peritoneal effluent inflow and drainage at low flow rates and pressure, which can be physiological for infants and small children, without alarming (low fill volume mode).
- Allow programming of individualized minimum drain volume and minimum drain time for each patient, according to the desired PD schedule and peritoneal catheter function. The factory default setting of the patient fill volume can be adopted initially; then, an individualized, optimal drain percentage should be determined. Attention should be paid that if the minimum drain volume percentage is set too low, an incomplete drain could result, and this could lead to an overfill of solution that in some circumstances may cause injury to the patient. On the contrary, if the minimum drain volume percentage is set too high, an increased number of alarms and a loss of dwell time could result. Usually, a nontidal drain phase ends, and the system moves on to the next fill when a minimum volume has been drained, a minimum drain time has elapsed, and the system has determined the patient to be empty.

In general, the ideal cycler for APD should be able not only to perform all treatment schedules in an accurate and safe way but also to optimize the performance of the selected PD regimen [164]. Future directions may enhance cycler development to utilize machine learning – taking the recorded treatment information to suggest, or even automatically attempt, an improved regimen. Examples of such self-programming of the cycler are the following:

- Dialysate inflow and outflow time could be adjusted on the basis of the flow rate that has been registered during the previous exchange.
- Online detection of net UF, related to fluid osmolarity, dwell time, and fill volume, could serve as the basis for an automatic feedback on the PD fluid composition in the following cycle (profiling of glucose concentration throughout the dialysis session). Bedsides production of dialysis solution could individualize PD treatment with respect to osmotic agent, buffer, sodium, and calcium contents [164].

Registration of Treatment Data

The introduction of microchips and computer technology has led to greater programming flexibility of the cyclers, as well as to the possibility of recording on an electronic device the patient's prescription, medical history, and treatment events. This system provides information on the home dialysis treatment and a means of monitoring patient compliance. This also provides a patient-specific database of therapy information. The cycler system includes a data card (memory card) which can store up to 60–90 days of actual treatment data. This database of therapy information can be downloaded from the memory card of the cycler when the patient goes to the dialysis unit for a visit or can be retrieved remotely as needed.

One example of the potential utilization of this recording system is the evaluation of peritoneal catheter functioning. The pattern of the peritoneal catheter's flow during each treatment cycle can be

analyzed with the help of graphs and charts and any catheter malfunction detected even if it has not yet caused cycler alarms or clinical symptoms. The PD prescription can be adapted to the drainage profile of each individual patient's catheter, thus minimizing the fill and drain dead times and the occurrence of minimum drain volume alarms. An application of this adaptation process is represented by optimization of tidal volume to the individual drainage profile, which eliminates the flow rate drop occurring beyond the so-called breakpoint of the drainage curve [97].

The recording of a PD session may also reveal an excessive incidence of cycler alarms during the nightly treatment, resulting in sleep deprivation and an impairment of the quality of life to both patient and caregiver [165]. Tube kinking and catheter malfunction are the most frequent causes of drain alarms. In some cases, unsuitable setting of alarm limits (e.g., the default adult settings of the cycler – such as low drain – may not be appropriate for a small pediatric patient) may generate the occurrence of an excessive number of useless and disturbing alarms.

The memory card of the cycler can be reprogrammed by the physician or the dialysis nurse to address patient prescription changes; when the patient inserts the card back into the cycler, all the settings are updated. Therefore, the use of these electronic devices eliminates the need for patients to program and manually record APD treatment data, thus shortening the training time and simplifying data collection and management by the dialysis team.

Transmission of Treatment Data

The possibility of a remote Internet connection between the home cycler and the dialysis unit makes the so-called teledialysis possible. APD treatment data can be visualized and monitored by the staff in the dialysis unit online (while the treatment is being administered at a patient's home) or offline in the morning after the end of the night APD session. Alternatively, data can be transferred electronically from the cycler's memory card to the personal computer of the dialysis unit on a regular basis (e.g., every 7–10 days). This provides ease of data review should there be any concerns observed by the patient or the caregiver related to cycler function or peritoneal catheter function. Information stored in the file of each patient should be examined and evaluated by the physician and dialysis nurse on a routine basis. Data can be organized in charts and graphs and statistically elaborated. Recently, a two-way technology has become available that allows for remote data monitoring and therapy adjustment from the dialysis unit – specifically, this provides a cost-effective opportunity to change a patient's PD prescription setting remotely [166]. Integration of advanced technology allows for early detection of therapy problems and provides the opportunity to facilitate APD prescription changes that may help reduce the need for hospitalization [167]. Furthermore, technology-based integration with dialysis teams and families may also reduce the feeling of isolation and detachment that the patient and family may experience in the course of long-term home PD, especially should they live a significant distance from the dialysis center.

There is limited data on the use of telemedicine in the pediatric PD program setting; however, one study [165] did demonstrate that the so-called telePD allowed timely identification of clinical and psychosocial problems and increased patient and family satisfaction with home PD treatment. Such problems were represented, for instance, by an imperceptible but progressive decrease of UF rate or by a prolongation of the drainage phase due to catheter malfunction that is still too small to release cycler alarms. A teledialysis system can also be integrated by videoconferencing equipment (digital camera; ISDN [Integrated Services Digital Network] line) to give private videoconferencing and video capture of images; thus, the dialysis and the exit site care procedure can be followed by the dialysis center server or by the physician's personal computer [168, 169]. Contrasting data on the use of telecare in a pediatric program suggested that the employed videophone equipment showed technical limitations and was not cost-effective [170]; therefore, this technology deserves further evaluation in pediatric home PD.

Monitoring of Patient Adherence to the Prescribed APD Treatment

Nonadherence is an important obstacle to achieving adequate PD therapy and a significant cause of morbidity, patient hospitalization, and dialysis technique failure. In a pediatric single-center analysis, at least some degree of nonadherence to the prescribed PD regimen was reported in 45% of patients [171]. Several methods to assess patient adherence to the PD prescription have been proposed, based on comparison of measured versus predicted creatinine excretion [172], home visits to check dialysis solution supply inventories [173, 174], patient self-report confidential questionnaires [175], or the comparison of self-reports of compliance with the rate of predicted versus measured Kt/V_{urea} and CrCl [176]. Given that no single method is able to provide a complete assessment of nonadherence in patients on home PD, these assessments should be used in an integrated way.

The electronic data registration system of the cyclers for APD provides an objective means to monitor patient adherence to the prescribed treatment. Comparison of the prescribed versus the actually delivered therapy shows any change the patient and/or caregiver may have made in the prescribed dialysis schedule on his or her initiative. Most frequently reported changes in the setting of nonadherence made by the patients or caregivers include changing session length or fill volume [171, 175] but can include all of the following:

- Skipping treatment cycles
- Shortening overall treatment time
- Manually changing treatment parameters
- Bypassing therapy phases or cycles
- Reducing fill volume by performing manual drains

In summary, recording and transmitting PD session data through an electronic device on a regular basis can enhance patient adherence to PD prescriptions, since the awareness of the recording makes the patient feel more confident of treatment control and the doctor-patient communication more explicit. It also helps the dialysis staff understand the reasons for inadequate depuration and accordingly change the PD prescription.

Strategies to Enhance Patient Adherence to PD Prescriptions

An approach to increasing the compliance of patients and caregivers to the prescribed PD schedule should be considered an essential component of the prescription process and a key factor in achieving the expected therapeutic results. Effective strategies to increase compliance require a structured, comprehensive care model with a team-based focus including the patient, caregiver(s), and dialysis staff.

Patient- and family-targeted interventions are mainly based on their active involvement in the choice of dialysis modality and on their education to perform home dialysis treatment [177].

Patient selection should include the following action points:

- Early patient/family referral to dialysis staff
- Evaluation of patient's clinical needs and patient and family lifestyle
- Structured, unbiased information on the available dialysis modalities
- Evaluation of physical and psychological ability of the caregiver(s) to perform dialysis tasks
- Assessment of patient home environment

Patient and family preparation for home PD [178] should:

- Start well before dialysis initiation.
- Involve a multidisciplinary team including nephrologist, renal nurse, renal dietitian, psychologist, social worker, school teacher, and child life staff.
- Make use of appropriate written information and other teaching aids.
- Encourage contacts with similar-aged children on home dialysis.
- Include a home visit and a liaison with the nursery/school/college and the family doctor.

Training for home PD procedures should involve two family members and could potentially be completed in the home environment by dialysis units with a well-organized home training program.

Ultimate goals of patient and family education are:

- To achieve an adequate level of knowledge, understanding, and participation in the choice of PD modality and in the process of PD prescription
- To reduce patient and family anxiety and stress by increasing awareness of the disease process and treatment options
- To convince the patient and family of the appropriateness and beneficial effects of the prescribed treatment and that adherence to the prescription will improve the outcome

Once PD treatment has started, regular contact (telephone, electronically, and/or telehealth) and support for the family should be planned; moreover, acquired knowledge and skills of performing home PD should be assessed at regular intervals.

Dialysis staff-targeted interventions to address the issue of patient adherence should increase staff ability to:

- Individualize the PD prescription and evaluate results.
- Explain the reasons for prescription changes.
- Manage treatment complications as much as possible on an outpatient basis.
- Test and recognize signs of patient noncompliance.

Dialysis staff education about compliance should be monitored and regularly updated.

Conclusions

PD therapy has experienced a remarkable evolution during the past 30 years in parallel to the development of safe and simple-to-use connecting devices, more biocompatible dialysis materials and solutions, and automatic machines for PD delivery that utilize computerized technology for improved prescription accuracy. All of these achievements have provided dialysis staff valuable tools to improve the overall efficacy and tolerability of PD treatment in children.

For CAPD, the use of an integrated Y-set, double-bag system, with a disinfectant-containing cap and a "flush before fill" mode, has been associated with a reduction in the incidence of peritonitis episodes due to touch contamination and has simplified PD connecting maneuvers, thus shortening patient and partner training.

Individualizing the PD prescription is routinely performed by the characterization of PM transport capacity, assessed by means of well-standardized functional tests that have been validated in pediatric patients. Early controversy over the approach to prescribing fill volume has given way to generally accepted guidelines for scaling to BSA according to clinical tolerance and IPP measurement, in order to ensure maximal recruitment of peritoneal exchange area.

Fluid balance is increasingly recognized as a crucial aspect of PD patient management, as the efficiency of water and salt removal has been clearly associated with patient outcome, especially in anuric patients. UF failure is an important cause of PD abandonment with conversion to hemodialysis.

Prospective randomized trials of dialysis adequacy and observational studies in adult patients have confirmed that RRF is a much stronger predictor of patient survival than peritoneal clearance. The PD prescription should be aimed to preserve RRF as long as possible, by gradually increasing the dialysis dose in steps, accurately targeting UF rate to maintain the patient's dry BW, and using the lowest possible dialysate glucose concentration required to achieve the desired UF volume. Prevention of RRF loss also involves avoidance of nephrotoxic agents. The potential role of angiotensin-converting enzyme inhibitors and ARB requires further investigation in children on PD. As RRF declines over time, the PD prescription should be adjusted to its decline in a timely fashion to prevent the adverse effects of chronic fluid overload. The ultimate goal of PD

modality selection and prescription is to identify, and possibly achieve, the optimal PD dose for each individual patient; this can be regarded as determining the amount of dialysis above which the additional expected benefit does not justify the increase in the burden on patient and family and of financial costs.

The evolution of APD has been closely linked to advances in the technology incorporated in the new cyclers, which has made APD delivery safer and more efficient. While the currently available cyclers can monitor technical parameters, there remain limitations with current dialysis technology that limit real-time data transfer from the cycler to the primary team. Teledialysis may help increase patient and caregiver confidence in performing therapy at home and reduce the need for patient hospitalization, thus improving academic/psychosocial outcomes and patient compliance with therapy.

References

1. Oreopoulos DG, Robson MD, Izatt S. A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). Trans Am Soc Artif Internal Organs. 1978;24:484–9.
2. Buoncristiani U, Bianchi P, Cozzani M, et al. A new safe, simple connection system for CAPD. Int J Urol Androl. 1980;1:50–3.
3. Churchill DN, Taylor DW, Vas SI, et al. Peritonitis in continuous ambulatory peritoneal dialysis (CAPD): a multicentre randomized clinical trial comparing the Y connector disinfectant system to standard systems. Perit Dial Int. 1989;9:159–63.
4. Bazzato G, Landini S, Coli U, et al. A new technique of continuous ambulatory peritoneal dialysis (CAPD): double bag system for freedom to the patient and significant reduction of peritonitis. Clin Nephrol. 1980;13:251–4.
5. Vulsma T, Menzel D, Abba FC, et al. Iodine-induced hypothyroidism in infants treated with continuous cyclic peritoneal dialysis. Lancet. 1990;336:812.
6. Mettang T, Pauli-Magnus C, Alscher DM, et al. Influence of plasticizer-free CAPD bags and tubings on serum, urine, and dialysate levels of phthalic acid esters in CAPD patients. Perit Dial Int. 2000;20:80–4.
7. Kiernan L, Kliger A, Gorban-Brennan N, et al. Comparison of continuous ambulatory peritoneal dialysis-related infections with different "Y-tubing" exchange systems. J Am Soc Nephrol. 1995;5:1835–8.
8. Monteon F, Corra-Rotter P, Paniagua R, Amato D. The Mexican Nephrology Collaborative Study Group, et al. Prevention of peritonitis with disconnect systems in CAPD. Kidney Int. 1998;54:2123–8.
9. Honda M. The 1997 report of the Japanese National Registry data on pediatric peritoneal dialysis patients. Perit Dial Int. 1999;19(Suppl 2):S473–8.
10. Verrina E, Cappelli V, Perfumo F. Selection of modalities, prescription, and technical issues in children on peritoneal dialysis. Pediatr Nephrol. 2009;24:1453–64.
11. Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24:1633–42.
12. Nolph KD, Twardowski ZJ. The peritoneal dialysis system. In: Nolph KD, editor. Peritoneal dialysis. Boston: Martinus Nijhof Publisher; 1985. p. 23.
13. Rippe B, Rosengren BI, Venturoli D. The peritoneal microcirculation in peritoneal dialysis. Microcirculation. 2001;8(5):303–20.
14. Rosengren BI, Rippe B. Blood flow limitation in vivo of small solute transfer during peritoneal dialysis in rats. J Am Soc Nephrol. 2013;14(6):1599–604.
15. Schaefer B, Bartosova M, Macher-Goeppinger S, et al. Quantitative histomorphometry of the healthy peritoneum. Sci Rep. 2016;6:21344.
16. Twardowski ZJ. Physiology of peritoneal dialysis. In: Nissenson AR, Fine RN, Gentile DE, editors. Clinical dialysis. Norwalk: Appleton & Lange; 1990.
17. Gotloib L, Shostak A, Bar-Sella P, et al. Fenestrated capillaries in human parietal and rabbit diaphragmatic peritoneum. Nephron. 1985;41:200–2.
18. Pecoits-Filho R. The peritoneal cavity: a room with a view to the endothelium. Perit Dial Int. 2005;25:432–4.
19. Krediet RT, Lindholm B, Rippe B. Pathophysiology of peritoneal membrane failure. Perit Dial Int. 2000;20(Suppl 4):22–42.
20. Flessner M, Henegar J, Bigler S, et al. Is the peritoneum a significant barrier in peritoneal dialysis? Perit Dial Int. 2003;23:542–9.
21. Krediet RT. The physiology of peritoneal transport and ultrafiltration. In: Gokal R, Khanna R, Krediet RT, Nolph K, editors. Textbook of peritoneal dialysis. Dordrecht: Kluwer; 2000. p. 135–73.
22. Flessner MF. The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol. 2005;288:433–42.
23. Fischbach M, Dheu C, Seugé-Dargnies L, et al. Adequacy of peritoneal dialysis: consider the membrane for optimal prescription. Perit Dial Int. 2007;27(Suppl 2):S167–70.
24. Haraldsson B. Assessing the individual peritoneal dialysis capacities of individual patients. A clinical tool based on the three pore model. Kidney Int. 1995;47:1187–98.
25. Fischbach M, Haraldsson B. Dynamic changes of total pore area available for peritoneal exchange in children. J Am Soc Nephrol. 2001;12:1524–9.

26. Schmitt CP, Haraldsson B, Doetschmann R, et al. Effects of pH-neutral, bicarbonate-buffered dialysis fluid on peritoneal transport in children. Kidney Int. 2002;61:1527–36.
27. Haas S, Schmitt CP, Bonzel KE, et al. Improved acidosis correction and recovery of mesothelial cell mass with neutral-pH bicarbonate dialysis solution among children undergoing automated peritoneal dialysis. J Am Soc Nephrol. 2003;14:2632–8.
28. Fischbach M, Terzic J, Chauvé S, et al. Effect of peritoneal dialysis fluid composition on peritoneal area available for exchange in children. Nephrol Dial Transplant. 2004;19:925–32.
29. Morgenstern BZ. Equilibration testing: close, but not quite right. Pediatr Nephrol. 1993;7:1309–12.
30. Warady BA, Alexander SR, Hossli S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol. 1996;7:2385–91.
31. Fischbach M, Terzic J, Laugel V, et al. Measurement of hydrostatic intraperitoneal pressure: a useful tool for the improvement of dialysis dose prescription. Pediatr Nephrol. 2003;18:976–80.
32. Ahmad S. Peritoneal dialysis. In: Ahmad S, editor. Manual of clinical dialysis. London: Science Press; 1999. p. 65–8.
33. Rippe B. Is lymphatic absorption important for ultrafiltration? Perit Dial Int. 1995;15:203–4.
34. Flessner MF. Transport kinetics during peritoneal dialysis. In: Leypoldt JK, Austin RG, editors. The artificial kidney: physiological modelling and tissue engineering. Texas: Landes; 1999.
35. Mactier RA, Khanna R, Moore H, et al. Kinetics of peritoneal dialysis in children: role of lymphatics. Kidney Int. 1988;34:82–8.
36. Schaefer F, Haraldsson B, Haas S, et al. Estimation of peritoneal mass transport by three-pore model in children. Kidney Int. 1998;54:1372–9.
37. Schroeder CH. Optimal peritoneal dialysis: choice of volume and solution. Nephrol Dial Transplant. 2004;19:782–4.
38. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int. 2008;108:S137–44.
39. Dart A, Feber J, Wong H, et al. Icodextrin reabsorption varies with age in children on automated peritoneal dialysis. Pediatr Nephrol. 2005;20:683–5.
40. Rusthoven E, van der Vlugt ME, van Lingen-van Bueren LJ, et al. Evaluation of intraperitoneal pressure and the effect of different osmotic agents on intraperitoneal pressure in children. Perit Dial Int. 2005;25:352–6.
41. Devuyst O, Rippe B. Water transport across the peritoneal membrane. Kidney Int. 2014;85(4):750–8.
42. Fischbach M, Stefanidis CJ, Watson AR. Guidelines by an ad hoc European committee on adequacy of the pediatric peritoneal dialysis prescription. Nephrol Dial Transplant. 2002;17:380–5.
43. Goldstein SL. Adequacy of dialysis in children: does small solute clearance really matter? Pediatr Nephrol. 2004;19:1–5.
44. Siddique I, Brimble KS, Walkin L, et al. Genetic polymorphisms and peritoneal membrane function. Perit Dial Int. 2015;35(5):517–29.
45. National Kidney Foundation. KDOQI clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis. 2006;48(Suppl1):S1–322.
46. Geary DF, Harvey EA, MacMillan JH, et al. The peritoneal equilibration test in children. Kidney Int. 1992;42:102–5.
47. Kohaut EC, Waldo FB, Benfield MR. The effect of changes in dialysate volume on glucose and urea equilibration. Perit Dial Int. 1994;14:1–4.
48. Warady BA, Alexander SR, Hossli S, et al. The relationship between intraperitoneal volume and solute transport in pediatric patients. J Am Soc Nephrol. 1995;5:1935–9.
49. Verrina E, Amici G, Perfumo F, et al. The use of PD Adequest mathematical model in pediatric patients on chronic peritoneal dialysis. Perit Dial Int. 1998;18:322–8.
50. Twardowski ZJ, Nolph KD, Khanna R, et al. Peritoneal equilibration test. Perit Dial Bull. 1987;7:138–47.
51. Schaefer F, Langebeck D, Heckert KH, et al. Evaluation of peritoneal solute transfer by the peritoneal equilibration test in children. Adv Perit Dial. 1992;8:410–5.
52. Waniewski J, Heimburger O, Werynski A, et al. Aqueous solute concentrations and evaluation of mass transport coefficients in peritoneal dialysis. Nephrol Dial Transplant. 1992;7(1):50–6.
53. Pride ET, Gustafson J, Graham A, et al. Comparison of a 2.5% and a 4.25% dextrose peritoneal equilibration test. Perit Dial Int. 2002;22:365–70.
54. Smit W. Estimates of peritoneal membrane function – new insights. Nephrol Dial Transplant. 2006;21(Suppl 2):ii16–9.
55. Schaefer F, Klaus G, Mehls O. Mid-European Pediatric Peritoneal Dialysis Study Group. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. J Am Soc Nephrol. 1999;10:1786–92.
56. Zialkowska H, Paczyk-Tomaszweska M, Debiaski A, et al. Bone metabolism and peritoneal membrane transport in children on chronic peritoneal dialysis. Perit Dial Int. 2003;23:487–92.
57. Warady BA, Jennings J. The short PET in pediatrics. Perit Dial Int. 2007;27:441–5.
58. La Milia V, Di Filippo S, Crepaldi M, et al. Mini-peritoneal equilibration test: A simple and fast method to assess free water and small solute transport across the peritoneal membrane. Kidney Int. 2005;68:840–6.
59. Schaefer F. The PET-iatrics of peritoneal solute transport: is short also good for the young ones ? Perit Dial Int. 2007;27:413–4.
60. Cano F, Rojo Azocar M, et al. The mini-PET in pediatric peritoneal dialysis: a useful tool to predict volume overload? Pediatr Nephrol. 2013;28:1121–6.

61. Reddingius RE, Schröder CH, Willems JL, et al. Measurement of peritoneal fluid handling in children on continuous ambulatory peritoneal dialysis using dextran 70. Nephrol Dial Transplant. 1995;10:866–70.
62. Bouts AHM, Davin JC, Groothoff JW, et al. Standard peritoneal permeability analysis in children. J Am Soc Nephrol. 2000;11:943–50.
63. Van Biesen W, Van der Tol A, Veys N, et al. The personal dialysis capacity test is superior to the peritoneal equilibration test to discriminate inflammation as the cause of fast transport status in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2006;1:269–74.
64. Sanderson KR, Warady BA. End-stage kidney disease in infancy: an educational review. Pediatr Nephrol. 2020;35(2):229–40.
65. Schmitt CP, Zaloszyc A, Schaefer B, et al. Peritoneal dialysis tailored to pediatric needs. Int J Nephrol. 2011;2011:940267. Epub 2011 Jun 8.
66. Fischbach M, Lahlou A, Eyer D, et al. Determination of individual ultrafiltration time (APEX) and purification phosphate time by peritoneal equilibration test: application to individual peritoneal dialysis modality prescription in children. Perit Dial Int. 1996;16(Suppl 1):S557–60.
67. Schmitt CP, Bakkaloglu SA, Klaus G, et al. Solutions for peritoneal dialysis in children: recommendations by the European Pediatric Dialysis Working Group. Pediatr Nephrol. 2011;26(7):1137–47.
68. Twardowski ZJ. Peritoneal dialysis glossary III. Adv Perit Dial. 1992;8:47–9.
69. Rees L, Schaefer F, Schmitt CP, Shroff R, Warady BA. Chronic dialysis in children and adolescents: challenges and outcomes. Lancet Child Adolesc Health. 2017;1:68–77.
70. Verrina E, Edefonti A, Gianoglio B, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
71. Mujais S, Childers RW. Profiles of automated peritoneal dialysis prescription in the US 1997–2003. Kidney Int. 2006;103:S84–90.
72. Velasco RF, Munoz JL, Saavedra VS, et al. Automated peritoneal dialysis as the modality of choice: a single-centre, 3-year experience with 458 children in Mexico. Pediatr Nephrol. 2008;23:465–71.
73. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2011. NAPRTCS Annual Report. http://www.emmes.com/study/ped/annlrept/annlrept.html .
74. Chiu M-C, Fai-Ngor Ng C, Lee L-P, et al. Automated peritoneal dialysis in children and adolescents-benefits; a survey of patients and parents on health-related quality of life. Perit Dial Int. 2007;27:S138–42.
75. Fischbach M, Terzic J, Gaugler C, et al. Impact of an increased intraperitoneal fill volume both on tolerance and dialysis effectiveness in children. Adv Perit Dial. 1998;14:258–64.
76. Fischbach M, Terzic J, Menouer S, et al. Impact of fill volume changes on peritoneal dialysis and tolerance in children. Adv Perit Dial. 2000;16:320–3.
77. Keshaviah P, Emerson PF, Vonesh EF, et al. Relationship between body size, fill volume and mass transfer area coefficient in peritoneal dialysis. J Am Soc Nephrol. 1994;4:1820–6.
78. Vidal E, van Stralen K, Chesnaye NC, et al. Infants requiring maintenance dialysis: outcomes of hemodialysis and peritoneal dialysis. Am J Kidney Dis. 2017;69:617–25.
79. Sanderson KR, Yu Y, Dai H, et al. Outcomes of infants receiving chronic peritoneal dialysis: an analysis of the USRDS Registry. Pediatr Nephrol. 2019;34:155–62.
80. Vonesh EF. Membrane transport models and computerized kinetic modeling applied to automated peritoneal dialysis. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 15–34.
81. Warady BA, Watkins SL, Fivush BA, et al. Validation of PD Adequest 2.0 for pediatric dialysis patients. Pediatr Nephrol. 2001;16:205–11.
82. Ho-dac-Pannekeet MM, Atasever B, Strujik DG, et al. Analysis of ultrafiltration failure in peritoneal dialysis patients by means of standard peritoneal permeability analysis. Perit Dial Int. 1997;17:144–50.
83. Mujais S, Nolph K, Blake P, et al. Evaluation and management of ultrafiltration problems in peritoneal dialysis. Perit Dial Int. 2000;20(Suppl 4):S5–21.
84. Holmes CJ, Shockley TR. Strategies to reduce glucose exposure in peritoneal dialysis patients. Perit Dial Int. 2000;20:S37–41.
85. Warady BA, Ellis EN, Fivush BA, et al. Flush before fill in children receiving automated peritoneal dialysis. Perit Dial Int. 2003;23:493–8.
86. Abu-Alfa AK, Burkart J, Piraino B, et al. Approach to fluid management in peritoneal dialysis. A practical algorithm. Kidney Int. 2002;62(Suppl 81):S8–16.
87. Jansen MAM, Termorshuizen F, Korevaar JC, et al. Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 2005;68:1199–205.
88. Freida P, Issad B. Continuous cyclic peritoneal dialysis prescription and power. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 98–108.
89. Fischbach M, Terzic J, Menouer S, et al. Optimal volume prescription for children on peritoneal dialysis. Perit Dial Int. 2000;20:603–6.
90. Diaz-Buzo JA. Continuous cycling peritoneal dialysis, PD Plus, and high-flow automated peritoneal dialysis: a spectrum of therapies. Perit Dial Int. 2000;20(Suppl 2):S93–7.
91. Amici G. Solute kinetics in automated peritoneal dialysis. Perit Dial Int. 2000;20(Suppl. 2):S77–82.
92. Posthuma N, ter Wee PM, Donker AJM, et al. Assessment of the effectiveness, safety, and biocompatibility of icodextrin in automated peritoneal dialysis. Perit Dial Int. 2000;20(Suppl 2):S106–13.

93. Rusthoven E, Krediet RT, Willems HL, et al. Peritoneal transport characteristics with glucose polymer-based dialysis fluid in children. J Am Soc Nephrol. 2004;15:2940–7.
94. Mujais S, Vonesh E. Profiling of peritoneal ultrafiltration. Kidney Int. 2002;62(Suppl 81):S17–22.
95. Edefonti A, Consalvo G, Picca M, et al. Dialysis delivery in children in nightly intermittent and tidal peritoneal dialysis. Pediatr Nephrol. 1995;9:329–32.
96. Hölttä T, Rönnholm K, Holmberg C. Adequacy of dialysis with tidal and continuous cycling peritoneal dialysis in children. Nephrol Dial Transplant. 2000;15:1438–42.
97. Amici G. Continuous tidal peritoneal dialysis. Prescription and power. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 134–41.
98. Brandes JC, Packard WJ, Watters SK, et al. Optimization of dialysate flow and mass transfer during automated peritoneal dialysis. Am J Kidney Dis. 1998;25:603–10.
99. Fischbach M, Issad B, Dubois V, et al. The beneficial influence on the effectiveness of automated peritoneal dialysis of varying the dwell time (short/long) and fill volume (small/large): a randomized controlled trial. Perit Dial Int. 2011;31:450–8.
100. Fischbach M, Schmitt CP, Shroff R, et al. Increasing sodium removal on peritoneal dialysis: applying dialysis mechanics to the peritoneal dialysis prescription. Kidney Int. 2016;89(4):761–6. Epub 2016 Jan 21.
101. Fischbach M, Zaloszyc A, Schaefer B, et al. Optimizing peritoneal dialysis prescription for volume control: the importance of varying dwell time and dwell volume. Pediatr Nephrol. 2014;29(8):1321–7.
102. Alflaiw A, Vas S, Oreopoulos D. Peritonitis in patients on automated peritoneal dialysis. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 213–28.
103. Maiorca R, Brunori G, Zubani R, et al. Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients. A longitudinal study. Nephrol Dial Transplant. 1995;10:2295–305.
104. Churchill DN, Taylor DW, Keshaviah PK. Canada-USA Peritoneal Dialysis Study Group, et al. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. J Am Soc Nephrol. 1996;7:198–207.
105. National Kidney Foundation. K/DOQI clinical practice guidelines for peritoneal dialysis adequacy. Am J Kidney Dis. 2000;37(Suppl 1):S65–136.
106. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001;12:2158–62.
107. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective randomised controlled trial. J Am Soc Nephrol. 2002;13:1307–20.
108. Lo W-K, Ho Y-W, Li C-C, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a prospective randomised trial. Kidney Int. 2003;64:649–56.
109. Churchill DN. Impact of peritoneal dialysis dose guidelines on clinical outcome. Perit Dial Int. 2005;25(Suppl 3):S95–8.
110. Wong CS, Hingorani S, Gillen DL, et al. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int. 2002;61:630–7.
111. Malhotra C, Murata GH, Tzamaloukas AH. Creatinine clearance and urea clearance in PD. What to do in case of discrepancy. Perit Dial Int. 1997;17:532–5.
112. Twardowski ZJ. Relationship between creatinine clearance and Kt/V in peritoneal dialysis: a response to the defense of the DOQI document. Perit Dial Int. 1999;19:199–203.
113. Lo W-K, Bargman JM, Burkart J, et al. Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. Perit Dial Int. 2006;26:520–2.
114. Mellits ED, Cheek DB. The assessment of body water and fatness from infancy to adulthood. Monogr Soc Res Child Dev. 1970;35:12–26.
115. Morgenstern BZ, Wühl E, Sreekumaran Nair K, et al. Anthropometric prediction of total body water in children who are on pediatric peritoneal dialysis. J Am Soc Nephrol. 2006;17:285–93.
116. Oh J, Wunsch R, Turzer M, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation. 2002;106:100–5.
117. Litwin M, Wuhl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol. 2005;16:1494–500.
118. Schmitt CP, Borzych D, Nau B, et al. Dialytic phosphate removal: a modifiable measure of dialysis efficacy in automated peritoneal dialysis. Perit Dial Int. 2009;29:465–71.
119. Kim DJ, Do JH, Huh WS, et al. Dissociation between clearances of small and middle molecules in incremental peritoneal dialysis. Perit Dial Int. 2001;21:462–6.
120. Paniagua R, Ventura MJ, Rodriguez E, et al. Impact of fill volume on peritoneal clearances and cytokine appearance in peritoneal dialysis. Perit Dial Int. 2004;24:156–62.
121. Waniewski J. Transit time, residence time, and the rate of approach to steady state for solute transport during peritoneal dialysis. Ann Biomed Eng. 2008;36:1735–43.
122. Montini G, Amici G, Milan S, et al. Middle molecule and small protein removal in children on peritoneal dialysis. Kidney Int. 2002;61:1153–9.

123. Bammens B, Evenpoel P, Verbecke K, et al. Removal of middle molecules and protein-bound solutes by peritoneal dialysis and relation with uremic symptoms. Kidney Int. 2003;64:2238–43.
124. Opatrnà S, Opatrny K, Racek J, et al. Effect of icodextrin-based dialysis solution on peritoneal leptin clearance. Perit Dial Int. 2003;23:89–91.
125. Paniagua R, Ventura MD, Avial-Diaz M, et al. NTproBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. Nephrol Dial Int. 2010;25:551–7.
126. Mitsnefes M, Stablein D. Hypertension in pediatric patients on long-term dialysis: A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Am J Kidney Dis. 2005;45:309–15.
127. Kramer AM, van Stralen K, Jager KJ, et al. Demographics of blood pressure and hypertension in children on renal replacement therapy in Europe. Kidney Int. 2011;80:1092–8.
128. Bakkaloglu SA, Borzych D, Soo HAI, et al. Cardiac geometry in children receiving chronic peritoneal dialysis: findings from the International Pediatric Dialysis Network (IPPN) Registry. Clin J Am Soc Nephrol. 2011;6(8):1926–33.
129. Hollta T, Happonen JM, Ronholm K, et al. Hypertension, cardiac state, and the role of volume overload during peritoneal dialysis. Pediatr Nephrol. 2001;16:324–31.
130. Paglialonga F, Consolo S, Edefonti A, et al. Blood pressure management in children on dialysis. Pediatr Nephrol. 2018;33(2):239–250. Epub 2017 Jun 9.
131. La Milia V, Di Filippo S, Crepaldi M, et al. Mini-PET: a simple and fast method to assess free water and small solute transport across the peritoneal membrane. Kidney Int. 2005;68:840–7.
132. Smit W, Struijk DG, Ho-dac MM, et al. Quantification of free water transport in peritoneal dialysis. Kidney Int. 2004;66:849–54.
133. Heimburger O, Waniewski J, Werynski A, et al. Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. Kidney Int. 1990;38:492–506.
134. Termorshuizen F, Korevaar JC, Dekker FW, et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) – 2. Am J Kidney Dis. 2003;41:1293–302.
135. Rumpsfeld M, McDonald SP, Johnson DV. Peritoneal small solute clearance is nonlinearly correlated to patient survival in the Australian and New Zealand peritoneal dialysis patient population. Perit Dial Int. 2009;29:637–46.
136. Chada V, Blowey DL, Warady BA. Is growth a valid outcome measure of dialysis clearance in children undergoing peritoneal dialysis? Perit Dial Int. 2001;21(Suppl 3):S179–84.
137. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, et al. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland. Nephrol Dial Transplant. 2006;21:736–42.
138. Bakkaloglu SA, Saygili A, Sever L, et al. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPED) report. Nephrol Dial Transplant. 2009;24:3525–32.
139. Feber J, Scharer K, Schaefer F, et al. Residual renal function in children on hemodialysis and peritoneal dialysis therapy. Pediatr Nephrol. 1994;8:579–83.
140. Fischbach M, Terzic J, Menouer S, et al. Effects of automated peritoneal dialysis on residual daily urinary volume in children. Adv Perit Dial. 2001;17:269–73.
141. Mehrotra R. Long-term outcomes in automated peritoneal dialysis: similar or better than in continuous ambulatory peritoneal dialysis. Perit Dial Int. 2009;29(Suppl 2):S111–4.
142. Dell'Aquila R, Berlingò G, Pellanda MV, et al. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis: are there differences in outcome? Contrib Nephrol. 2009;25:110–4.
143. Roszowska-Blaim M, Skrzypczyk P, Drozdz D, et al. Residual renal function in children treated with continuous ambulatory peritoneal dialysis or automated peritoneal dialysis – a preliminary study. Adv Perit Dial. 2009;25:103–9.
144. van Olden RW, Guchelaar HJ, Struijk DG, et al. Acute effects of high-dose furosemide on residual renal function in CAPD patients. Perit Dial Int. 2003;23(4):339–47.
145. Li PK, Chow KM, Wong TY, et al. Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. Ann Intern Med. 2003;139:105–12.
146. Suzuki H, Kanno Y, Sugahara S, et al. Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am J Kidney Dis. 2004;43:1056–64.
147. Akbari A, Knoll G, Ferguson D, et al. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in peritoneal dialysis: systematic review and meta-analysis of randomized controlled trials. Perit Dial Int. 2009;29:554–61.
148. Phakdeekitcharoen B, Leelasa-nguan P. Effects of an ACE inhibitor or angiotensin receptor blocker on potassium in CAPD patients. Am J Kidney Dis. 2004;44:738–46.
149. Litwin M, Grenda R, Sladowska J, et al. Add-on therapy with angiotensin II receptor I blocker in children with chronic kidney disease already treated with angiotensin-converting enzyme inhibitors. Pediatr Nephrol. 2006;21(11):1716–22.
150. Höltta T, Ronholm K, Jalanko H, et al. Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control. Pediatr Nephrol. 2000;14:889–97.

151. Rees L, Azocar M, Borzych D, et al. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22(12):2303–12.
152. Paglialonga F, Edefonti A. Nutrition assessment and management in children on peritoneal dialysis. Pediatr Nephrol. 2009;24:721–30.
153. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22:1689–702.
154. Schaefer F, Wolf S, Klaus G, et al. Higher Kt/V urea associated with greater protein catabolic rate and dietary protein intake in children treated with CCPD compared to CAPD. Adv Perit Dial. 1994;10:310–4.
155. Aranda RA, Pecoits-Filho RFS, Romao JE Jr, et al. Kt/V in children on CAPD: how much is enough? Perit Dial Int. 1999;19:588–9.
156. Fischbach M, Terzic J, Lahlou A, et al. Nutritional effects of Kt/V in children on peritoneal dialysis: are there benefits from larger dialysis doses? Adv Perit Dial. 1995;11:306–8.
157. Cano F, Azocar M, Cavada G, et al. Kt/V and nPNA in pediatric peritoneal dialysis: a clinical or a mathematical association ? Pediatr Nephrol. 2006;21:114–8.
158. Brem AS, Lambert C, Hill C, et al. Outcome data on pediatric dialysis from the end-stage renal disease clinical indicators project. Am J Kidney Dis. 2000;36:310–7.
159. Bakkaloglu SA, Ekim M, Kocak G, et al. Impact of dialysis adequacy on cardiac function in pediatric CAPD patients. Perit Dial Int. 2001;21:395–400.
160. Warady B, Schaefer F, Alexander SR, Firanek C, Mujais S. Care of the pediatric patient on peritoneal dialysis. Clinical process for optimal outcomes. McGaw Park: Baxter Healthcare Corporation; 2004. p. 84–5.
161. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemoter Rep. 1970;54:225–35.
162. Schaefer F, Wühl E, Feneberg R, Mehls O, Scharer K. Assessment of body composition in children with chronic renal failure. Pediatr Nephrol. 2000;14:673–8.
163. Ronco C, Brendolan A, Zanella M. Evolution of machines for automated peritoneal dialysis. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 142–61.
164. Ronco C, Amerling R, Dell'Aquila R, et al. Evolution of technology for automated peritoneal dialysis. Contrib Nephrol. 2006;150:291–309.
165. Edefonti A, Boccola S, Picca M, et al. Treatment data during pediatric home peritoneal dialysis. Pediatr Nephrol. 2003;18:560–4.
166. Milan Manani S, Rosner MH, Virzì GM, et al. Experience with remote monitoring for automated peritoneal dialysis patients. Nephron. 2019 Jan;30:1–9. [Epub ahead of print].
167. Uchiyama K, Washida N, Yube N, et al. The impact of a remote monitoring system of healthcare resource consumption in patients on automated peritoneal dialysis (APD): A simulation study. Clin Nephrol. 2018;90(5):334–40.
168. Gallar P, Vigil A, Rodriguez I, et al. Two-year experience with telemedicine in the follow-up of patients in home peritoneal dialysis. J Telemed Telecare. 2007;13:288–92.
169. Nakamoto H. Telemedicine system for patients on continuous ambulatory peritoneal dialysis. Perit Dial Int. 2007;27(Suppl 2):S21–6.
170. Cargill A, Watson AR. Telecare support for patients undergoing chronic peritoneal dialysis. Perit Dial Int. 2003;23:91–4.
171. Chua AN, Warady BA. Adherence of pediatric patients to automated peritoneal dialysis. Pediatr Nephrol. 2011;26(5):789–93.
172. Nolph KD, Twardowski ZJ, Khanna R, Prowant BF, et al. Predicted and measured daily creatinine production in CAPD: identifying non-compliance. Perit Dial Int. 1995;15:22–5.
173. Ellis EN, Blaszak C, Wright S, et al. Effectiveness of home visits to pediatric peritoneal dialysis patients. Perit Dial Int. 2012;32(4):419–23.
174. Bernardini J, Nagy M, Piraino B. Pattern of non compliance with dialysis exchanges in peritoneal dialysis patients. Am J Kidney Dis. 2000;35:1104–10.
175. Blake PG, Korbert SM, Blake R, et al. A multicenter study of non compliance with continuous ambulatory peritoneal dialysis exchanges in US and Canadian patients. Am J Kidney Dis. 2000;35:506–14.
176. Amici G, Viglino G, Gandolfo C, et al. Compliance study in peritoneal dialysis using PD Adequest software. Perit Dial Int. 1996;16(Suppl 1):S176–8.
177. Watson AR, Hayes WN, Vondrak K, et al. European Paediatric Dialysis Working Group. Factors influencing choice of renal replacement therapy in European paediatric nephrology units. Pediatr Nephrol. 2013;28(12):2361–8. Epub 2013 Jul 11.
178. Watson AR, Gartland C. Guidelines by an ad hoc European committee for elective chronic peritoneal dialysis in pediatric patients. Perit Dial Int. 2001;21:240–4.

Peritoneal Dialysis Solutions

14

Elizabeth Harvey

Introduction

The peritoneal dialysis solution (PDS) is the cornerstone of peritoneal dialysis (PD), responsible for both fluid removal and metabolic control. As eloquently stated by Rippe, "the optimal electrolyte composition of a dialysis solution is that which best serves the homeostatic needs of the body" [1]. The absolute requirements for a PDS are a buffer to manage acidosis, an osmotic agent to produce ultrafiltration (UF), and electrolytes including sodium, chloride, calcium, and magnesium to maintain homeostasis and prevent metabolic bone disease. Yet more than half a century since the introduction of PD as a chronic therapy for replacement of renal function, the ideal PDS remains elusive. This likely reflects the diverse nature and diet of patients on PD, the need to customize treatment based on individual peritoneal transport characteristics, the type of dialysis (continuous ambulatory peritoneal dialysis (CAPD) versus automated peritoneal dialysis (APD)), dwell time, residual renal function, age and growth requirements, and accumulating data on the beneficial and harmful effects of PDS including their interaction with other components of CKD management [2].

This chapter will review PD solutions including biocompatibility, key composition, specific solutions, new solutions, and membrane preservation strategies.

Biocompatibility

Increasing length of time on PD has been associated with an increase in small solute transport and decreased ultrafiltration, both of which are associated with an increased risk of technique failure and death. The pathological correlate of these functional changes was first elucidated by Williams et al. in their landmark description of the changes in the peritoneal membrane associated with uremia and PD. These changes were characterized by loss of the mesothelial layer, marked increase in the thickness of the submesothelial compact collagenous zone, and a progressive hyalinizing vasculopathy, with worsening of severity correlating with duration of PD [3]. UF failure was associated with increased blood vessel density.

These changes were attributed in part to the use of "bio-incompatible" PD fluids, characterized by low pH (<6), high lactate concentration (35–40 mmol/L), high osmolarity, high glucose concentration, and high glucose degradation products (GDPs) [4]. This ushered in the era of "biocompatible" fluids including neutral pH solutions, alternate osmotic agents such as

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icodextrin, bicarbonate dialysate, and low GDP solutions.

Glucose Degradation Products GDPs are generated during heat sterilization and prolonged storage of glucose containing solutions [5, 6]. GDPs impair mesothelial cell function, stimulate local cytokine production, and are thought to be key contributors to the peritoneal alterations seen with long-term PD [6]. GDPs bind to proteins and lipids to produce advanced glycation end products (AGEs) which in the peritoneum contribute to peritoneal fibrosis. GDPs are rapidly absorbed across the peritoneal membrane, resulting in elevated levels of AGEs in patients with renal failure, and are implicated in complications of renal failure such as vasculopathy and amyloidosis [7].

The production of GDPs can be reduced in an acid solution, and the early lactate-based PDS, many of which are still in use, have an unphysiological pH of 5.2 which may be associated with infusion pain. A breakthrough in manufacturing was the development of the multichamber bag which allowed separation of the buffer source (lactate and/or bicarbonate) from the glucose which could be in an acid milieu, resulting in lower GDP production during sterilization [6]. Neutral pH of the whole solution was achieved by mixing the two compartments just prior to instillation. However, even solutions considered to be low in GDPs have significant variability in the GDP concentrations, hampering interpretation of clinical trial results [8]. Two chamber bags are most commonly available, with Gambrosol Trio™ (Fresenius Med Corp) utilizing a three-chamber bag which allows for three different glucose concentrations from a single bag, depending on which of the three chambers are mixed together before infusion.

Neutral pH Solutions The concern that pH was a factor not just in GDP production, but in damage to the peritoneal membrane, as well as clinical consequences of pain on infusion, led to the development of neutral pH solutions such as Physioneal™, Balance™, and Bicavera™ (see Table 14.1), also made possible by the multichamber bag. With bicarbonate-based solutions, calcium and magnesium must be separated from bicarbonate during heating and storage to prevent precipitation of calcium carbonate and magnesium carbonate.

Clinical Data with Biocompatible Solutions Unfortunately, multiple studies on these "biocompatible" solutions with neutral pH and low GDPs have yielded conflicting results on clinically relevant outcomes, most likely due to study design, duration, and power [9, 10]. Biocompatible solutions have been associated both with an increased risk of peritonitis and shorter time to the first peritonitis episode [11, 12] and a lower rate of peritonitis and longer time to the first peritonitis [13, 14]. In meta-analyses and systematic reviews, several themes have emerged, namely, *better preservation of residual renal function* especially urine volume and *less inflow pain* [12, 15–20]. Several studies have shown that biocompatible solutions have been associated with lower ultrafiltration and increased peritoneal solute transport at initiation, which stays stable over time, compared to deterioration in ultrafiltration and increasing solute transport over time with conventional PDS (cPDS) [13, 14]. Conversely, two studies of prevalent adult patients switched to a low GDP solution have shown decreased ultrafiltration and overhydration compared to conventional solutions [21, 22] but with lower blood C-reactive protein (CRP) values in the low GDP solution group. It has been speculated that the preservation of residual renal function seen with the low GDP solutions may in part be due to overhydration [23]. Overall, while no harm has been attributed to these newer solutions, there has been no improvement in patient or technique survival demonstrated to date [8, 10, 15, 24, 25].

Encapsulating sclerosing peritonitis (EPS) is a devastating complication of long-term peritoneal dialysis [26] (see Chap. 39). Interestingly, both Japanese [27] and Dutch [28] registries demonstrate a reduced incidence of EPS over the last decade. Whether this is due in part or wholly to

Table 14.1 Composition of common PD solutions

Solution/manufacturer/ number of chambers	Osmotic agent	Osmotic agent concentration	Osmolarity mOsm/L	Na mmol/l (mEq/L)	Ca mmol/l (mEq/L)	Mg mmol/l (mEq/L)	Lactate mmol/l	Bicarbonate mmol/L	pH	GDPs
Extraneal™ Baxter 1 chamber	Icodextrin 7.5%	Icodextrin 75 g/L	284	133 (133)	1.75 (3.5)	0.25 (0.5)	40	0	5.2	Low
Nutrineal™ PD4 Baxter 1 chamber	Amino acid 1.1%	Amino acids 87 mmol/L	365	132 (132)	1.25 (2.5)	0.25 (0.5)	40	0	6.4	
Physioneal™ 40 Baxter 2 chambers	Glucose 1.36% 2.27% 3.86%	Glucose monohydrate 15 g/L 25 g/L 42.5 g/L	344 395 483	132(132) 132(132) 132(132)	1.25 (2.5) 1.25 (2.5) 1.25 (2.5)	0.25 (0.5) 0.25 (0.5) 0.25 (0.5)	15 15 15	25 25 25	7.4	Low 253[a]
PD4™ Baxter 1 chamber	Dextrose 1.5% 2.5% 4.25%	Dextrose 15 g/L 25 g/L 42.5 g/L	345 395 484	132(132) 132(132) 132(132)	1.25 (2.5) 1.25 (2.5) 1.25 (2.5)	0.25 (0.5) 0.25 (0.5) 0.25 (0.5)	40 40 40	0 0 0	5.2	
PD101™ Baxter 1 chamber	Dextrose 0.5% 1.5% 2.5% 4.25%	Dextrose 5 g/L 15 g/L 25 g/L 42.5 g/L	296 347 397 485	132 (132) 132 (132) 132 (132) 132 (132)	1.62 (3.25) 1.62 (3.25) 1.62 (3.25) 1.62 (3.25)	0.75 (1.5) 0.75 (1.5) 0.75 (1.5) 0.75 (1.5)	35 35 35 35	0 0 0 0	5.2	
Balance™ Fresenius 1.25 mmol/l Ca 2 chambers	Glucose 1.5% 2.3% 4.25%	15 G/L 22.73 G/L 42.5 G/L	356 399 509	134 (134) 134 (134) 134 (134)	1.25 (2.5) 1.25 (2.5) 1.25 (2.5)	0.5 (1.0) 0.5 (1.0) 0.5 (1.0)	35 35 35	0 0 0	7.0	Low 42[a]
Balance™ Fresenius 1.75 mmol/l Ca 2 chambers	Glucose 1.5% 2.3% 4.25%	15 G/L 22.73 G/L 42.5 G/L	368 401 511	134 (134) 134 (134) 134 (134)	1.75 (3.5) 1.75 (3.5) 1.75 (3.5)	0.5 (1.0) 0.5 (1.0) 0.5 (1.0)	35 35 35	0 0 0	7.0	
Bicavera™ Fresenius 2 chambers	Glucose 1.5% 2.3% 4.25%	Glucose monohydrate 15 G/L 22.73 G/L 42.5 G/L	358 401 511	134 (134) 134 (134) 134 (134)	1.75 (3.5) 1.75 (3.5) 1.75 (3.5)	0.5 (1.0) 0.5 (1.0) 0.5 (1.0)	0 0 0	34 34 34	7.4 7.4 7.4	Low 42[a]

(continued)

Table 14.1 (continued)

Solution/manufacturer/ number of chambers	Osmotic agent	Osmotic agent concentration	Osmolarity mOsm/L	Na mmol/l (mEq/L)	Ca mmol/l (mEq/L)	Mg mmol/l (mEq/L)	Lactate mmol/l	Bicarbonate mmol/L	pH	GDPs
Gambrosol trio™ 10 Gambro 3 chambers	Glucose 1.5% 2.5% 3.9%	Glucose 15 G/L 25 G/L 39 G/L	357 409 483	133 132 131	1.79 (3.58) 1.75 (3.5) 1.7 (3.4)	0.26 (0.52) 0.25 (0.5) 0.24 (0.48)	41 40 39	0 0 0	5.5–6.5 5.5–6.5 5.5–6.5	Low 65[a]

GDP glucose degradation product
[a]Mean GDP concentration in μmol/L of 3-deoxyglycosone

more biocompatible PDS cannot be ascertained at this point.

The longitudinal analysis of the Global Fluid Study in adults examined the long-term peritoneal solute transport rate (PSTR) in patients using biocompatible solutions (7.5 years) versus cPDS (12.8 years) [29] and found a progressive increase in PSTR over time with cPDS, while biocompatible solutions were associated with stability of the PSTR by 2 years. The early increase in PSTR seen with the biocompatible solution in the balANZ trial [30] was not seen in this study, likely reflecting study methodology, different biocompatible solutions, and timing of peritoneal equilibration testing [31]. The use of biocompatible PDS also appeared to attenuate the elevated PSTR seen during episodes of peritonitis [29], possibly by reducing the severity of peritonitis as suggested in the balANZ study [14]. Whether the use of biocompatible solutions will result in a lower incidence of EPS over time remains to be seen.

Pediatric Clinical Data In a prospective study of 401 children by the International Pediatric Peritoneal Dialysis Network (IPPN), the use of biocompatible PDS was associated with a marginal improvement in daily urine output, but did not reduce the risk of developing oligoanuria [32]. In a prospective cohort study of 65 children, the use of neutral pH/low GDP solutions was associated with higher free water transport compared to acid pH/high GDP solutions [33].

Pathology Studies *In vivo* benefit of biocompatible solutions has been suggested by the morphological study of 46 adults (23 biocompatible PDS and 23 cPDS) matched for time on dialysis [34]. Biocompatible PDS was associated with improved mesothelial layer integrity and less hyalinizing vasculopathy. Similarly, another peritoneal morphology study of adults at termination of PD showed that the use of neutral pH and low GDP solution was associated with less membrane fibrosis, less vascular sclerosis, and less AGE accumulation compared to acidic cPDS [35]. Despite an increase in the number of peritoneal capillaries, the neutral pH solutions were associated with lower peritoneal equilibration (PET) scores and preserved UF volumes.

However, the seminal peritoneal morphology study of children on PD lays waste to the theory that "biocompatible" PDS preserves the peritoneal membrane and places the focus again on the osmotic agent, glucose, as the culprit in long-term membrane dysfunction [36, 37]. This study performed a comprehensive analysis of peritoneal biopsies on children with end-stage kidney disease before commencing PD (90 patients) and while on PD (82 patients) with control specimens on 56 children with normal kidney function. It showed a marked early (6–12 month) increase in peritoneal blood microvessel density, an increase in endothelial surface area per peritoneal volume, and an increase in submesothelial thickness despite the use of neutral pH solutions with low GDP concentrations. Multivariate analysis showed that increasing glucose exposure was associated with total vessel density. Additionally, vessel density correlated positively with 2-hour dialysate-to-plasma (D/P) creatinine and inversely with 2-hour dialysate-to-dialysate at time zero (D/Do) glucose on PET and predicted solute transport at 3 and 6 months. Cluster analysis showed marked angiogenesis in younger children with short PD vintage and submesothelial fibrosis in older children on long-term PD. While it is uncertain if these findings are generalizable to adults, the early, marked peritoneal angiogenesis observed in this study potentially explains the faster peritoneal transport and lower UF seen in adult studies using neutral pH and low GDP solutions [30].

PD Solution Components

pH/Buffer End-stage renal disease (ESRD) is characterized by metabolic acidosis. Correction of this acidosis is a vital component of any renal replacement therapy including PD. To that end, PDS must contain a buffer. Early attempts to use bicarbonate in single-chamber bags led to precipitation of calcium carbonate [38]. Acetate was used initially but was quickly discontinued

due to infusion pain, prolonged acidic pH of the infused solution, peritoneal membrane damage and loss of UF, systemic alkalosis, and an association with EPS [39–41]. Therefore, solutions with L-lactate in concentrations of 35–40 mmol/L with an acidic pH of approximately 5.2 became widely used. Instillation into the abdomen is associated with rapid equilibration of the pH in the abdominal fluid to 7.4 over 10 minutes, followed by a gradual drop in peritoneal lactate due to diffusion into the blood across the concentration gradient, where it is then metabolized to bicarbonate. Recent animal studies show that the neutralization of pH is achieved both by bicarbonate diffusion out of the blood into the PD fluid and local production of bicarbonate by peritoneal carbonic anhydrase isoforms, with bicarbonate transport not mediated by the water channel aquaporin 1 [42]. Absorbed lactate is rapidly metabolized via the Krebs cycle or via gluconeogenesis, and stable chronic dialysis patients have normal serum lactate levels. However, during intercurrent illness, lactate levels may become elevated in the absence of hypoxemia or gut ischemia, precipitating unnecessary investigations [43].

By contrast, a brief randomized crossover study of 25 children comparing lactate versus bicarbonate solutions during a 4-hour PET demonstrated a persistently acidic PD fluid up to an hour of dwell time with the lactate-buffered solution of 35 mmol/L [44]. This has potential implications for children on cyclic PD where the short dwell times would predispose to constant exposure of the peritoneal membrane to an acidic pH.

The creation of the multichamber bag allowed introduction of bicarbonate-based solutions with bicarbonate at high pH separated from glucose and electrolytes in an acid milieu, resulting in lower creation of GDPs during sterilization, a neutral pH after mixing, and at least 24-hour stability. Two solutions were initially commercially produced, Physioneal™, a bicarb (25 mmol/L)/lactate (15 mmol/L) solution, and Bicavera™, a pure bicarbonate (34 mmol/L) solution. Both were shown in adults to achieve acidosis correction. Additionally, pure bicarbonate use was associated with increased protein catabolic rates, lower peritonitis rates, and better preservation of residual renal function [38].

Single buffer PDS may be associated with elevated blood pCO2 (bicarbonate-buffered solutions) and peritoneal bicarbonate loss (lactate-buffered solutions), whereas mixed buffer solutions (lactate + bicarbonate) may be more physiological in their regulation, based on studies of effluent and plasma acid-base concentrations in both adults and children [40, 45].

The use of bicarbonate/lactate solutions with a total buffer of 39–40 mmol/l has been associated with the development of alkalosis [46], most notable in Japanese adults due to lower dietary protein intake [47]. This has prompted the development of solutions with a total buffer of 35 mmol/L (bicarbonate 25 mmol/L and lactate 10 mmol/L) with two different calcium concentrations (1.25 mmol/L and 1.75 mmol/L) which have been shown to reduce alkalosis and correct acidosis while maintaining similar creatinine removal and UF [47].

Balance™ Balance™ (Fresenius Medical Care) is a neutral pH, lactate-based solution with low GDPs, produced in a two-chamber bag. The specific composition is outlined in Table 14.1. The balANZ study conducted in Australia and New Zealand was a randomized trial of 185 incident adult PD patients with residual renal function comparing Balance™ to cPDS over a 2-year period. Significant outcomes from primary and secondary analyses [30, 48, 49] are summarized as follows: the use of Balance™ was associated with initial lower peritoneal UF at 3 and 6 months, which improved over the study duration; a longer time to anuria; reduced peritonitis rates and severity; increased peritoneal transport at 1 month which remained stable compared to a progressive increase with cPDS; and comparable technique survival. Increased solute transport over time correlated with GDP exposure and not glucose exposure.

Pediatric Experience In children on APD, Bicavera™ has been shown to improve acidosis correction compared to lactate-based cPDS. It was also associated with higher peritoneal cancer

antigen-125 (CA-125) levels in keeping with recovery of the mesothelial cell layer and improved *in vivo* mesothelial cell tolerance to high glucose concentrations [50]. Schmitt et al. subsequently compared the efficacy of two neutral pH and low GDP solutions (Balance™ 35 mmol/L lactate and Bicavera™ 34 mmol/L bicarbonate) in children on APD and demonstrated equal acidosis control [51]. However, the bicarbonate solution was associated with better preservation of ultrafiltration.

Alkalosis is common in children treated with pure bicarbonate or bicarbonate/lactate solutions on APD, especially with an icodextrin day dwell [52].

There are no published studies specifically using Balance™ in children. Of potential relevance is a study of adults on APD comparing Balance™ to cPDS. Balance™ was associated with a higher effluent CA125 rate of appearance and concentration, suggesting improved biocompatibility [53].

Published pediatric guidelines suggest the use of a neutral pH and low GDP solution in children, with the choice of buffer dependent on local availability and automated delivery system, and buffer concentration tailored to the patient's acid basis status to correct acidosis and avoid alkalosis [54]. A pediatric PD program thus requires a variety of solutions with varying base type and concentration to meet the metabolic needs of growing children.

Osmotic Agent Removal of excess salt and water to achieve euvolemia and improve blood pressure control is a critical component of PD. To that end, the PDS must contain an osmotic agent to achieve fluid removal. Osmotic agents in the currently available PDS include glucose (dextrose), icodextrin, and amino acids. Experimental solutions such as carnitine and polyglucose will be reviewed later.

Glucose Glucose in supraphysiological concentrations to achieve an osmolality higher than uremic serum remains the most widely used osmotic agent worldwide. Solutions containing 1.5%, 2.5%, and 4.25% glucose were introduced with the advent of PD and were found to produce ultrafiltration in children on CAPD [55, 56]. With instillation of a volume of PDS of 1100 ml/m^2 BSA in children above approximately 2 years of age, it has been demonstrated that children and adults have comparable peritoneal kinetics for glucose absorption and UF [57, 58]. Glucose works to achieve UF largely through the ultrasmall pores or aquaporins [59].

While it is an effective osmotic agent, glucose is readily absorbed across the peritoneal membrane, contributing to hyperglycemia, obesity, insulin resistance, anorexia, and dyslipidemia in PD patients. Additionally, hyperosmolar glucose-containing solutions and GDPs are key players in the structural alterations in the peritoneal membrane seen with long-term PD.

The creation of the multichamber bag for PDS resulted in the manufacture of solutions low in GDPs and with neutral pH. A crossover comparison of a lactate single chamber versus bicarbonate two-chamber solution in 25 children demonstrated similar UF and peritoneal transport kinetics for the two solutions, with a 10% lower removal of creatinine and phosphate with the bicarbonate-based solution [44]. A subsequent study of 21 children comparing the two solutions over 12 weeks each demonstrated rapid absorption of GDPs across the peritoneal membrane and a reduction in AGEs in children treated with the two-chamber bicarbonate-based, low GDP solution [60]. As a result, the 2011 European Pediatric PD guidelines endorsed the use of multichamber PD fluids for use in children [54], along with the lowest concentration of glucose and lowest number of cycles possible to achieve euvolemia.

With loss of residual renal function, patients require more hypertonic solution to maintain UF and solute clearance, placing them at risk for alteration in body composition. However, one longitudinal study in 136 anuric adults on PD demonstrated no increase in body fat, no loss of fat-free muscle mass, and maintenance of normalized protein catabolic rate (nPCR) despite increasing exposure to hypertonic dialysate [61].

By contrast, tube-fed anuric, or oliguric infants are frequently obese, with contributing factors being delayed motor milestones, excessive glucose exposure to achieve UF, and uremic inhibition of endogenous growth hormone.

One source of confusion in the literature and in clinical practice is the different labeling of the glucose content in PD solutions between North America and Europe. European labeling is for anhydrous glucose equivalent, while in North America, solutions are labeled for dextrose content. Thus a 1.36% Physioneal™ solution contains 15 G/L of glucose monohydrate, equivalent to anhydrous glucose of 13.6 G/L; a 2.27% solution contains 25 G/L of glucose monohydrate or 22.7 G/L anhydrous glucose; and a 3.86% solution contains 42.5 G/L glucose monohydrate or 38.6 G/L of anhydrous glucose. The carbohydrate content and UF capacity of these solutions are equivalent to North American labeled solutions of 1.5%, 2.5%, and 4.25% dextrose, respectively.

Icodextrin (Extraneal™) Icodextrin is a polyglucose solution derived from starch with an average molecular weight of 16,200 daltons. It is an isosmolar (284 mOsm/L), non-glucose-containing, lactate-buffered (40 mmol/L) solution with a pH of 5.2 and low GDPs (Table 14.1). It exerts UF through colloid osmosis, resulting in salt and water removal through the small pores, without activation of aquaporins, and without sodium sieving. Approximately 20–40% is absorbed from the peritoneal cavity through the lymphatics over an 8–12-hour dwell, resulting in a sustained gradient for UF. Icodextrin is metabolized by α-amylase to maltose, maltotriose, and maltotetraose. Serum metabolites reach steady state in 7–10 days and disappear within the same time frame when the solution is discontinued. Approximately 20% of icodextrin and its metabolites are removed through dialysis or via the urine. Tissue maltases convert the metabolites to glucose within the cells, without producing hyperglycemia, unlike conventional glucose-based solutions [62–64].

First introduced into clinic care in the early 1990s, icodextrin gained widespread use for the long overnight dwell in adults on CAPD [64] and was subsequently adopted for the long day dwell in children on APD [54, 65, 66]. In adults, icodextrin has been shown to be associated with improved UF and mitigation of uncontrolled fluid overload independent of peritoneal transport type [67, 68], improved preservation of residual renal function [69], reduction in insulin resistance in nondiabetic patients [70], improved atherogenic lipid profiles [71], and reduced technique failure [72]. Glucose-sparing regimens incorporating icodextrin, amino acid dialysate, and conventional glucose-containing PDS have also been shown to improve atherogenic lipid profiles compared to regimens with only glucose-based PD fluids [73]. Twice daily icodextrin exchanges and the use of "bimodal" or combined icodextrin/glucose solutions have also been associated with improved UF in adults [63, 74, 75]. However, the latter combined solutions are not currently commercially available and have not been studied in children. Although used as part of a membrane-sparing strategy, icodextrin use has been associated with EPS and with markers of peritoneal fibrogenesis [76]. More recently, a dual-chamber neutral icodextrin solution (pH ~ 6.8) has become available in Japan. Preliminary clinical evaluation in adults suggests equivalent salt and water removal but improved biocompatibility similar to other neutral pH PD solutions based on mesothelial cell proliferation assays [77].

Pediatric Studies Early pediatric experience demonstrated UF similar to 3.86% glucose over a 12-hour dwell and serum icodextrin metabolites comparable to those seen in adults [65]. Addition of a single day dwell of icodextrin, approximately 1100 ml/m^2, provided an increased Kt/V of 0.52 ± 0.07 weekly [45]. A second study using a day dwell of 1100 ml/m^2 confirmed an increase in weekly Kt/V from 1.99 to 2.54 and weekly creatinine clearance from 35 to 65 L/1.73m^2, without increased loss of albumin but with an increased loss of essential and nonessential amino acids [66].

Using a long day dwell volume of 630 ± 191 ml/m^2, Canepa et al. demonstrated a linear increase in fluid removal up to 8 hours, with a plateau until the end of the dwell [45]. The disappearance of icodextrin from the peritoneal cavity was compatible with removal via lymphatic absorption, with an average of 45% absorption. The caloric value of the absorbed icodextrin was low, approximately 3.4% of recommended daily caloric intake. A subsequent report on eight children suggested an inverse relationship between UF and age, with infants more likely to absorb icodextrin rather than achieve UF [78]. However, UF was not correlated with infused volume. A retrospective study of 50 children on automated PD treated with an icodextrin day dwell showed a linear correlation between fill volume and net ultrafiltration, with a fill volume of ≥550 ml/m^2 associated with UF in 88% of children [79].

Clinical Considerations There are several clinical considerations that must be appreciated when using icodextrin, as outlined in the excellent review by Silver et al. [62].

Rash Skin rash occurs in 5–10% of patients. Acute generalized pruritic exfoliative rash may occur early after starting icodextrin, necessitating discontinuation, with rapid resolution of symptoms. Milder forms involving peeling of the palms and soles may not require icodextrin withdrawal unless distressing to the patient. A later blistering rash in sun-exposed areas occurring 3–6 months after exposure has also been described, taking several weeks to resolve after removal of icodextrin.

Falsely Elevated Glucose Measurements The accumulation of non-glucose sugars (icodextrin metabolites) may interfere with glucose measurements by nonspecific methods such as commonly employed glucose strips or glucometers [80]. This has resulted in hypoglycemia in diabetics whose insulin was adjusted on the basis of a spuriously elevated reading. This risk exists while the patient is on icodextrin and for up to 2 weeks after discontinuation. Serum glucose should therefore be measured by glucose-specific assays in patients utilizing icodextrin.

Amylase Interpretation for Diagnosis of Pancreatitis Serum amylase activity is reduced in patients receiving icodextrin. This appears to be due to a competitive interaction with amylase substrate resulting in a low serum amylase, which may mask the diagnosis of pancreatitis in PD patients. Lipase should be measured in PD patients on icodextrin suspected of having pancreatitis.

Sterile Peritonitis The early use of icodextrin was associated with the development of sterile peritonitis, subsequently linked to contamination with a peptidoglycan produced by *Bacillus acidocaldarius*, a bacterium which may contaminate starch. Improved manufacturing has reduced but likely not completely eliminated this contaminant.

Miscellaneous Side Effects Clinically insignificant mild hyponatremia and mild elevation in alkaline phosphatase have both been described with the use of icodextrin.

Pediatric-Specific Contraindications Icodextrin should not be used in patients with glycogen storage disease or lactic acidosis.

Antibiotic Stability Of relevance to pediatrics where a significant proportion of patients are on overnight cycling is the stability of antibiotics in icodextrin. Cefazolin, tobramycin, cotrimoxazole, and vancomycin have been shown to be stable for 24 hours in Physioneal™ and Extraneal™ under conditions mimicking CCPD [81]. Ceftazidime is stable for 24 hours in Extraneal™, but not in Physioneal™.

Amino Acid (Nutrineal™) Nutrineal™ (Baxter Corporation) is a 1.1% amino acid dialysis solution with UF capacity similar to a 1.36% (1.5%) glucose-based PDS [82–84]. It contains both essential (valine, leucine, lysine, isoleucine, methionine, histidine, threonine, phenylalanine, tryptophan) and nonessential (arginine, alanine,

proline, glycine, serine, tyrosine) amino acids. The preparation currently available in North America is a high lactate (40 mmol/l), low calcium (1.25 mmol/L), and low magnesium (0.25 mmol/L) solution (Table 14.1). However, solutions with higher calcium and magnesium and lower lactate were initially available, with modification of buffer and amino acid content in response to early clinical studies [85]. Peritoneal solute transport characteristics of Nutrineal™ are similar to glucose solutions [84].

Nutrineal™ was first introduced in the 1980s in response to concerns about protein losses and malnutrition in PD patients. Early pediatric studies using a single exchange in CAPD patients showed absorption of 80–86% of the amino acid from a single dwell, net positive nitrogen balance for a 24-hour period [83, 86], and reduced losses of amino acids not contained in the amino acid solution. Administration of a single daily dwell for 6–12 months in eight children on CAPD demonstrated improvement of plasma essential amino acid levels but elevated urea and minimal improvement in cellular amino acid levels [87]. Adult studies showed mixed results in terms of nutritional benefit from a single daily dwell, with acidosis and elevated urea as common side effects. A more recent retrospective study has shown similar improvement in nutritional parameters in adults using either oral essential amino acid supplementation or a single daily exchange of amino acid dialysate [88].

Anorexia and decreased caloric intake are common in PD patients, and many receive overnight tube feeds. If an amino acid dialysate (AAD) is utilized as a day dwell in this situation, the amino acids are utilized as calories, resulting in acidosis and elevated urea [89]. Working on the theory that an AAD coupled with adequate glucose administration would allow for better incorporation of amino acids into protein, Canepa et al. studied AAD as part of a cyclic dialysis regimen. They utilized a mixture of ¼ Nutrineal™, ½ 2.27 (2.5) % dextrose, and ¼ 3.86 (4.25)% dextrose during CCPD in ten children [90]. The solution was well tolerated, and despite absorption of approximately 50% of the infused amino acids, elevation in urea was not seen, suggesting improved utilization of the amino acids. This short-term study achieved the three requisites for improved protein synthesis, namely, hyperinsulinemia, elevated plasma amino acid levels, and a favorable nonprotein calorie/nitrogen intake ratio. The use of this regimen for 1 year resulted in positive nitrogen balance, a rise in serum albumin, and improved linear growth [91]. Subsequently Tjiong et al. have shown improved protein synthesis using amino acid plus glucose solutions in fed adult CAPD patients [92] and also in adults on automated PD [93], supporting the notion of "dialysate as food" [94].

The product monograph states that Nutrineal™ is contraindicated in patients with known hypersensitivity to any of the amino acids or excipients in the solution, an elevated urea above 38 mmol/L (106 mg/dL), symptoms of uremia, metabolic acidosis, liver insufficiency, severe hypokalemia, and, most importantly for pediatrics, inborn errors of amino acid metabolism.

A multicenter outbreak of sterile peritonitis from a single batch of Nutrineal™ was reported in 2011 in adults [95, 96], with no etiology reported. Several patients were able to resume Nutrineal™ from a different lot without recurrence of the chemical peritonitis. Similarly, in a study in children using a 1:1 dilution of Nutrineal™ and glucose dialysate, five of seven children developed sterile peritonitis which did not respond to antibiotics but which resolved with cessation of Nutrineal™ [97].

Nutrineal™ has been used as part of the "PEN" membrane-sparing regimen which utilizes Physioneal™, Extraneal™, and Nutrineal™ (discussed below) [98].

As noted, Nutrineal™ is a lactate-buffered AAD. Aminobic™ (Fresenius Medical Care) is a bicarbonate-buffered 1% amino acid dialysate with bicarbonate 24 mmol/L, Mg 0.5 mmol/L, calcium 1.25 mol/L, and pH of 7.2–7.6 [99]. In comparison to a lactate-based glucose-containing PDS of similar osmolality with pH 5.5, Aminobic™ was associated with improved viability and reduced cellular stress response in human peritoneal mesothelial cells [99]. In one *in vivo* study, Aminobic™ was associated with a

small but significant increase in permeability to larger proteins, notably β2 microglobulin, albumin, and IgG [100]. However, no comparison of Nutrineal™ and Aminobic™ exists, and Aminobic™ does not appear to be commercially available currently.

Electrolyte Composition

Sodium Removal of excess salt and water to control hypertension and normalize extracellular volume status is one of the basic goals of peritoneal dialysis. Sodium concentrations in cPDS average 132 mmol/L (132 mEq/L). Hence, sodium removal is primarily by convection through ultrafiltration (UF), due to the low concentration gradient for diffusion between the PDS and serum. Sodium removal and UF rate are thus proportional and related to the mechanics of dialysis and the PDS, with typical sodium removal of 100 mmol/L UF in CAPD, 80 mmol/L UF in APD, and 130 mmol/L UF with a long icodextrin dwell [1].

Low-Sodium Solutions Despite two decades of published experimentation with low-sodium PDS, they are not yet commercially available, and the ideal solution or number of exchanges has not been fully elucidated. Lowering the dialysate sodium concentration results in greater diffusive sodium removal but loss of ultrafiltration due to a lower osmolar gradient. Low-sodium solutions must therefore be compensated with the addition of more glucose [1, 101, 102].

Pediatric Considerations In infants and children on PD, hyponatremia is relatively common, especially in patients with high output renal impairment due to urinary sodium loss [103] and in anuric or anephric infants due to dialytic sodium loss in excess of intake [104]. These patients require sodium supplementation. Additionally, growing children require a positive salt balance to prevent worsening growth impairment. A subset of children on APD may have hypernatremia when treated with hypertonic glucose and short dwell times [105], due to sodium sieving, as described in intermittent peritoneal dialysis [106]. These patients might benefit from a lower sodium dialysate. In general, low-sodium PDS likely has a minimal role in pediatric PD.

Calcium

The original commercially available PD solutions contained a calcium concentration of 1.62–1.75 mmol/L (3.2–3.5 mEq/L), and these remain available throughout the world. Mass transfer studies demonstrated net absorption of calcium from these high calcium (HC) solutions, with greater absorption with lower glucose concentrations due to convective removal of some calcium during ultrafiltration [107]. With the advent of calcium carbonate as a non-aluminum phosphate binder, hypercalcemia became common, so lower calcium (LC) PDS with calcium 1.25 mmol/L (2.5 mEq/L) and lower magnesium 0.25 mmol/L (0.5 mEq/L) (see below) were developed and became widely used in the early 1990s. Mass transfer studies showed a negative or neutral calcium balance with greater removal with higher glucose solutions as expected, allowing for supplementation with oral calcium to achieve phosphate control while preventing hypercalcemia [108–110]. What is clear in all the subsequent studies is that patients on a LC PDS tolerated higher doses of calcium containing phosphate binders with fewer episodes of hypercalcemia [111]. However, longitudinal studies showed conflicting results, with some demonstrating good tolerance with maintenance of normal serum Ca, Mg, and PTH levels [110, 112, 113], while others documented a fall in ionized calcium and a persistent rise in serum PTH [114–116], highlighting the need to individualize the PDS prescription for any given patient [117]. More recent studies suggest that whether a LC PDS is beneficial or not relates to the target outcome. In a retrospective study of 236 adults on PD, Kang et al. noted that patients on a low calcium (LC) dialysate (1.25 mmol/L, 2.5 mEq/L) had a greater decrease in bone mineral density and higher PTH and alkaline phosphatase levels compared to those treated with a high calcium

(HC) dialysate (1.75 mmol/L, 3.25 mEq/L) [118]. By contrast, Wang et al. showed better left ventricular diastolic function and preservation of residual renal function in adults using a LC versus HC solution [119]. Haris et al. demonstrated reversal of adynamic bone disease in adults using a LC PDS [120]. Zhao et al. found the combination of a LC and HC solution to provide the best control of serum calcium and PTH [121].

Commercially available PDSs have the same calcium concentration regardless of the glucose content. However, kinetic modeling and clinical studies show that calcium transfer across the peritoneum is dependent on serum-ionized calcium, PDS calcium content, and PDS glucose concentration which determines UF. Higher degrees of UF result in increased removal of calcium [122]. Rippe suggests that in order to maintain neutral calcium balance during a 4-hour dwell, there should be higher calcium concentrations in higher glucose solutions. He proposes calcium of 1.38 mmol/L (2.76 mEq/L) for 1.5% glucose, 1.7 mmol/L (3.4 mEq/L) for 2.5% glucose, and 2.2 mmol/L (4.4 mEq/L) for 4.25% glucose. Thus, patients requiring larger amounts of UF are at risk for more negative calcium balance.

Pediatric Considerations Mass transfer calcium studies have been done almost exclusively on adults on CAPD, and a paucity of data exists for children or for automated PD. A further consideration in children is the need for net positive calcium balance during growth. Hypocalcemia and secondary hyperparathyroidism are common in infants on APD, especially if they are on LC PDS, are receiving renal formulas low in phosphate, and thus are not receiving large doses of calcium-containing phosphate binders [123, 124]. Thus, the calcium content of the PDS used must take into account the locally available PDSs and the individual needs of the patient, including their UF requirements. Maintenance of normal calcium, phosphate, and PTH requires coordination between the dialysis prescription, PDS, diet, supplements, phosphate binders, and activated vitamin D. A pediatric program should have available both HC and LC PDS to meet the needs of all patients.

Magnesium

The original commercially available PD solutions contained a magnesium concentration of 0.75 mmol/L (1.5 mEq/L). A number of factors lead to the development of lower-magnesium PD solutions. It was recognized that hypermagnesemia was common in patients with ESRD due to an imbalance between gut absorption and dialytic removal. The realization of the toxicity of aluminum containing phosphate binders in patients with ESRD led to the use of alternate phosphate-binding agents, including calcium carbonate and magnesium carbonate. Finally, an association between higher serum magnesium levels and low PTH and adynamic bone disease was suggested [125]. Thus, PDSs with a lower magnesium content of 0.25 mmol/L (0.5 mEq/L) were introduced, were shown to maintain serum magnesium in the normal range, and gained widespread popularity [110, 126], despite concerns about potential depletion of tissue magnesium [127]. Subsequently, reports of hypomagnesemia in PD patients emerged, necessitating magnesium supplementation [128] or a switch to higher-magnesium PD fluids [129]. More concerning is the accumulating data that a higher serum magnesium may be protective against vascular and coronary calcification and may contribute to suppression of PTH [130]. Newer solutions such as Balance™ have an intermediate magnesium concentration of 0.5 mmol/L (1 mEq/L) (Table 14.1).

Thus, the optimal PDS magnesium concentration remains unknown, but accumulating evidence is in favor of either a reversion to higher magnesium solutions or oral supplementation with magnesium as needed to maintain a high normal serum magnesium.

Alternate PD Solutions and Membrane-Sparing Strategies

Carnitine Carnitine is a water-soluble molecule important in fatty acid metabolism. Depletion of muscle and plasma-free carnitine may occur in patients on PD due to losses of carnitine in the dialysate, resulting in elevation of acylcarnitine and an elevated acyl/free carnitine ratio. Adult patients on APD have lower carnitine levels than their CAPD counterparts [131]. Dialysis-related carnitine disorder may be associated with erythropoietin-stimulating agent (ESA) resistance, hypotension, abnormal lipid metabolism, and muscle weakness. Carnitine can be supplemented by the IV or intraperitoneal (IP) route [131, 132]. Oral carnitine is considered contraindicated in patients on dialysis due to potential accumulation of trimethylamine produced by metabolism of carnitine by gut bacteria [133], although there is published data on improvement in plasma carnitine levels [134, 135] and apolipoprotein B levels [136] in children on PD supplemented with oral carnitine.

A study in rats showed that L-carnitine exerts an osmotic effect similar to glucose, with half the water transport facilitated by aquaporin-1 water channels [137]. The same authors conducted a 5-day study in four adults on CAPD. A solution of 1.5% glucose and 0.25% L-carnitine as the overnight dwell yielded higher ultrafiltration than with a 2.5% glucose solution and similar uremic solute removal [137]. Plasma carnitine levels rose substantially and were not in steady state by 5 days, although the percent absorption from each dwell fell progressively, with increasing amounts recovered from the dialysate each day.

A further 4-month randomized study of insulin sensitivity was done in 27 adult patients on CAPD (15 carnitine, 12 glucose group) using a single exchange of a solution of either 2.5% or 1.5% glucose with 0.1% carnitine added, with two glucose exchanges and an overnight icodextrin exchange. Compared to the control group who received three glucose exchanges and the overnight icodextrin exchange, the L-carnitine group showed improved insulin sensitivity and preserved urine volume [138].

These studies suggest a potential role for L-carnitine-containing dialysis solutions as a membrane-preserving strategy and/or to prevent or treat carnitine deficiency, but further data is required on long-term safety and efficacy. No pediatric data exists, and no commercial L-carnitine-containing solution is yet available.

Dialysis Solutions with Dissolved Molecular Hydrogen (H2) Molecular hydrogen (H2) has been shown to have antioxidant and anti-inflammatory properties. PDS can be loaded with H2 by placing the bag in H2-enriched electrolyzed water. In rats, PDS with infused H2 has been shown to induce less peritoneal damage than the same PDS alone [139]. In a 2-week study in six prevalent Japanese patients, H2-infused PDS was clinically well tolerated, with a trend toward improvement in effluent CA125 and mesothelin in some patients [140]. More clinical experience is obviously required with this novel therapy. Additionally, H2 is rapidly lost from the PDS upon exposure to air, despite wrapping the bags in foil, so significant logistical considerations must be overcome before this could become commercially available.

Polyglucose Solutions Polydispersity is the ratio of weight-average molecular weight (Mw) to number-average molecular weight (Mn), while ultrafiltration efficiency is the ratio of UF to carbohydrate absorbed. Icodextrin, with a polydispersity of 2.6, has superior UF efficiency compared to glucose when used over a long dwell. Based on theoretical considerations using the three-pore peritoneal model, alternate solutions to icodextrin to provide sustained UF have been explored. Experimental studies in rabbits have shown that polyglucose solutions with low polydispersity are effective osmotic agents [141]. A 6 K polymer solution with a Mw of 6.4 kilodaltons (KDa) and polydispersity of 2.3 was compared to a 19 K polymer solution with a Mw of 18.8 kDa and polydispersity of 2.0. The 6 K solution was associated with greater UF and superior UF efficiency but at the expense of more absorption of the polymer. Further rabbit studies by the

same authors have shown that an 11% glucose polymer solution with a Mw of 18–19 kDa and a polydispersity of 2 provides higher UF without greater carbohydrate absorption [142]. These initial studies suggest that altering both the molecular weight distribution and the concentration of glucose polymers can provide prolonged UF without increased carbohydrate absorption. These solutions are not yet commercially available.

Hyperbranched Polyglycerol Hyperbranched polyglycerol (HPG) is a hydrophilic, nontoxic, non-immunogenic, water-soluble branched polyether polymer, which is being used in many biomedical applications. It has limited accumulation in internal organs after intravenous injection, although may accumulate in the reticuloendothelial system with repeated exposure. It does not activate platelets or the coagulation or complement systems. HPG-based PD solutions have been produced with concentrations varying from 2.5% to 15%, osmolality of 294–424 mOsm/kg, and neutral pH of 6.6–7.4. In a rat PD model utilizing a single exchange, HPG PD solutions produced equal or superior solute and fluid removal and were associated with less damage to the peritoneal membrane histologically [143] as compared to cPDS.

In a 3-month study in rats, HPG PDS was associated with stable blood chemistry, with less peritoneal membrane structural change and neoangiogenesis, and with less upregulation of inflammatory pathways, as compared with cPDS [144].

The kinetics of HPG in uremia must be further elucidated. HPG solutions have theoretical advantage and may compete with icodextrin as a single daily exchange in the future, but much more clinical experience is required [145].

PEN Study The PEN study compared a regimen of Physioneal™ (1–2 exchanges/day), Extraneal™ (1 overnight exchange), and Nutrineal™ (1 exchange daily) compared to 3–4 exchanges of Dianeal™ daily in incident adult PD patients over 12 months, followed by a 6-month conversion of the PEN group to Dianeal™. The studies measured multiple peritoneal markers of inflammation and demonstrated an improvement in urine volume in the PEN group and increased levels of anti-fibrotic markers and adiponectin and an associated reduction in some inflammatory markers in the PEN group, suggesting better preservation of peritoneal membrane integrity [146] [98]. However, a significant flaw was the absence of peritoneal morphology to corroborate improved membrane integrity.

Two other studies have shown this regimen to be well tolerated clinically but with a suggestion of increased deaths in diabetic patients [147]. There is no published pediatric experience with this regimen.

Conclusion

Misra et al. suggest that the ideal biocompatible solution must provide sustained ultrafiltration and solute clearance; have no adverse effects and have potential nutritional or metabolic benefits if absorbed; be associated with no interference with peritoneal host defenses; and cause no peritoneal inflammation or long-term peritoneal damage [9]. Despite significant advances in the knowledge of the beneficial and detrimental effects of peritoneal dialysis, the ideal PDS does not yet exist. In pediatrics, prescription of PD is further confounded by varying requirements based on age, size, and growth, along with regional differences in delivery systems and solution availability.

PDSs should be considered “drugs” and ordered with knowledge of their composition, risks, and potential benefits. The decision to use a particular PDS is a complex one based on what is available to the clinician in their region of practice, the delivery system (cycler versus CAPD), and a determination of the most appropriate content of buffer, calcium, osmotic agent, and magnesium. An ideal solution may not exist for an individual patient, requiring additional medical therapy to maintain homeostasis.

In general, for children, recommendations are to use neutral pH and low GDP biocompatible solutions; to minimize exposure to hypertonic glucose; to use a buffer which will correct acidosis without causing alkalosis; and to utilize membrane sparing strategies which may include the use of icodextrin, amino acid solutions, or newer osmotic agents [2, 45, 54].

In pediatrics, a "one size fits all" strategy will not be successful. Thus, a pediatric program must have a variety of solutions with varying buffer type and concentration, a variety of osmotic agents, and variable calcium concentrations to meet the needs of the majority of pediatric PD patients.

References

1. Rippe B, Venturoli D. Optimum electrolyte composition of a dialysis solution. Perit Dial Int. 2008;28(Suppl 3):S131–6.
2. Verrina EE, Cannavo R, Schaefer B, Schmitt CP. Are current peritoneal dialysis solutions adequate for pediatric use? Contrib Nephrol. 2012;178:16–22.
3. Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, et al. Morphologic changes in the peritoneal membrane of patients with renal disease. J Am Soc Nephrol. 2002;13(2):470–9.
4. Jorres A, Bender TO, Finn A, Witowski J, Frohlich S, Gahl GM, et al. Biocompatibility and buffers: effect of bicarbonate-buffered peritoneal dialysis fluids on peritoneal cell function. Kidney Int. 1998;54(6):2184–93.
5. Hanrahan CT, Himmele R, Diaz-Buxo JA. The challenges of heat sterilization of peritoneal dialysis solutions: is there an alternative? Adv Perit Dial Conf Perit Dial. 2012;28:126–30.
6. Erixon M, Wieslander A, Lindén T, Carlsson O, Forsbäck G, Svensson E, et al. How to avoid glucose degradation products in peritoneal dialysis fluids. Perit Dial Int. 2006;26(4):490–7.
7. Grantham CE, Hull KL, Graham-Brown MPM, March DS, Burton JO. The potential cardiovascular benefits of low-glucose degradation product, biocompatible peritoneal Dialysis fluids: a review of the literature. Perit Dial Int. 2017;37(4):375–83.
8. Cho Y, Johnson DW. Does the use of neutral pH, low glucose degradation product peritoneal dialysis fluids lead to better patient outcomes? Curr Opin Nephrol Hypertens. 2014;23(2):192–7.
9. Misra PS, Nessim SJ, Perl J. "Biocompatible" neutral pH low-GDP peritoneal Dialysis solutions: much ado about nothing? Semin Dial. 2017;30(2):164–73.
10. Nataatmadja M, Cho Y, Johnson DW. Evidence for biocompatible peritoneal Dialysis solutions. Contrib Nephrol. 2017;189:91–101.
11. Cho Y, Badve SV, Hawley CM, McDonald SP, Brown FG, Boudville N, et al. Association of biocompatible peritoneal dialysis solutions with peritonitis risk, treatment, and outcomes. Clin J Am Soc Nephrol. 2013;8(9):1556–63.
12. Sikaneta T, Wu G, Abdolell M, Ng A, Mahdavi S, Svendrovski A, et al. The trio trial - a randomized controlled clinical trial evaluating the effect of a biocompatible peritoneal Dialysis solution on residual renal function. Perit Dial Int. 2016;36(5):526–32.
13. Farhat K, Douma CE, Ferrantelli E, Ter Wee PM, Beelen RHJ, van Ittersum FJ. Effects of conversion to a bicarbonate/lactate-buffered, neutral-pH, low-GDP PD regimen in prevalent PD: a 2-year randomized clinical trial. Perit Dial Int. 2017;37(3):273–82.
14. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol. 2012;23(6):1097–107.
15. Cho Y, Johnson DW, Badve SV, Craig JC, Strippoli GF, Wiggins KJ. The impact of neutral-pH peritoneal dialysates with reduced glucose degradation products on clinical outcomes in peritoneal dialysis patients. Kidney Int. 2013;84(5):969–79.
16. Haag-Weber M, Kramer R, Haake R, Islam MS, Prischl F, Haug U, et al. Low-GDP fluid (Gambrosol trio) attenuates decline of residual renal function in PD patients: a prospective randomized study. Nephrol Dial Transplant. 2010;25(7):2288–96.
17. Kim S, Oh KH, Oh J, Kim SJ, Chung W, Song YR, et al. Biocompatible peritoneal dialysis solution preserves residual renal function. Am J Nephrol. 2012;36(4):305–16.
18. Seo EY, An SH, Cho JH, Suh HS, Park SH, Gwak H, et al. Effect of biocompatible peritoneal dialysis solution on residual renal function: a systematic review of randomized controlled trials. Perit Dial Int. 2014;34(7):724–31.
19. Yohanna S, Alkatheeri AM, Brimble SK, McCormick B, Iansavitchous A, Blake PG, et al. Effect of neutral-pH, low-glucose degradation product peritoneal Dialysis solutions on residual renal function, urine volume, and ultrafiltration: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2015;10(8):1380–8.
20. Wang J, Zhu N, Yuan W. Effect of neutral pH and low-glucose degradation product-containing peritoneal dialysis solution on residual renal function in peritoneal dialysis patients: a meta-analysis. Nephron. 2015;129(3):155–63.
21. Lichodziejewska-Niemierko M, Chmielewski M, Dudziak M, Ryta A, Rutkowski B. Hydration status of patients dialyzed with biocompatible peritoneal Dialysis fluids. Perit Dial Int. 2016;36(3):257–61.
22. Szeto CC, Kwan BC, Chow KM, Cheng PM, Kwong VW, Choy AS, et al. The effect of neutral peritoneal Dialysis solution with low glucose-

degradation-product on the fluid status and body composition–a randomized control trial. PLoS One. 2015;10(10):e0141425.
23. Kooman JP, Cornelis T, van der Sande FM, Leunissen KM. Is the effect of low-GDP solutions on residual renal function mediated by fluid state? An enigmatic question which still needs to be solved. Perit Dial Int. 2016;36(3):239–42.
24. Cho Y, Johnson DW, Craig JC, Strippoli GF, Badve SV, Wiggins KJ. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2014;3:CD007554.
25. Bargman JM. Slouching towards Bethlehem: the beast of biocompatibility. Nephrol Dial Transplant. 2010;25(7):2050–1.
26. Moinuddin Z, Summers A, Van Dellen D, Augustine T, Herrick SE. Encapsulating peritoneal sclerosis-a rare but devastating peritoneal disease. Front Physiol. 2014;5:470.
27. Nakayama M, Miyazaki M, Honda K, Kasai K, Tomo T, Nakamoto H, et al. Encapsulating peritoneal sclerosis in the era of a multi-disciplinary approach based on biocompatible solutions: the NEXT-PD study. Perit Dial Int. 2014;34(7):766–74.
28. Betjes MG, Habib SM, Boeschoten EW, Hemke AC, Struijk DG, Westerhuis R, et al. Significant decreasing incidence of encapsulating peritoneal sclerosis in the Dutch population of peritoneal Dialysis patients. Perit Dial Int. 2017;37(2):230–4.
29. Elphick EH, Teece L, Chess JA, Do JY, Kim YL, Lee HB, et al. Biocompatible solutions and long-term changes in peritoneal solute transport. Clin J Am Soc Nephrol. 2018;13(10):1526–33.
30. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial. Nephrol Dial Transplant. 2012;27(12):4445–53.
31. Cho Y, Johnson DW. PD solutions and peritoneal health. Clin J Am Soc Nephrol. 2018;13(10):1455–7.
32. Ha IS, Yap HK, Munarriz RL, Zambrano PH, Flynn JT, Bilge I, et al. Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. Kidney Int. 2015;88(3):605–13.
33. Raaijmakers R, Coester A, Smit W, Krediet RT, Schroder CH. Free water transport in children on peritoneal dialysis is higher with more biocompatible dialysis solutions, higher with older age and declines with time. Nephrol Dial Transplant. 2012;27(3):1183–90.
34. del Peso G, Jimenez-Heffernan JA, Selgas R, Remon C, Ossorio M, Fernandez-Perpen A, et al. Biocompatible Dialysis solutions preserve peritoneal mesothelial cell and Vessel Wall integrity. A case-control study on human biopsies. Perit Dial Int. 2016;36(2):129–34.
35. Hamada C, Honda K, Kawanishi K, Nakamoto H, Ito Y, Sakurada T, et al. Morphological characteristics in peritoneum in patients with neutral peritoneal dialysis solution. J Artif Organs. 2015;18(3):243–50.
36. Schaefer B, Bartosova M, Macher-Goeppinger S, Sallay P, Voros P, Ranchin B, et al. Neutral pH and low-glucose degradation product dialysis fluids induce major early alterations of the peritoneal membrane in children on peritoneal dialysis. Kidney Int. 2018;94(2):419–29.
37. Blake PG. Is the peritoneal dialysis biocompatibility hypothesis dead? Kidney Int. 2018;94(2):246–8.
38. Feriani M. Twenty years of bicarbonate solutions. Contrib Nephrol. 2012;178:1–5.
39. Pedersen FB, Ryttov N, Deleuran P, Dragsholt C, Kildeberg P. Acetate versus lactate in peritoneal dialysis solutions. Nephron. 1985;39(1):55–8.
40. Heimburger O, Mujais S. Buffer transport in peritoneal dialysis. Kidney Int Suppl. 2003;88:S37–42.
41. Kawaguchi Y, Kawanishi H, Mujais S, Topley N, Oreopoulos DG. Encapsulating peritoneal sclerosis: definition, etiology, diagnosis, and treatment. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int. 2000;20(Suppl 4):S43–55.
42. Sow A, Morelle J, Hautem N, Bettoni C, Wagner CA, Devuyst O. Mechanisms of acid-base regulation in peritoneal dialysis. Nephrol Dial Transplant. 2018;33(5):864–73.
43. Trinh E, Saiprasertkit N, Bargman JM. Increased serum lactate in peritoneal Dialysis patients presenting with Intercurrent illness. Perit Dial Int. 2018;38(5):363–5.
44. Schmitt CP, Haraldsson B, Doetschmann R, Zimmering M, Greiner C, Boswald M, et al. Effects of pH-neutral, bicarbonate-buffered dialysis fluid on peritoneal transport kinetics in children. Kidney Int. 2002;61(4):1527–36.
45. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int Suppl. 2008;108:S137–44.
46. Feriani M, Carobi C, La Greca G, Buoncristiani U, Passlick-Deetjen J. Clinical experience with a 39 mmol/L bicarbonate-buffered peritoneal dialysis solution. Perit Dial Int. 1997;17(1):17–21.
47. Nakayama M, Kawaguchi Y, Akiba T, Kim M, Naito H, Hara S, et al. A new peritoneal dialysis fluid for Japanese patients: a randomized non-inferiority clinical trial of safety and efficacy. Clin Exp Nephrol. 2017;21(5):895–907.
48. Blake PG. Balance about balANZ. Perit Dial Int. 2012;32(5):493–6.
49. Nataatmadja MS, Johnson DW, Pascoe EM, Darssan D, Hawley CM, Cho Y, et al. Associations between peritoneal glucose exposure, glucose degradation product exposure, and peritoneal membrane transport characteristics in peritoneal Dialysis patients: secondary analysis of the balANZ trial. Perit Dial Int. 2018;38(5):349–55.
50. Haas S, Schmitt CP, Arbeiter K, Bonzel KE, Fischbach M, John U, et al. Improved acidosis correction and recovery of mesothelial cell mass with neutral-pH bicarbonate dialysis solution among chil-

dren undergoing automated peritoneal dialysis. J Am Soc Nephrol. 2003;14(10):2632–8.
51. Schmitt CP, Nau B, Gemulla G, Bonzel KE, Holtta T, Testa S, et al. Effect of the dialysis fluid buffer on peritoneal membrane function in children. Clin J Am Soc Nephrol. 2013;8(1):108–15.
52. Vande Walle J, Raes AM, Dehoorne J, Mauel R. Use of bicarbonate/lactate-buffered dialysate with a nighttime cycler, associated with a daytime dwell with icodextrin, may result in alkalosis in children. Adv Perit Dial Conf Perit Dial. 2004;20:222–5.
53. De Los Rios T, Perez-Martinez J, Portoles J, Lichodziejewska-Niemierko M, Rivera M, Nowicki M, et al. Effect of balance solution on the peritoneal membrane in automated peritoneal Dialysis. Perit Dial Int. 2016;36(5):569–72.
54. Schmitt CP, Bakkaloglu SA, Klaus G, Schroder C, Fischbach M, European Pediatric Dialysis Working G. Solutions for peritoneal dialysis in children: recommendations by the European Pediatric Dialysis Working Group. Pediatr Nephrol. 2011;26(7):1137–47.
55. Balfe JW, Vigneux A, Willumsen J, Hardy BE. The use of CAPD in the treatment of children with end-stage renal disease. Perit Dial Int. 1981;1(4):35–8.
56. Eastham EJ, Kirpalani H, Francis D, Gokal R, Jackson RH. Paediatric continuous ambulatory peritoneal dialysis. Arch Dis Child. 1982;57(9):677–80.
57. Warady BA, Alexander SR, Hossli S, Vonesh E, Geary D, Watkins S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol. 1996;7(11):2385–91.
58. Twardoswki ZB, Nolph KO, Khanna R, Prowant BF, Ryan LP, Moore HL, et al. Peritoneal equilibration test. Perit Dial Int. 1987;7(3):138–48.
59. Rippe B, Venturoli D, Simonsen O, de Arteaga J. Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. Perit Dial Int. 2004;24(1):10–27.
60. Schmitt CP, von Heyl D, Rieger S, Arbeiter K, Bonzel KE, Fischbach M, et al. Reduced systemic advanced glycation end products in children receiving peritoneal dialysis with low glucose degradation product content. Nephrol Dial Transplant. 2007;22(7):2038–44.
61. Fan S, Davenport A. Does increased glucose exposure lead to increased body fat and reduced lean body mass in anuric peritoneal dialysis patients? Eur J Clin Nutr. 2014;68(11):1253–4.
62. Silver SA, Harel Z, Perl J. Practical considerations when prescribing icodextrin: a narrative review. Am J Nephrol. 2014;39(6):515–27.
63. Dousdampanis P, Trigka K, Bargman JM. Bimodal solutions or twice-daily icodextrin to enhance ultrafiltration in peritoneal dialysis patients. Int J Nephrol. 2013;2013:424915.
64. Mistry CD, Gokal R, Peers E. A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter investigation of Icodextrin in Ambulatory Peritoneal Dialysis. Kidney Int. 1994;46(2):496–503.
65. de Boer AW, Schroder CH, van Vliet R, Willems JL, Monnens LA. Clinical experience with icodextrin in children: ultrafiltration profiles and metabolism. Pediatr Nephrol. 2000;15(1–2):21–4.
66. van Hoeck KJ, Rusthoven E, Vermeylen L, Vandesompel A, Marescau B, Lilien M, et al. Nutritional effects of increasing dialysis dose by adding an icodextrin daytime dwell to Nocturnal Intermittent Peritoneal Dialysis (NIPD) in children. Nephrol Dial Transplant. 2003;18(7):1383–7.
67. Cho Y, Johnson DW, Badve S, Craig JC, Strippoli GF, Wiggins KJ. Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials. Nephrol Dial Transplant. 2013;28(7):1899–907.
68. Akonur A, Sloand J, Davis I, Leypoldt J. Icodextrin simplifies PD therapy by equalizing UF and sodium removal among patient transport types during long dwells: a modeling study. Perit Dial Int. 2016;36(1):79–84.
69. Chang TI, Ryu DR, Yoo TH, Kim HJ, Kang EW, Kim H, et al. Effect of Icodextrin solution on the preservation of residual renal function in peritoneal Dialysis patients: a randomized controlled study. Medicine. 2016;95(13):e2991.
70. de Moraes TP, Andreoli MC, Canziani ME, da Silva DR, Caramori JC, Ponce D, et al. Icodextrin reduces insulin resistance in non-diabetic patients undergoing automated peritoneal dialysis: results of a randomized controlled trial (STARCH). Nephrol Dial Transplant. 2015;30(11):1905–11.
71. Kanda E, Ai M, Iwamoto A, Okazaki M, Maeda Y, Sasaki S, et al. Relationship between Icodextrin use and decreased level of small low-density lipoprotein cholesterol fractioned by high-performance gel permeation chromatography. BMC Nephrol. 2013;14:234.
72. Wang IK, Li YF, Chen JH, Liang CC, Liu YL, Lin HH, et al. Icodextrin decreases technique failure and improves patient survival in peritoneal dialysis patients. Nephrology. 2015;20(3):161–7.
73. Sniderman AD, Sloand JA, Li PK, Story K, Bargman JM. Influence of low-glucose peritoneal dialysis on serum lipids and apolipoproteins in the IMPENDIA/EDEN trials. J Clin Lipidol. 2014;8(4):441–7.
74. Dousdampanis P, Musso CG, Trigka K. Icodextrin and peritoneal dialysis: advantages and new applications. Int Urol Nephrol. 2018;50(3):495–500.
75. Panzer SE, Teitelbaum I. Alternative dialysis strategies with icodextrin. Contrib Nephrol. 2012;178:11–5.
76. Lopez-Anton M, Lambie M, Lopez-Cabrera M, Schmitt CP, Ruiz-Carpio V, Bartosova M, et al. miR-21 promotes Fibrogenesis in peritoneal Dialysis. Am J Pathol. 2017;187(7):1537–50.
77. Shimada S, Mori T, Koizumi K, Sato S, Oba-Yabana I, Ohsaki Y, et al. Efficacy and biocompatibility of neutral Icodextrin peritoneal Dialysis fluid. Adv Perit Dial Conf Perit Dial. 2016;32:46–50.

78. Dart A, Feber J, Wong H, Filler G. Icodextrin re-absorption varies with age in children on automated peritoneal dialysis. Pediatr Nephrol. 2005;20(5):683–5.
79. Rousso S, Banh TM, Ackerman S, Piva E, Licht C, Harvey EA. Impact of fill volume on ultrafiltration with icodextrin in children on chronic peritoneal dialysis. Pediatr Nephrol. 2016;31(10):1673–9.
80. Dogan K, Kayalp D, Ceylan G, Azak A, Senes M, Duranay M, et al. Falsely elevated glucose concentrations in peritoneal Dialysis patients using Icodextrin. J Clin Lab Anal. 2016;30(5):506–9.
81. Deslandes G, Gregoire M, Bouquie R, Le Marec A, Allard S, Dailly E, et al. Stability and compatibility of antibiotics in peritoneal Dialysis solutions applied to automated peritoneal Dialysis in the pediatric population. Perit Dial Int. 2016;36(6):676–9.
82. Oren A, Wu G, Anderson GH, Marliss E, Khanna R, Pettit J, et al. Effective use of amino acid dialysate over four weeks in CAPD patients. Perit Dial Bull. 1983;29(2):66–72.
83. Hanning RM, Balfe JW, Zlotkin SH. Effectiveness and nutritional consequences of amino acid-based vs glucose-based dialysis solutions in infants and children receiving CAPD. Am J Clin Nutr. 1987;46(1):22–30.
84. Olszowska A, Waniewski J, Werynski A, Anderstam B, Lindholm B, Wankowicz Z. Peritoneal transport in peritoneal dialysis patients using glucose-based and amino acid-based solutions. Perit Dial Int. 2007;27(5):544–53.
85. Rippe B, Venturoli D. Peritoneal transport kinetics with amino acid-based and glucose-based peritoneal dialysis solutions. Perit Dial Int. 2007;27(5):518–22.
86. Canepa A, Perfumo F, Carrea A, Piccardo MT, Ciardi MR, Cantaluppi A, et al. Continuous ambulatory peritoneal dialysis (CAPD) of children with amino acid solutions: technical and metabolic aspects. Perit Dial Int. 1990;10(3):215–20.
87. Canepa A, Perfumo F, Carrea A, Giallongo F, Verrina E, Cantaluppi A, et al. Long-term effect of amino-acid dialysis solution in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1991;5(2):215–9.
88. Unverdi S, Ceri M, Uz E, Akgul B, Altay M, Kirac Y, et al. The effectiveness of oral essential aminoacids and aminoacids containing dialysate in peritoneal dialysis. Ren Fail. 2014;36(9):1416–9.
89. Garibotto G, Sofia A, Canepa A, Saffioti S, Sacco P, Sala M, et al. Acute effects of peritoneal dialysis with dialysates containing dextrose or dextrose and amino acids on muscle protein turnover in patients with chronic renal failure. J Am Soc Nephrol. 2001;12(3):557–67.
90. Canepa A, Carrea A, Menoni S, Verrina E, Trivelli A, Gusmano R, et al. Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. Kidney Int. 2001;59(5):1967–73.
91. Brem AS, Maaz D, Shemin DG, Wolfson M. Use of amino acid peritoneal dialysate for one year in a child on CCPD. Perit Dial Int. 1996;16(6):634–6.
92. Tjiong HL, Rietveld T, Wattimena JL, van den Berg JW, Kahriman D, van der Steen J, et al. Peritoneal dialysis with solutions containing amino acids plus glucose promotes protein synthesis during oral feeding. Clin J Am Soc Nephrol. 2007;2(1):74–80.
93. Tjiong HL, van den Berg JW, Wattimena JL, Rietveld T, van Dijk LJ, van der Wiel AM, et al. Dialysate as food: combined amino acid and glucose dialysate improves protein anabolism in renal failure patients on automated peritoneal dialysis. J Am Soc Nephrol. 2005;16(5):1486–93.
94. Verger C. Peritoneal dialysis solution and nutrition. Contrib Nephrol. 2012;178:6–10.
95. Geerse DA, Rutherford P, Bogers JC, Konings CJ. Sterile peritonitis associated with the use of amino-acid solution in eight peritoneal dialysis patients. Perit Dial Int. 2011;31(1):90–1.
96. Os I, Gudmundsdottir H, Draganov B, von der Lippe E. Sterile peritonitis associated with amino acid-containing dialysate–a single center experience in Norway. Perit Dial Int. 2011;31(1):103.
97. Kari JA, El-Desoky S, Abuduhair AA, Habib H. Sterile peritonitis with high-dose amino acid-containing peritoneal dialysis solution in children. Perit Dial Int. 2012;32(2):204–6.
98. Yung S, Lui SL, Ng CK, Yim A, Ma MK, Lo KY, et al. Impact of a low-glucose peritoneal dialysis regimen on fibrosis and inflammation biomarkers. Perit Dial Int. 2015;35(2):147–58.
99. Bender TO, Witowski J, Aufricht C, Endemann M, Frei U, Passlick-Deetjen J, et al. Biocompatibility of a bicarbonate-buffered amino-acid-based solution for peritoneal dialysis. Pediatr Nephrol. 2008;23(9):1537–43.
100. Plum J, Fussholler A, Schoenicke G, Busch T, Erren C, Fieseler C, et al. In vivo and in vitro effects of amino-acid-based and bicarbonate-buffered peritoneal dialysis solutions with regard to peritoneal transport and cytokines/prostanoids dialysate concentrations. Nephrol Dial Transplant. 1997;12(8):1652–60.
101. Blake PG. Sodium levels in peritoneal Dialysis solution: how low should we go? Am J Kidney Dis. 2016;67(5):719–21.
102. Rutkowski B, Tam P, van der Sande FM, Vychytil A, Schwenger V, Himmele R, et al. Low-sodium versus standard-sodium peritoneal Dialysis solution in hypertensive patients: a randomized controlled trial. Am J Kidney Dis. 2016;67(5):753–61.
103. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12(11):2418–26.
104. Paulson WD, Bock GH, Nelson AP, Moxey-Mims MM, Crim LM. Hyponatremia in the very young chronic peritoneal dialysis patient. Am J Kidney Dis. 1989;14(3):196–9.
105. Fischbach M, Zaloszyc A, Schaefer B, Schmitt CP. Should sodium removal in peritoneal dialysis

be estimated from the ultrafiltration volume? Pediatr Nephrol. 2017;32(3):419–24.
106. Vande Walle JG, Raes AM, De Hoorne J, Mauel R. Need for low sodium concentration and frequent cycles of 3.86% glucose solution in children treated with acute peritoneal dialysis. Adv Perit Dial Conf Perit Dial. 2005;21:204–8.
107. Martis L. Calcium carbonate as a phosphate binder: is there a need to adjust peritoneal dialysate calcium concentrations for patients usingcaco3? Perit Dial Int. 1989;9:325–8.
108. Banalagay EE, Bernardini J, Piraino B. Calcium mass transfer with 10-hour dwell time using 1.25 versus 1.75 mmol/L calcium dialysate. Adv Perit Dial Conf Perit Dial. 1993;9:271–3.
109. Bender FH, Bernardini J, Piraino B. Calcium mass transfer with dialysate containing 1.25 and 1.75 mmol/L calcium in peritoneal dialysis patients. Am J Kidney Dis. 1992;20(4):367–71.
110. Hutchison AJ, Merchant M, Boulton HF, Hinchcliffe R, Gokal R. Calcium and magnesium mass transfer in peritoneal dialysis patients using 1.25 mmol/L calcium, 0.25 mmol/L magnesium dialysis fluid. Perit Dial Int. 1993;13(3):219–23.
111. Weinreich T, Passlick-Deetjen J, Ritz E. Low dialysate calcium in continuous ambulatory peritoneal dialysis: a randomized controlled multicenter trial. The Peritoneal Dialysis Multicenter Study Group. Am J Kidney Dis. 1995;25(3):452–60.
112. Hutchison AJ, Gokal R. Towards tailored dialysis fluids in CAPD–the role of reduced calcium and magnesium in dialysis fluids. Perit Dial Int. 1992;12(2):199–203.
113. Kawanishi H, Tsuchiya T, Namba S, Takahashi N, Toyota T, Fukuma K, et al. Clinical application of low calcium peritoneal dialysate. ASAIO Trans. 1991;37(3):M404–6.
114. Buijsen CG, Struijk DG, Huijgen HJ, Boeschoten EW, Wilmink JM. Can low-calcium peritoneal dialysis solution safely replace the standard calcium solution in the majority of chronic peritoneal dialysis patients? Perit Dial Int. 1996;16(5):497–504.
115. Rotellar C, Kinsel V, Goggins M, Tarman G, Stull M, Mazzoni MJ, et al. Does low-calcium dialysate accelerate secondary hyperparathyroidism in continuous ambulatory peritoneal dialysis patients? Perit Dial Int. 1993;13(Supp 2):S471–2.
116. Weinreich T. Low or high calcium dialysate solutions in peritoneal dialysis? Kidney Int Suppl. 1996;56:S92–6.
117. Bro S, Brandi L, Daugaard H, Olgaard K. Calcium concentration in the CAPD dialysate: what is optimal and is there a need to individualize? Perit Dial Int. 1997;17(6):554–9.
118. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Low-calcium dialysate as a risk factor for decline in bone mineral density in peritoneal dialysis patients. Scand J Urol Nephrol. 2012;46(6):454–60.
119. Wang Z, Wen Y, Liang J, Liang X, Shi W. The influence of low calcium dialysate on left ventricular diastolic function in peritoneal dialysis patients. Ren Fail. 2016;38(10):1665–71.
120. Haris A, Sherrard DJ, Hercz G. Reversal of adynamic bone disease by lowering of dialysate calcium. Kidney Int. 2006;70(5):931–7.
121. Zhao HP, Wu B, Lu LX, Qiao J, Wu XL, Wang M. Effect of combining different calcium concentration dialysate on calcium balance in peritoneal dialysis patients. Chin Med J. 2012;125(22):4009–13.
122. Simonsen O, Venturoli D, Wieslander A, Carlsson O, Rippe B. Mass transfer of calcium across the peritoneum at three different peritoneal dialysis fluid Ca2+ and glucose concentrations. Kidney Int. 2003;64(1):208–15.
123. Haffner D, Schaefer F. Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. Pediatr Nephrol. 2013;28(4):537–45.
124. Wesseling-Perry K, Salusky IB. Phosphate binders, vitamin D and calcimimetics in the management of chronic kidney disease-mineral bone disorders (CKD-MBD) in children. Pediatr Nephrol. 2013;28(4):617–25.
125. Navarro JF. Serum magnesium and parathyroid horone levels in dialysis patients. Kidney Int. 2000;57:2654.
126. Nolph KD, Prowant B, Serkes KD, Morgan L, Baker B, Chary C, et al. Multicenter evaluation of a new peritoneal dialysis solution with a high lactate and a low magnesium concentration. Perit Dial Int. 1983;3:63–5.
127. Weinreich T, Huynh U, Zitta S, Binder D, Gatenbein H, Binswanger U. Peritoneal dialysate magnesium – how low is safe? Perit Dial Int. 1994;14(2):195–6.
128. Ejaz AA, McShane AP, Gandhi VC, Leehey DJ, Ing TS. Hypomagnesemia in continuous ambulatory peritoneal dialysis patients dialyzed with a low-magnesium peritoneal dialysis solution. Perit Dial Int. 1995;15(1):61–4.
129. Eisenman K, Holley JL. A higher magnesium dialysate concentration treats hypomagnesemia. Perit Dial Int. 2005;25(6):604–5.
130. Tzanakis IP, Oreopoulos DG. Beneficial effects of magnesium in chronic renal failure: a foe no longer. Int Urol Nephrol. 2009;41:363–71.
131. Di Liberato L, Arduini A, Rossi C, Di Castelnuovo A, Posari C, Sacchetta P, et al. L-carnitine status in end-stage renal disease patients on automated peritoneal dialysis. J Nephrol. 2014;27(6):699–706.
132. Boer W. Intraperitoneal administration of carnitine in 3 carnitnie-deficient patients on PD: effect on plasma and dialysate carnitine concentrations. Perit Dial Int. 2008;28(Suppl 4 Abstract PP-088):S38.
133. Schreiber B. Levocarnitine and dialysis: a review. Nutr Clin Pract. 2005;20(2):218–43.
134. Warady BA, Borum P, Stall C, Millspaugh J, Taggart E, Lum G. Carnitine status of pediatric patients on continuous ambulatory peritoneal dialysis. Am J Nephrol. 1990;10(2):109–14.

135. Verrina E, Caruso U, Calevo MG, Emma F, Sorino P, De Palo T, et al. Effect of carnitine supplementation on lipid profile and anemia in children on chronic dialysis. Pediatr Nephrol. 2007;22(5):727–33.
136. Kosan C, Sever L, Arisoy N, Caliskan S, Kasapcopur O. Carnitine supplementation improves apolipoprotein B levels in pediatric peritoneal dialysis patients. Pediatr Nephrol. 2003;18(11):1184–8.
137. Bonomini M, Pandolfi A, Di Liberato L, Di Silvestre S, Cnops Y, Di Tomo P, et al. L-carnitine is an osmotic agent suitable for peritoneal dialysis. Kidney Int. 2011;80(6):645–54.
138. Bonomini M, Di Liberato L, Del Rosso G, Stingone A, Marinangeli G, Consoli A, et al. Effect of an L-carnitine-containing peritoneal dialysate on insulin sensitivity in patients treated with CAPD: a 4-month, prospective, multicenter randomized trial. Am J Kidney Dis. 2013;62(5):929–38.
139. Nakayama M, Zhu WJ, Watanabe K, Gibo A, Sherif AM, Kabayama S, et al. Dissolved molecular hydrogen (H2) in Peritoneal Dialysis (PD) solutions preserves mesothelial cells and peritoneal membrane integrity. BMC Nephrol. 2017;18(1):327.
140. Nakayama M, Watanabe K, Hayashi Y, Terawaki H, Zhu WJ, Kabayama S, et al. Translational research of peritoneal Dialysis solution with dissolved molecular hydrogen. Contrib Nephrol. 2018;196:162–70.
141. Leypoldt JK, Hoff CM, Piscopo D, Carr SN, Svatek JM, Holmes CJ. Ultrafiltration characteristics of glucose polymers with low polydispersity. Perit Dial Int. 2013;33(2):124–31.
142. Leypoldt JK, Hoff CM, Akonur A, Holmes CJ. Low-polydispersity glucose polymers as osmotic agents for peritoneal Dialysis. Perit Dial Int. 2015;35(4):428–35.
143. Mendelson AA, Guan Q, Chafeeva I, da Roza GA, Kizhakkedathu JN, Du C. Hyperbranched polyglycerol is an efficacious and biocompatible novel osmotic agent in a rodent model of peritoneal dialysis. Perit Dial Int. 2013;33(1):15–27.
144. Du C, Mendelson AA, Guan Q, Dairi G, Chafeeva I, da Roza G, et al. Hyperbranched polyglycerol is superior to glucose for long-term preservation of peritoneal membrane in a rat model of chronic peritoneal dialysis. J Transl Med. 2016;14(1):338.
145. Rippe B. Hyperbranched polyglycerol: a future alternative to polyglucose in peritoneal dialysis fluids? Perit Dial Int. 2013;33(1):5–7.
146. Lui SL, Yung S, Yim A, Wong KM, Tong KL, Wong KS, et al. A combination of biocompatible peritoneal dialysis solutions and residual renal function, peritoneal transport, and inflammation markers: a randomized clinical trial. Am J Kidney Dis. 2012;60(6):966–75.
147. Szeto CC, Johnson DW. Low GDP solution and glucose-sparing strategies for peritoneal Dialysis. Semin Nephrol. 2017;37(1):30–42.

Peritoneal Dialysis During Infancy

15

Enrico Vidal and Joshua Zaritsky

Introduction

During recent years, an increasing number of publications have reported satisfactory outcomes with respect to morbidity, mortality, growth, and development in newborns and infants undergoing maintenance peritoneal dialysis (PD) [1–6]. A very young age at dialysis initiation still has a negative prognostic implication, but this alone is not a contraindication to any form of renal replacement therapy (RRT). As a consequence, more and more infants are successfully treated with PD, and over the years the question of whether or not to start dialysis has shifted to how to improve dialysis delivery to these fragile patients.

Although transplantation is the ideal RRT for children, technical aspects limit the feasibility of the procedure in the first year of life. Thus, dialysis is used as a bridge to successful early transplantation with PD the modality of choice. Despite European data showing similar hard outcomes in infants on PD or hemodialysis (HD) therapy [5], figures from the North American Renal Trials and Collaborative Studies (NAPRTCS) show that 94% of children who initiated dialysis during the first year of life were treated with PD [4]. Data from the European Registry for Children on Renal Replacement Therapy (ESPN/ERA-EDTA Registry) also showed that the vast majority (87%) of incident dialysis infants (≤12 months) were started on PD [5].

Both technical challenges and dialysis access are likely the primary reasons behind the overwhelming preference of PD over HD in these young patients. Not only is a fistula or graft not feasible in an infant due to small vasculature, but a well-functioning HD access through the use of a central venous catheter can also be very difficult to obtain in very small infants, and the rates of both infectious and mechanical complications are exceedingly high [7]. HD access revision rates in this age range are estimated at 35% [8], a value that is higher than that reported in other series including older children [9]. The potential for stenosis of the central vein is also high, which may in turn limit the ability to create a fistula in the future for these patients who are faced with a lifetime of end-stage renal disease (ESRD) care.

Incidence and Etiology

The development of ESRD in an infant and the subsequent need for long-term RRT is a rare occurrence. Data from international registries showed an ESRD incidence ranging from 7 to

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10 cases per million age-related population in infants aged 0–2 years [10, 11]. According to the 2011 NAPRTCS report, 13.2% of all children who initiated dialysis from 1992 to 2010 were younger than 1 year at RRT initiation [12]. Similar data are available from the ESPN/ERA-EDTA Registry, which has reported that 11% of all children who initiated chronic dialysis from 1991 to 2013 were infants [5]. Interestingly, Ronnholm et al. reported a much higher percentage (47%) of young children at the University of Helsinki, presumably due to the high rate of congenital nephrotic syndrome in Finland [1]. The incidence of ESRD resulting in the provision of chronic dialysis in infants also appears to vary regionally, with a recent report of the International Pediatric Peritoneal Dialysis Network (IPPN) suggesting that centers in low-income countries (gross national income <$12,000) rarely offer PD to young patients, with only 8% of their dialysis patients being <3 years old [13].

As opposed to what might give rise to new-onset ESRD in older children, the most frequent causes of ESRD in this age group are congenital anomalies of kidney and urinary tract (CAKUT), including renal hypoplasia/dysplasia and obstructive uropathy (e.g., posterior urethral valves). These abnormalities account for nearly half of the cases. The next most common diagnoses are congenital nephrotic syndrome, autosomal recessive polycystic kidney disease (ARPKD), and cortical necrosis related to perinatal asphyxia [12]. Among the cohort of 3450 dialysis patients younger than 4 years of age registered in the United States Renal Data System (USRDS) between 1990 and 2010, the percentage of children with greater than 1 comorbidity increased from 3.9% to 31.1% between 1990 to 1994 and 2005 to 2010, indicating that the youngest patients on dialysis have become more medically complex [14]. Along with three other registries, namely, the IPPN, the Australia and New Zealand Dialysis and Transplantation Registry (ANZDATA), and the Japanese Society for Dialysis Therapy registry, the ESPN/ERA-EDTA Registry provided information on the largest cohort of neonates, starting chronic dialysis to date in 2014 [15]. In the first year after starting RRT, 73% of 111 patients were reported to have comorbidities. No determinants of survival could be identified, except that the presence of a neurological disorder was associated with a significant fivefold increased risk of death: this can have profound ethical implications for both the patient's family and the healthcare team, regarding the decision to start RRT.

Ethical Considerations: Should Dialysis Be Initiated?

Clearly, one of the most difficult issues that families and pediatric nephrology teams are confronted with is the decision regarding when and if chronic dialysis therapy should be initiated for neonates and infants with ESRD. In a survey of 938 European patients younger than 18 years, median eGFR at the start of dialysis therapy increased with age from 6.3 mL/min/1.73 m^2 in infants younger than 1 year to 13.5 mL/min/1.73 m^2 in adolescents, reflecting the tendency to delay the initiation of dialysis therapy in the infant age group [16]. Despite advances in dialysis technology and clinical expertise that now makes it possible to provide dialysis to this patient population safely and effectively, the concept of proceeding with a lifetime of ESRD care is unavoidably complex.

Comorbidities, such as neurocognitive delay, growth delay, the prospect of multiple hospitalizations, and the need for supplemental tube feeding, contribute to the ethical dilemma experienced by many families and healthcare providers. In up to one third of cases, the presence of significant nonrenal abnormalities, such as neurological abnormalities or pulmonary hypoplasia, can further complicate the clinical picture [17]. In fact, the survival rate of the youngest infants (0–2 years) who have received chronic dialysis has historically been quite poor, with 2-year mortality rates as high as 30% [18]; however, more recent data has revealed that survival of infants on dialysis has improved markedly and now closely approximates that of older children receiving maintenance dialysis [4].

It is also noteworthy that a substantial percentage of children with in utero evidence of severe kidney disease never presents for consideration of chronic dialysis. Advanced ultrasound techniques facilitate prenatal diagnosis of renal disease in most affected children. Severely impaired kidney function in utero results in renal oligo- or anhydramnios due to decreased fetal urine output. In a recent study, a German group characterized the postnatal overall survival and the degree of renal impairment in a series of 103 pregnancies with renal oligohydramnios [19]. After diagnosis, 38 families opted for termination of pregnancy, 8 infants died in utero, and 8 cases were lost to follow-up. The decision to interrupt a pregnancy was associated with onset of renal oligohydramnios, underlying renal disease, and the presence of extrarenal manifestations. Among the 49 survivors, 11 received palliative care, 42 received initial active care, and 35 (34% of the original pregnancy cohort) eventually survived until discharge. About one-third (12 out of 35) of the survived infants needed dialysis in the first 6 weeks after birth, but this was only on a temporary basis in 5 of them and continued as a chronic therapy in 7. The postnatal need for dialysis was not associated with onset of renal oligohydramnios.

In adult patients, the four principles of medical ethics, autonomy, beneficence, nonmaleficence, and justice, are characteristically applied when confronted with the decision on whether to withhold or withdraw dialysis. However, in the case of infants, the wishes of the parents, who are usually entitled to make decisions regarding the medical care their children receive, must also be taken into consideration. Overall, the principle criterion used to make this decision should be "the best interest of the child." This ethical dilemma is not all that uncommon in the neonatal intensive care unit and occurs in other situations, such as in the case of the infant with hypoplastic left heart syndrome [20]. Ideally, the decision of providing or withholding dialysis represents a consensus opinion of the parents, nephrologist, neonatologist, and other members of a multidisciplinary team after a thorough review of the patient's clinical status, the family's dynamics, and a review of the data that exists within the medical literature on the outcome of young infants with ESRD. A checklist with guiding questions might be used in the decision-making process and should include a variety of potentially influential aspects, such as the presence of comorbidities, which could impact medical care and outcome, the availability of equipment, expertise, and financial resources, the possibility of future transplantation, and the predicted quality of life for the child and family [21]. Despite the best efforts to this end, there remains substantial potential for disagreement regarding the best course of action to take because of the multiple patient and social factors that often exist, along with the different prior experiences of healthcare team members with similar patient scenarios. Whereas the nephrology team and family members most often come to a conclusion that is agreeable to all, on occasion, a hospital ethics committee may be consulted for their opinion.

Twenty years ago, Geary and colleagues surveyed the opinions of pediatric caregivers from around the globe, regarding the decision process surrounding the initiation of chronic dialysis in infants <1 year of age [22]. In that survey, a substantial percentage (50%) of physicians responded that it was usually acceptable for parents to refuse dialysis for children less than 1 month of age, in contrast to the situation when children were 1–12 months of age at presentation, at which time dialysis refusal was deemed less acceptable. Factors felt to be most influential by the physicians with respect to their opinions regarding withholding dialysis were the presence of "coexistent serious medical abnormalities" and the "anticipated morbidity for the child." As a follow-up to that survey, 10 years later, Teh et al. reported on the results of a similar multination survey of both nephrologists and nurses on this topic, to determine if the perspectives of healthcare providers had changed subsequent to the introduction of advances in care and additional personal and published experiences [23]. Of note, only 30% of the 270 nephrologists indicated that they would offer chronic dialysis therapy to all children less than 1 month of age and

50% to all children aged 1–12 months. The figure of 30% was decreased from the figure of 41% reported in the prior survey. In the more recent assessment, a minority of physicians (27%) believed that the parents could not refuse dialysis for infants less than 1 month of age, a figure that increased to 50% for children aged 1–12 months. Noteworthy was the finding that nurses were more likely than physicians to consider the presence of oliguria or anuria as a contraindication to initiating dialysis, and they placed more emphasis on the parent's right to decide. Whereas a difference of opinions among healthcare staff may be fairly common in these scenarios, a consensus should ideally be reached before speaking with families and during the parental decision-making process.

Peritoneal Dialysis Access

Long-term PD mandates the surgical placement of a Tenckhoff catheter. A chronic PD catheter can be inserted in infants as young as newborns with few long-term complications of the procedure itself. The most important consideration for the successful placement and function of a PD catheter in the young infant is the experience of the surgeon [24]. This can be particularly problematic at centers caring for a small volume of infants overall, where the need to provide dialysis to a very young infant may be a rare event. Because of the importance of the access and the desire for the outcome of placement to be without complication, the surgical placement should ideally be limited to only a few surgeons per center. In some circumstances, it may be preferable to refer the patient to another, more experienced center for access placement, in a manner similar to what has been recommended for a vascular access.

If complications, such as dialysate leakage, are to be avoided, placement of the catheter 2–3 weeks before its eventual use is ideal, so that there is an opportunity for ingrowth of the Dacron cuffs of the catheter into the surrounding tissues. The provision of fibrin sealant at the peritoneum as a means of achieving a tight closure when a delay in PD initiation is not possible has been practiced [25]. The need for an access revision early after PD catheter placement is most common during infancy and is often secondary to mechanical dysfunction. Borzych-Duzalka et al. reported that nearly 40% of infants initiated on PD at <1 year of age required PD catheter revision, most frequently >60 days after the initiation of dialysis [26]. Additional considerations in the chronic setting are the orientation of the subcutaneous tunnel of the catheter, the exit-site orientation and location, the potential need for an omentectomy, and the timing of placement of a gastrostomy tube (G-tube).

Observational data from the NAPRTCS suggests that catheters with a downward-pointed exit-site are associated with the lowest peritonitis rates, a technique (along with the preference for two-cuffed catheters) that should characterize all PD catheters placed in children. This is especially relevant in infants and young children because of their increased rates of peritonitis compared to older children [12, 27]. The exit-site should also be placed outside of the diaper area and away from any potential ostomy site, with the superficial cuff located approximately 2 cm from the skin surface. Occasionally, this necessitates placement of the exit-site on the chest wall [28]. Given the small size of the neonatal/infant patient, these requirements can be difficult to accommodate and, as noted above, require a very skilled and experienced surgeon.

One somewhat controversial aspect of catheter placement is the decision whether to routinely perform an omentectomy. The basis for its performance in children is that catheter obstruction (usually due to omental wrapping) represents the main reason for access revision and magnifies the risk of technique failure compared with infectious causes, especially in small children [26]. Although children appear to be at higher risk for omental obstruction compared to adults, most of the data in support of omentectomy comes from the adult literature, while there are no well-designed studies in children addressing this topic. One retrospective study of children by Cribs et al. did demonstrate a decrease risk of early catheter failure with omentectomy [29]. Similarly,

in a retrospective study of 92 pediatric patients (mean age 5 years), Conlin et al. demonstrated that the outflow obstruction rate was 5% in patients who received an omentectomy vs 10% in patients who did not [30]. On the contrary, in a recent series of 154 PD catheters, Radtke et al. found that omentectomy did not reduce the incidence of catheter obstruction in pediatric patients, whereas the type of catheter (straight or curled) and presumably the size of the holes at the catheter tip might influence the incidence of PD catheter obstruction [31].

One additional unique consideration for catheter placement in this age group is the timing and location of placement relative to the common need for a gastrostomy tube (G-tube) in order to accommodate nutritional requirements. As noted above, the catheter exit-site should ideally be placed at a distance (often the contralateral side) from the site of a current or potential G-tube to decrease the risk of contamination and possible peritonitis. Likewise, it is recommended that when possible, the PD catheter be placed either simultaneously with or after the placement of a G-tube to avoid contamination of the peritoneum from gastric contents [24, 27, 32]. Data from the Standardized Care to Improve Outcomes in Pediatric End-Stage Renal Disease (SCOPE) collaborative – a quality improvement initiative that aims to reduce PD-associated infections in pediatric patients on chronic PD – demonstrated that G-tube placement after PD catheter insertion was associated with a threefold increased risk of peritonitis [33]. When the catheter placement precedes G-tube placement, the latter procedure should take place under prophylactic antibiotic and antifungal therapy and with the patient drained of PD fluid [27]. In addition, there is some evidence that an open gastrostomy (Stamm procedure) in contrast to a percutaneous procedure (PEG) is preferred in this setting as well, to decrease the risk of peritonitis associated with gastrostomy placement [24, 34]. PD should be held for 2–3 days following the gastrostomy procedure if possible (Fig. 15.1).

Prescription

The dialysis prescription in infants is characterized by some key details that differentiate it from the prescription used in older children and adults (Table 15.1).

When scaled to body weight, the surface area of the infant peritoneal membrane is almost twice that of a 70 kg adult. Thus, in small children the

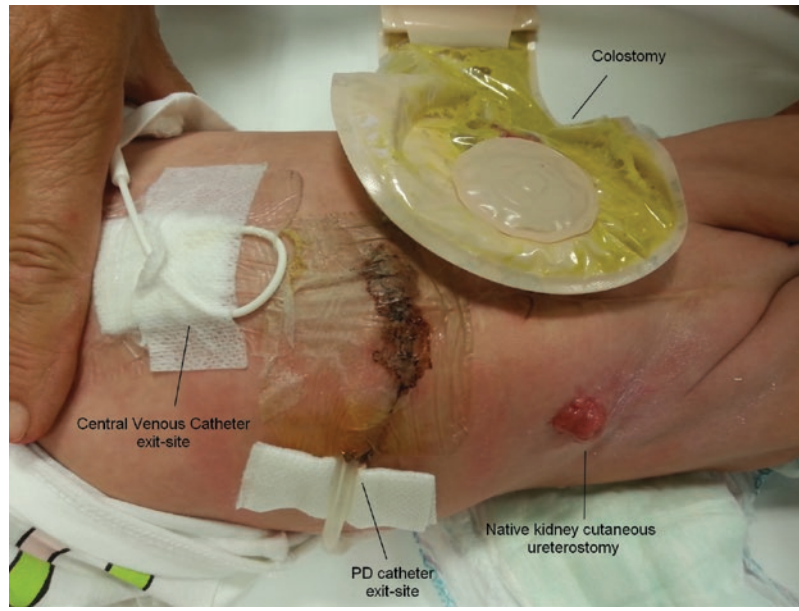

Fig. 15.1 Placement of a PD access in infants should often take into account the presence of multiple ostomies

Table 15.1 Key factors for individualizing dialysis prescription in infants

1. Exchange volume	The size of the peritoneal cavity, the weight of the infant, feeding difficulties, presence of pulmonary disease, and the degree of uremic toxicity may affect exchange volume The initial exchange volume should be low (300–400 mL/m^2) in order to reduce abdominal pressure resulting in dialysate leakage. It should be slowly increased during the PD course to a maximum of 600–800 mL/m^2 Low fill volumes are safer for infants but result in poor clearance and low UF and induce a hyper-permeable exchange (functional hyperpermeability) Automated PD can be performed in infants with fill volumes greater than 100 ml using pediatric tubing and standard cyclers with pediatric software. The use of smaller fill volumes (<50–60 mL) may lead to several pitfalls. For infants with fill volumes of <100 mL, short-term dialysis needs to be performed manually with the use of commercially available two chamber sets with a controlled temperature
2. Dialysate composition	Infants should ideally receive biocompatible fluids with neutral pH to allow for long-term preservation of the peritoneal membrane function. In some infants, the use of bicarbonate-containing solution can result in alkalosis, with subsequent hypoventilation and hypercapnia. In these cases, a lower buffer content dialysate is recommended An initial dialysis solution of 1.5% dextrose concentration should be used, but polyuric infants may absorb fluid from low glucose exchanges, whereas anuric children may require higher glucose fluids for adequate UF. The use of icodextrin in infants may result in poor efficacy, due to its enhanced absorption from a peritoneal membrane with physiological high permeability (high pore density)
3. Time and number of exchanges	Infants require shorter dwell times (30–40 min), more frequent exchanges (12–16) and longer duration of dialysis (10–12 h) than older children
4. Monitoring fluid balances	Infants and small children receiving chronic PD are particularly prone to chronic hypotension, because of the risk for hyponatremic hypovolemia that is related to their primary renal disease (salt losing nephropathies), specific nutritional needs, and peritoneal membrane characteristics Accurate record of body weight and blood pressure and frequent assessment of "dry weight" are essential to avoid high glucose concentration PD solutions and excessive UF In infants undergoing chronic PD, the systolic BP levels should be targeted at least at the 50th percentile adjusted for age, gender, and height In case of intercurrent illness or dehydration, infants treated with PD should be carefully evaluated with respect to opportunities to initiate intravenous rehydration and to modify the dialysis prescription (reduced treatment time, increased dwell time, minimized dialysate glucose content, long low-glucose daytime dwell for resorption of fluid and electrolytes on demand)

use of a weight-based fill volume results in a relatively low fill volume, which can result in inadequate ultrafiltration and reduced dialysis efficiency due to two main mechanisms: (1) the development of "functional hyperpermeability," characterized by apparent ultrafiltration failure secondary to enhanced lymphatic uptake and the rapid loss of the glucose-related osmotic gradient, and (2) the "geometry of diffusion," a concept that addresses the rapid equilibration of solute that occurs across the peritoneal membrane when using small fill volumes [35]. In contrast, the provision of an exchange volume scaled to body surface area (BSA) takes into consideration the age-independent relationship of BSA to peritoneal surface area and makes the fill volume homogeneous across all ages [36].

Peritoneal blood and lymphatic vessel density decreases with age, from the highest levels in infancy; thus, solute removal rates decrease proportionately [37]. This situation also leads to a reduced ultrafiltration capacity because of the increased resorption speed of the osmotic agent, so infants require shorter dialysis cycles than do older children to maintain the osmotic gradient.

Typically, initial dialysis exchange volumes in an infant should be 300–400 mL/m^2 and are increased as clinically warranted and tolerated. Accordingly, the recommended maintenance exchange fill volume for patients below age 2 years is generally 600–800 mL/m^2 [24], to maintain the intraperitoneal pressure between 8 and 10 cm of water [38]. A high intraperitoneal hydrostatic pressure counteracts ultrafiltration,

interferes with food intake, and increases the risk of hernia formation, leakage, and emesis/gastroesophageal reflux.

The lower dialysate fill volume that is employed in the neonate generally necessitates the use of manual exchanges early in the course of PD, with the use of commercially available two chamber sets that allow inflow and outflow volumes to be measured with an accuracy of 1 mL. In this setting, dwell times are initially every 30–60 min, and the dialysis is provided continuously, a schedule that most often requires a one-to-one level of nursing support. Manual exchanges in infants should be performed in a hospital setting, and infants are seldom discharged home until the infant is able to tolerate fill volumes larger than 100 mL and automated PD (APD) using cyclers can be performed. APD is typically conducted at night over a 10–12 h period with or without a single daytime exchange. The last (daytime) fill volume should be one-half the night fill volume and may be required, for example, in cycling PD patients with a high solute load or when clearance is not sufficient. However, it should be recognized that daytime exchanges with glucose containing dialysis solutions might contribute to early satiety or anorexia, due to feelings of fullness from the indwelling dialysate, or the adverse effect of absorption of dialysate glucose on appetite.

The composition of PD solutions is important, and the use of dialysate with the highest dextrose concentrations should be restricted because of the associated risk of complications such as encapsulating peritoneal sclerosis, a particularly serious issue because of the potential long-term need of a functional peritoneum for the youngest patients [39]. Guidelines from the European Pediatric Dialysis Working (EPDW) Group recommend the use of biocompatible multichambered PD fluids, which are low in glucose degradation products (GDP) and reduce lactate exposure [40]. The choice of PD solutions is largely dependent upon their availability in different regions of the world. In the United States, only lactate-buffered solutions containing either glucose or icodextrin as the osmotic agent, are available, while additional bicarbonate-buffered solutions are available in Europe and other areas. Given that small infants might have many years of ESRD ahead, the use of the new, more biocompatible dialysis solutions may prove to be particularly beneficial to the pediatric patient population, although this remains to be proven by well-conducted trials in both children and adults. Hass et al. did demonstrate an improved correction of acidosis in a small cohort of pediatric patients switched to BicaVera® (Fresenius Medical Care, Bad Homburg, Germany) – a 34 mmol/L bicarbonate solution [41]. Additionally, Fischbach demonstrated decreased inflow pain with Physioneal® (bicarbonate-based; Baxter Healthcare, McGaw Park, Illinois, USA) versus Dianeal® (lactate-based; Baxter Healthcare, McGaw Park, Illinois, USA). The use of Physioneal® was also associated with a lower IPP, which could improve clinical tolerance in cases where larger fill volumes are necessary [42]. In small patients using PD with bicarbonate-containing solutions, consideration of sleep-disordered breathing is important as subsequent metabolic alkalosis can potentially lead to hypoventilation and hypercapnia [43].

Compared to adults, icodextrin (Extraneal®) is rarely employed in place of dextrose as the osmotic agent in PD solutions for infants and young children, with rare published reports. Whereas de Boer et al. showed that in 11 children (median age 10.3 years), a 12 h exchange with 7.5% icodextrin produced ultrafiltration comparable to a 3.86% dextrose solution [44], Dart et al. reported poor ultrafiltration in very young children (median age 2.8 years) with its use [45]. This poor efficacy was due to enhanced absorption of icodextrin, with half of the patients showing absorption even when dwell times were reduced from 10 to 6 h. The higher density of lymphatic vessels in young infants provides a morphological correlate to these functional observations [37].

Given the substantial nutritional needs of this patient population, amino acid-based solutions would seem to be a natural choice. Some, but not all, of the few studies that have been performed in pediatrics have demonstrated an improved nutritional state using these solutions. Although the

use of glucose and amino acid admixtures to ensure the effective incorporation of the additional nitrogen load into protein was associated with promising preliminary results in eight children a decade ago, little additional research on this topic has been conducted with children [46]. In large part, this may be because similar outcomes can be achieved more physiologically and possibly more economically with supplemental nasogastric or gastrostomy tube feedings.

A dialysis schedule based on frequent exchanges, short dwell times, and a low fill volume may lead to adequate urea but relatively poor creatinine and phosphate elimination in infants, which appears as a characteristic discrepancy of high Kt/V and low creatinine clearance. Although small-molecule clearance in the form of Kt/V measurements are widely used as a means of evaluating the efficiency of dialysis, care must always be taken to individualize therapy, even in cases of adequate or even high urea clearance, because of the absence of definitive data linking urea clearance to clinical outcome in the infant population. Small solute clearance is just one minor part of the effectiveness of dialysis, and in fact "optimum" dialysis, rather than "adequate" dialysis, is what pediatric nephrologists should aim for with their patients [47]. Outcome parameters that should be taken into consideration include linear growth and weight gain, increase in head circumference, and neurocognitive/psychomotor development. Additional qualitative targets of dialysis adequacy are the avoidance of hypovolemia and sodium depletion, because of their significant influence on growth and associated risk of severe complications [48].

Nutrition and Growth

Meeting the nutritional needs of infants can be challenging, especially with the severely oliguric/anuric patient who must receive formula volumes as high as 150 mL/kg of body weight per day. In the setting of ESRD during infancy, the provision of adequate nutrition takes on particular importance because the neonatal/infant period is typically characterized by accelerated brain growth and a linear growth rate of nearly 25 cm/year. Remarkably, half of postnatal brain growth normally takes place in the first year of life, and one-third of the normal final adult height is achieved during the initial 2 years of life [49].

However, infants with ESRD can lose more than two standard deviation score (SDS) of height and adversely impact their final height if their clinical status is compromised by suboptimal care and/or complications of their disorder [50]. There is also data linking poor growth with mortality in children with ESRD. Both Furth et al. [51] and Wong et al. [52] demonstrated an independent association between a decrease in height-SDS and an increased risk of death, with impaired growth likely serving as a surrogate of overall well-being. Encouragingly, longitudinal analysis from the ESPN/ERA-EDTA Registry demonstrated that although final height remains suboptimal in small children with ESRD, it has consistently improved over time from −2.12 SDS in children 0–4 years of age who started dialysis before 1990 to −1.72 SDS among those starting dialysis between 1990 and 1999 [53].

Most noteworthy is the fact that this early period of growth is primarily dependent upon the provision of optimal nutrition, with the growth hormone/insulin-like growth factor (IGF) axis having less importance when compared to its influence later in life. KDOQI pediatric nutrition guidelines provide recommendations for the content and frequency of monitoring infants/young children for growth/nutrition status and recommend that patients with ESRD receive 100% of the estimated energy requirements (EER) for chronological age, with adjustments based on changes in either weight or growth [48].

There are several nutritional considerations that need to be addressed when PD is conducted. Specifically, neonates and infants can experience excessive losses of protein via PD, with studies demonstrating average losses of 250 mg of protein per kg of body weight or almost twice the peritoneal protein losses seen in older children [54]. In order to avoid the negative consequences of protein depletion, current guidelines recommend an allowance for dietary protein of at least 1.8 g/kg/day for the first 6 months of life, 1.5 g/

kg/day for months 7–12, and 1.3 g/kg/day for 1–3 years, taking into account the dietary reference intakes and peritoneal losses. In the case of congenital nephrotic syndrome, in which a bilateral nephrectomy has not been performed, ongoing urinary losses of protein also need to be accounted for [55].

Infants receiving PD also experience excessive sodium (Na) losses across the peritoneal membrane, due to the need for high ultrafiltration rates in relation to body weight. As a rule of thumb, 80 mmol sodium is removed per liter of ultrafiltrate (UF). Hence, an anuric 5 kg infant with 300 mL daily UF will lose almost 5 mmol/kg Na per day, more than twice the daily urine losses of a healthy child. If the child receives 500 mL standard formula milk per day, the Na intake will only be about 3–10 mmol. At normal serum Na concentrations, the Na losses from UF are normally greater than the quantity ingested from infant formula. This may result in a negative Na balance until a steady state is achieved at a low serum Na concentration. Without adequate supplementation (Table 15.2), the consequences of the resultant hyponatremia, low intravascular volume, and systemic arterial hypotension can be catastrophic and include both blindness due to anterior ischemic optic neuropathy and cerebral edema [56].

In most cases, the nutritional targets defined by the guidelines for neonates and young infants on PD are not achievable without the implementation of either nasogastric (NG) or G-tube feeding. Children with ESRD suffer from poor appetite and early satiety that may be, in part, due to elevated circulating concentrations of proinflammatory cytokines and increased levels of hormones involved in energy balance (i.e., ghrelin and obestatin) [57, 58]. The generation of an increased IPP secondary to the presence of dialysis fluid might also play a role. Compounding the problem is a high rate of poor gastrointestinal motility and gastroesophageal reflux, which can lead to the loss of up to one-third of feeding volumes via vomiting [57, 59]. Thus, the need to allow feeds to be provided over extended periods of time (e.g., nocturnal drip feeds) mandates the use of tube feedings. Not surprisingly, the institution of tube feeding can also help alleviate the intolerable stress placed on families, in which sufficient oral intake cannot be achieved and growth suffers.

Whereas historically NG tubes were preferentially used because of the simplicity of placement (although not necessarily simple from the perspective of the parent and patient), frequently associated complications of this approach to therapy, in addition to the unsightly appearance, include recurrent emesis, nasal trauma associated with tube replacement, and inhibition of the normal development of oral motor skills [60]. On the other hand, G-tubes/buttons are not as frequently associated with the development of altered oral motor skills, are not regularly associated with emesis, and are not visible. They also offer the advantage of being available for prolonged use into the post-renal transplant period, where they can be essential to ensure proper hydration and enhance medication administration in the young infant [61].

The use of enteral nutrition has been associated with improved linear growth in infants on PD, but this outcome is not universal [62]. In fact, a significant increase in weight-for-age and body mass index-for-age, but not height-for-age has been reported in children with ESRD after G-tube feeding, and 50% of tube-fed subjects were overweight or obese at the most recent evaluation [63]. Although recombinant human growth hormone (rhGH) has not been adequately investigated in infants, small trials suggest that very early treatment with rhGH in patients with early-onset ESRD may improve growth [64]. Institution of rhGH in the first year of life might be consid-

Table 15.2 Method for estimating sodium needs in anuric infants on PD

	Age-related dietary reference intake		Losses from ultrafiltration
Total daily sodium requirements (mmol) =	0–6 mo = (0.9 × kg of body weight) 7–12 mo = (1.7 × kg of body weight)	+	(8 × [ml of UF/100])

ered in young infants, who are failing to grow adequately despite the provision of an adequate dietary intake.

Complications

Several studies indicate young age as a risk factor for infectious complications, morbidity, and mortality in children on dialysis. The most common complication associated with PD continues to be peritonitis, which is also the most frequent cause for hospitalization in children receiving PD [65]. On the basis of previous studies describing infant dialysis, cohort-specific peritonitis incidence ranges from 0.58 to 1.7 episodes per patient-year [1–3]. In the 2011 annual report of the North American Pediatric Renal Trials and Collaborative studies (NAPRTCS), which includes data collected over a 20-year period, a total of 4248 episodes of peritonitis in 6658 years of follow-up are reported, yielding an annualized rate of 0.64 or 1 episode every 18.8 months [12]. The annualized rate decreases with the age of the patients, with the youngest (<1 year) having an annualized rate of 0.79, while children older than 12 years have a rate of 0.57. The occurrence of peritonitis is associated with high mortality and can also impact on structure and function of the peritoneal membrane, thus reducing the long-term availability of effective PD in children [65].

Several risk factors can influence the incidence of peritonitis during infancy, and an understanding of these is important if one aims to optimize prevention and patient outcome. Surgical expertise and antibiotic prophylaxis are keys to minimize the risks for early-onset peritonitis after PD catheter insertion [27]. As mentioned before, the catheter design associated with a lower risk of infection in children appears to be the double-cuffed swan-neck catheter, with its inherent downward-directed exit-site. However, infants with limited subcutaneous tissue of the abdominal wall, particularly if hypoproteinemic, are at risk for distal cuff extrusion [66], with a subsequent higher risk of leakage, exit-site infection, and eventually peritonitis. This risk can be reduced by delaying the onset of dialysis for 2–3 weeks after implantation [67]. Some authors have also suggested that regular monitoring of intraperitoneal pressure in infants on PD might help prevent the development of hernias from anatomically weak sites [68]. Concerns also exist that a downward exit-site may be a risk factor for infections in small children using diapers. The proximity of the catheter exit-site to the diaper region or to gastrostomy/vesicostomy/nephrostomy sites has been associated with a higher incidence of gram-negative peritonitis (“diaper peritonitis”) as compared with older children [69]. In some centers, this issue has been successfully addressed by placing the PD catheter exit-site outside the diaper area, in the presternal area [55].

Infants on chronic PD with oliguria frequently have hypoproteinemia and hypogammaglobulinemia resulting from malnutrition and peritoneal protein losses [3]. The presence of hypogammaglobulinemia is commonly complicated by the development of recurrent infections and, specifically, might be a risk factor for the development of bacterial peritonitis in patients receiving PD. There is no evidence for routine administration of prophylactic intravenous immunoglobulins in all infants [70], but replacement therapy should be considered if very low immunoglobulins levels (<4 g/L) are found [24, 71].

Infants who develop peritonitis early after PD catheter implantation and while hospitalized have different clinical characteristics compared to those who only develop peritonitis as an outpatient. In a recent report from the SCOPE collaborative, Zaritsky et al. examined the epidemiology of peritonitis in 156 infants, who had a PD catheter placed in the first year of life [33]. The study included patients who started chronic PD as an inpatient and remained hospitalized. The authors found that 65 out of 156 infants (42%) had at least one episode of bacterial peritonitis within 1 year after PD catheter implantation, resulting in an overall annualized peritonitis rate of 0.76 episodes per patient-year. An extremely high incidence of peritonitis was observed early, during the initial hospital stay after PD catheter placement (1.73 episodes per patient-year). The diag-

nosis of polycystic kidney disease (namely, ARPKD), history of pulmonary hypoplasia, the use of a curled PD catheter or plastic adaptor, nephrectomy prior to or concurrent with PD catheter insertion, and G-tube insertion after catheter placement were significantly more common in patients who experienced peritonitis compared to those without peritonitis. Infants with an episode of peritonitis during their initial hospitalization were also younger and were more likely to have a diagnosis of ARPKD and a history of pulmonary hypoplasia, as compared to those patients who developed peritonitis only as outpatients. Moreover, the vast majority of inhospital peritonitis was associated with the prior need for nephrectomy, perhaps a surrogate for the diagnosis of ARPKD, a condition associated with severe comorbidities, a higher risk of infection, and mortality. In this disease, unilateral or bilateral nephrectomy often represents an inevitable therapeutic approach to ameliorate respiratory impairment and nutritional management and also to facilitate PD initiation. The relative lower incidence of outpatient peritonitis in this study may reflect an exposure to fewer or less severe risk factors in nonhospitalized infants but may also be due to the use of quality improvement methods aimed at implementing standardized practices for PD catheter care by trained staff and parents according to the SCOPE bundles [72, 73].

Hospitalization and Long-Term Outcomes

Hospitalization rates for infants on PD are higher than that for older children [3]. In a NAPRTCS analysis, Carey et al. demonstrated that – while on maintenance dialysis – about 75% of children younger than 2 years required hospitalization [10]. An analysis of the ESPN/ERA-EDTA Registry data showed a gradual decrease over 30 years of follow-up (from 1980 to 2010) in infection-related hospitalizations in children on PD, except for peritonitis [74]. The greater likelihood of longer hospitalization and the increased risk of complications, potentially resulting in additional surgical procedures, are factors that significantly impact the biological and economic cost of dialysis for infants. It follows that efforts should be directed to implement all strategies aimed at preventing and reducing peritonitis in infant PD, including the use of improvement science models [73].

Whereas mortality data have improved in children overall on dialysis over the past few decades, the highest mortality rates are seen in those patients who receive dialysis during the first year of life [75]. The most recent NAPRTCS results, based on data collected from 2000 to 2012, show a 3-year patient survival of 78.6% and 84.6% in patients who initiate dialysis during the first month and first year of life, respectively [4]. Combined data from four other registries shows a slightly lower survival rate for those patients who initiated chronic dialysis within the first month of life with 2- and 5-year survival rates of 81% and 76%, respectively [15]. Finally, a recent retrospective review of the USRDS database for data on infants who initiated PD from 1990 to 2014 has shown an increased risk for mortality in all infants who initiated PD in the earlier initiation era (1990–1999) vs the later era (2000–2014) (aHR of 1.95), for females vs males (aHR 1.43), and for those with a primary diagnosis of cystic kidney diseases vs CAKUT (aHR 1.84). In 2000–2014, patient survival at 1 and 5 years was 86.8% and 74.6% for those who initiated PD as neonates and 89.6% and 79.3% for those who did so as older infants [6]. Overall, the most commonly identified causes of death on dialysis were cardiorespiratory disease (25.8%) and infection (22.8%).

The most important predictor of mortality in this PD patient age group remains the presence of nonrenal disease [50, 75–77]. Wood et al., and later Van Stralen et al., clearly showed that comorbidities such as anuria, neurological complications, and pulmonary hypoplasia were associated with the greatest risk of mortality in infants undergoing dialysis [15, 76]. A recent publication of the IPPN examining 1830 patients aged 0–19 years found that the presence of at least one comorbidity was associated with a 4-year survival of 73% versus 90% survival in those with-

out a comorbidity ($p < 0.001$) [17]. Data on the influence of comorbidities on survival is likely impacted by regional differences, as countries with a lower gross national income appear to be more restrictive in terms of making PD available to very young patients and those with significant extrarenal complications [13].

Conclusions

Peritoneal dialysis has long been considered the modality of choice when treating neonates and infants with ESRD needing chronic RRT. Its popularity and success largely derive from its simplicity and effectiveness in even the smallest patients.

PD during infancy helps to meet the nutritional demands of patients through the effective removal of solute and fluid. The substantial nutritional needs of this patient population also require an enteral nutrition program to address the marked increases in height, weight, and brain development that the young infant should be experiencing.

Dialysis access-associated infections, specifically peritonitis, are leading causes of hospitalization and death among infants receiving PD. Clinical practice improvement techniques and standardization have been shown to lower infection in older children [78] and should be included in all pediatric PD programs.

Over the last decade, there has been a steady improvement in survival rates with recent studies, showing excellent survival 1 year after therapy initiation, even in patients who first receive dialysis when they are less than 1 month of age. Nevertheless, ethical issues/concerns pertaining to the provision of dialysis remain present, especially when extrarenal comorbidities exist.

References

1. Laakkonen H, Hölttä T, Lönnqvist T, Holmberg C, Rönnholm K. Peritoneal dialysis in children under two years of age. Nephrol Dial Transplant. 2008;23(5):1747–53.
2. Hijazi R, Abitbol CL, Chandar J, Seeherunvong W, Freundlich M, Zilleruelo G. Twenty-five years of infant dialysis: a single center experience. J Pediatr. 2009;155(1):111–7. https://doi.org/10.1016/j.jpeds.2009.01.007.
3. Vidal E, Edefonti A, Murer L, Gianoglio B, Maringhini S, Pecoraro C, Sorino P, Leozappa G, Lavoratti G, Ratsch IM, Chimenz R, Verrina E, Italian Registry of Paediatric Chronic Dialysis. Peritoneal dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. Nephrol Dial Transplant. 2012;27(1):388–95. https://doi.org/10.1093/ndt/gfr322.
4. Carey WA, Martz KL, Warady BA. Outcome of patients initiating chronic peritoneal dialysis during the first year of life. Pediatrics. 2015;136(3):e615–22.
5. Vidal E, van Stralen KJ, Chesnaye NC, Bonthuis M, Holmberg C, Zurowska A, Trivelli A, Da Silva JEE, Herthelius M, Adams B, Bjerre A, Jankauskiene A, Miteva P, Emirova K, Bayazit AK, Mache CJ, Sánchez-Moreno A, Harambat J, Groothoff JW, Jager KJ, Schaefer F, Verrina E, ESPN/ERA-EDTA Registry. Infants requiring maintenance dialysis: outcomes of hemodialysis and peritoneal dialysis. Am J Kidney Dis. 2017;69(5):617–25. https://doi.org/10.1053/j.ajkd.2016.09.024.
6. Sanderson KR, Yu Y, Dai H, Willig LK, Warady BA. Outcomes of infants receiving chronic peritoneal dialysis: an analysis of the USRDS registry. Pediatr Nephrol. 2019;34(1):155–62. https://doi.org/10.1007/s00467-018-4056-6.
7. Paglialonga F, Consolo S, Pecoraro C, Vidal E, Gianoglio B, Puteo F, Picca S, Saravo MT, Edefonti A, Verrina E. Chronic haemodialysis in small children: a retrospective study of the Italian Pediatric Dialysis Registry. Pediatr Nephrol. 2016;31(5):833–41. https://doi.org/10.1007/s00467-015-3272-6.
8. Shroff R, Wright E, Ledermann S, Hutchinson C, Rees L. Chronic hemodialysis in infants and children under 2 years of age. Pediatr Nephrol. 2003;18(4):378–83.
9. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. Pediatr Nephrol. 1997;11(1):74–7.
10. Carey WA, Talley LI, Sehring SA, Jaskula JM, Mathias RS. Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American Pediatric Renal Trials and Collaborative Studies special analysis. Pediatrics. 2007;119(2):e468–73.
11. ANZDATA Registry. 41st report, Chapter 11: Paediatric patients with end stage kidney disease requiring renal replacement therapy. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. 2018. Available at: http://www.anzdata.org.au.
12. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) Annual Report, 2011. https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf. Accessed 15 Dec 2018.

13. Schaefer F, Borzych-Duzalka D, Azocar M, Munarriz RL, Sever L, Aksu N, Barbosa LS, Galan YS, Xu H, Coccia PA, Szabo A, Wong W, Salim R, Vidal E, Pottoore S, Warady BA, IPPN Investigators. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry. Perit Dial Int. 2012;32(4):399–409.
14. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. JAMA. 2013;309(18):1921–9. https://doi.org/10.1001/jama.2013.4208.
15. van Stralen KJ, Borzych-Dużalka D, Hataya H, Kennedy SE, Jager KJ, Verrina E, Inward C, Rönnholm K, Vondrak K, Warady BA, Zurowska AM, Schaefer F, Cochat P, ESPN/ERA-EDTA Registry; IPPN Registry; ANZDATA Registry; Japanese RRT Registry. Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. Kidney Int. 2014;86(1):168–74. https://doi.org/10.1038/ki.2013.561.
16. van Stralen KJ, Tizard EJ, Jager KJ, Schaefer F, Vondrak K, Groothoff JW, Podracká L, Holmberg C, Jankauskiené A, Lewis MA, van Damme-Lombaerts R, Mota C, Niaudet P, Novljan G, Peco-Antic A, Sahpazova E, Toots U, Verrina E. Determinants of eGFR at start of renal replacement therapy in paediatric patients. Nephrol Dial Transplant. 2010;25(10):3325–32. https://doi.org/10.1093/ndt/gfq215.
17. Neu AM, Sander A, Borzych-Duzalka D, Watson AR, Vallés PG, Ha IS, Patel H, Askenazi D, Balasz-Chmielewska I, Lauronen J, Groothoff JW, Feber J, Schaefer F, Warady BA, IPPN Investigators. Comorbidities in chronic pediatric peritoneal dialysis patients: a report of the International Pediatric Peritoneal Dialysis Network. Perit Dial Int. 2012;32(4):410–8.
18. Brunner FP, Fassbinder W, Broyer M, Oulès R, Brynger H, Rizzoni G, Challah S, Selwood NH, Dykes SR, Wing AJ. Survival on renal replacement therapy: data from the EDTA Registry. Nephrol Dial Transplant. 1988;3(2):109–22.
19. Mehler K, Gottschalk I, Burgmaier K, Volland R, Büscher AK, Feldkötter M, Keller T, Weber LT, Kribs A, Habbig S. Prenatal parental decision-making and postnatal outcome in renal oligohydramnios. Pediatr Nephrol. 2018;33(4):651–9. https://doi.org/10.1007/s00467-017-3812-3.
20. Mavroudis C, Mavroudis CD, Farrell RM, Jacobs ML, Jacobs JP, Kodish ED. Informed consent, bioethical equipoise, and hypoplastic left heart syndrome. Cardiol Young. 2011;21(Suppl 2):133–40. https://doi.org/10.1017/S1047951111001715.
21. Willem L, Knops N, Mekahli D, Cochat P, Edefonti A, Verrina E, Groothoff J, Lagae L, Pirenne J, Dobbels F, Borry P, Van Geet C, Levtchenko E. Renal replacement therapy in children with severe developmental disability: guiding questions for decision-making. Eur J Pediatr. 2018;177(12):1735–43. https://doi.org/10.1007/s00431-018-3238-3.
22. Geary DF. Attitudes of pediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133(1):154–6.
23. Teh JC, Frieling ML, Sienna JL, Geary DF. Attitudes of caregivers to management of end-stage renal disease in infants. Perit Dial Int. 2011;31(4):459–65. https://doi.org/10.3747/pdi.2009.00265.
24. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ, European Paediatric Dialysis Working Group. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). Pediatr Nephrol. 2013;28(9):1739–48. https://doi.org/10.1007/s00467-012-2300-z.
25. Rusthoven E, van de Kar NA, Monnens LA, Schröder CH. Fibrin glue used successfully in peritoneal dialysis catheter leakage in children. Perit Dial Int. 2004;24(3):287–9.
26. Borzych-Duzalka D, Aki TF, Azocar M, White C, Harvey E, Mir S, Adragna M, Serdaroglu E, Sinha R, Samaille C, Vanegas JJ, Kari J, Barbosa L, Bagga A, Galanti M, Yavascan O, Leozappa G, Szczepanska M, Vondrak K, Tse KC, Schaefer F, Warady BA, International Pediatric Peritoneal Dialysis Network (IPPN) Registry. Peritoneal dialysis access revision in children: causes, interventions, and outcomes. Clin J Am Soc Nephrol. 2017;12(1):105–12. https://doi.org/10.2215/CJN.05270516.
27. Warady BA, Bakkaloglu S, Newland J, Cantwell M, Verrina E, Neu A, Chadha V, Yap HK, Schaefer F. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86. https://doi.org/10.3747/pdi.2011.00091.
28. Chadha V, Jones LL, Ramirez ZD, Warady BA. Chest wall peritoneal dialysis catheter placement in infants with a colostomy. Adv Perit Dial. 2000;16:318–20.
29. Cribbs RK, Greenbaum LA, Heiss KF. Risk factors for early peritoneal dialysis catheter failure in children. J Pediatr Surg. 2010;45(3):585–9. https://doi.org/10.1016/j.jpedsurg.2009.06.019.
30. Conlin MJ, Tank ES. Minimizing surgical problems of peritoneal dialysis in children. J Urol. 1995;154(2 Pt 2):917–9.
31. Radtke J, Schild R, Reismann M, Ridwelski RR, Kempf C, Nashan B, Rothe K, Koch M. Obstruction of peritoneal dialysis catheter is associated with catheter type and independent of omentectomy: a comparative data analysis from a transplant surgical and a pediatric surgical department. J Pediatr Surg. 2018;53(4):640–3. https://doi.org/10.1016/j.jpedsurg.2017.06.028.
32. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25(4):699–704. https://doi.org/10.1007/s00467-009-1309-4.
33. Zaritsky JJ, Hanevold C, Quigley R, Richardson T, Wong C, Ehrlich J, Lawlor J, Rodean J, Neu A, Warady

BA, SCOPE Investigators. Epidemiology of peritonitis following maintenance peritoneal dialysis catheter placement during infancy: a report of the SCOPE collaborative. Pediatr Nephrol. 2018;33(4):713–22. https://doi.org/10.1007/s00467-017-3839-5.
34. von Schnakenburg C, Feneberg R, Plank C, Zimmering M, Arbeiter K, Bald M, Fehrenbach H, Griebel M, Licht C, Konrad M, Timmermann K, Kemper MJ. Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int. 2006;26(1):69–77.
35. Fischbach M, Terzic J, Menouer S, Haraldsson B. Optimal volume prescription for children on peritoneal dialysis. Perit Dial Int. 2000;20(6):603–6.
36. Warady BA, Alexander SR, Hossli S, Vonesh E, Geary D, Watkins S, Salusky IB, Kohaut EC. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol. 1996;7(11):2385–91.
37. Schaefer B, Bartosova M, Macher-Goeppinger S, Ujszaszi A, Wallwiener M, Nyarangi-Dix J, Sallay P, Burkhardt D, Querfeld U, Pfeifle V, Lahrmann B, Schwenger V, Wühl E, Holland-Cunz S, Schaefer F, Schmitt CP. Quantitative histomorphometry of the healthy peritoneum. Sci Rep. 2016;6:21344. https://doi.org/10.1038/srep21344.
38. Fischbach M, Terzic J, Laugel V, Escande B, Dangelser C, Helmstetter A. Measurement of hydrostatic intraperitoneal pressure: a useful tool for the improvement of dialysis dose prescription. Pediatr Nephrol. 2003;18(10):976–80.
39. Vidal E, Edefonti A, Puteo F, Chimenz R, Gianoglio B, Lavoratti G, Leozappa G, Maringhini S, Mencarelli F, Pecoraro C, Ratsch IM, Cannavò R, De Palo T, Testa S, Murer L, Verrina E, Italian Registry of Pediatric Chronic Dialysis. Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients: the experience of the Italian Registry of Pediatric Chronic Dialysis. Nephrol Dial Transplant. 2013;28(6):1603–9. https://doi.org/10.1093/ndt/gft061.
40. Schmitt CP, Bakkaloglu SA, Klaus G, Schröder C, Fischbach M, European Pediatric Dialysis Working Group. Solutions for peritoneal dialysis in children: recommendations by the European Pediatric Dialysis Working Group. Pediatr Nephrol. 2011;26(7):1137–47. https://doi.org/10.1007/s00467-011-1863-4.
41. Haas S, Schmitt CP, Arbeiter K, Bonzel KE, Fischbach M, John U, Pieper AK, Schaub TP, Passlick-Deetjen J, Mehls O, Schaefer F. Improved acidosis correction and recovery of mesothelial cell mass with neutral-pH bicarbonate dialysis solution among children undergoing automated peritoneal dialysis. J Am Soc Nephrol. 2003;14(10):2632–8.
42. Fischbach M, Terzic J, Chauvé S, Laugel V, Muller A, Haraldsson B. Effect of peritoneal dialysis fluid composition on peritoneal area available for exchange in children. Nephrol Dial Transplant. 2004;19(4):925–32.
43. Sharma N, Harvey E, Amin R. Sleep-disordered breathing in 2 pediatric patients on peritoneal dialysis. Perit Dial Int. 2016;36(1):109–12. https://doi.org/10.3747/pdi.2014.00205.
44. de Boer AW, Schröder CH, van Vliet R, Willems JL, Monnens LA. Clinical experience with icodextrin in children: ultrafiltration profiles and metabolism. Pediatr Nephrol. 2000;15(1–2):21–4.
45. Dart A, Feber J, Wong H, Filler G. Icodextrin reabsorption varies with age in children on automated peritoneal dialysis. Pediatr Nephrol. 2005;20(5):683–5.
46. Canepa A, Verrina E, Perfumo F, Carrea A, Menoni S, Delucchi P, Gusmano R. Value of intraperitoneal amino acids in children treated with chronic peritoneal dialysis. Perit Dial Int. 1999;19(Suppl 2):S435–40.
47. Rees L. Assessment of dialysis adequacy: beyond urea kinetic measurements. Pediatr Nephrol. 2019;34(1):61–9. https://doi.org/10.1007/s00467-018-3914-6.
48. KDOQI Work Group. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53(3 Suppl 2):S11–104. https://doi.org/10.1053/j.ajkd.2008.11.017.
49. Reed RB, Stuart HC. Patterns of growth in height and weight from birth to eighteen years of age. Pediatrics. 1959;24:904–21.
50. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7.
51. Furth SL, Stablein D, Fine RN, Powe NR, Fivush BA. Adverse clinical outcomes associated with short stature at dialysis initiation: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics. 2002;109(5):909–13.
52. Wong CS, Hingorani S, Gillen DL, Sherrard DJ, Watkins SL, Brandt JR, Ball A, Stehman-Breen CO. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int. 2002;61(2):630–7.
53. Harambat J, Bonthuis M, van Stralen KJ, Ariceta G, Battelino N, Bjerre A, Jahnukainen T, Leroy V, Reusz G, Sandes AR, Sinha MD, Groothoff JW, Combe C, Jager KJ, Verrina E, Schaefer F, ESPN/ERA-EDTA Registry. Adult height in patients with advanced CKD requiring renal replacement therapy during childhood. Clin J Am Soc Nephrol. 2014;9(1):92–9. https://doi.org/10.2215/CJN.00890113.
54. Quan A, Baum M. Protein losses in children on continuous cycler peritoneal dialysis. Pediatr Nephrol. 1996;10(6):728–31.
55. Rönnholm KA, Holmberg C. Peritoneal dialysis in infants. Pediatr Nephrol. 2006;21(6):751–6.
56. Vidal E, Schaefer F. Hypotension in infants on chronic peritoneal dialysis: mechanisms, complications, and management. Adv Perit Dial. 2015;31:54–8.
57. Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. Kidney Int. 2006;69(5):794–7.

58. Monzani A, Perrone M, Prodam F, Moia S, Genoni G, Testa S, Paglialonga F, Rapa A, Bona G, Montini G, Edefonti A. Unacylated ghrelin and obestatin: promising biomarkers of protein energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2018;33(4):661–72. https://doi.org/10.1007/s00467-017-3840-z.
59. Rees L. Long-term peritoneal dialysis in infants. Perit Dial Int. 2007;27(Suppl 2):S180–4.
60. Dello Strologo L, Principato F, Sinibaldi D, Appiani AC, Terzi F, Dartois AM, Rizzoni G. Feeding dysfunction in infants with severe chronic renal failure after long-term nasogastric tube feeding. Pediatr Nephrol. 1997;11(1):84–6.
61. Wong H, Mylrea K, Cameron A, Manion I, Bass J, Feber J, Filler G. Caregiver attitudes towards gastrostomy removal after renal transplantation. Pediatr Transplant. 2005;9(5):574–8.
62. Rees L, Azocar M, Borzych D, Watson AR, Büscher A, Edefonti A, Bilge I, Askenazi D, Leozappa G, Gonzales C, van Hoeck K, Secker D, Zurowska A, Rönnholm K, Bouts AH, Stewart H, Ariceta G, Ranchin B, Warady BA, Schaefer F, International Pediatric Peritoneal Dialysis Network (IPPN) Registry. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22(12):2303–12. https://doi.org/10.1681/ASN.2010020192.
63. Sienna JL, Saqan R, Teh JC, Frieling ML, Secker D, Cornelius V, Geary DF. Body size in children with chronic kidney disease after gastrostomy tube feeding. Pediatr Nephrol. 2010;25(10):2115–21. https://doi.org/10.1007/s00467-010-1586-y.
64. Mencarelli F, Kiepe D, Leozappa G, Stringini G, Cappa M, Emma F. Growth hormone treatment started in the first year of life in infants with chronic renal failure. Pediatr Nephrol. 2009;24(5):1039–46. https://doi.org/10.1007/s00467-008-1084-7.
65. Chadha V, Schaefer FS, Warady BA. Dialysis-associated peritonitis in children. Pediatr Nephrol. 2010;25(3):425–40. https://doi.org/10.1007/s00467-008-1113-6.
66. Rinaldi S, Sera F, Verrina E, Edefonti A, Perfumo F, Sorino P, Zacchello G, Andreetta B, Ardissino G, Bassi S, Capasso G, Caringella DA, Gianoglio B, Gusmano R, Rizzoni G. The Italian Registry of Pediatric Chronic Peritoneal Dialysis: a ten-year experience with chronic peritoneal dialysis catheters. Perit Dial Int. 1998;18(1):71–4.
67. Patel UD, Mottes TA, Flynn JT. Delayed compared with immediate use of peritoneal catheter in pediatric peritoneal dialysis. Adv Perit Dial. 2001;17:253–9.
68. Aranda RA, Romão Júnior JE, Kakehashi E, Domingos W, Sabbaga E, Marcondes M, Abensur H. Intraperitoneal pressure and hernias in children on peritoneal dialysis. Pediatr Nephrol. 2000;14(1):22–4.
69. Warady BA, Feneberg R, Verrina E, Flynn JT, Müller-Wiefel DE, Besbas N, Zurowska A, Aksu N, Fischbach M, Sojo E, Donmez O, Sever L, Sirin A, Alexander SR, Schaefer F, IPPR. Peritonitis in children who receive long-term peritoneal dialysis: a prospective evaluation of therapeutic guidelines. J Am Soc Nephrol. 2007;18(7):2172–9.
70. Lalan S, Dai H, Warady BA. Hypogammaglobulinemia in infants receiving chronic peritoneal dialysis. Pediatr Nephrol. 2017;32(3):503–9. https://doi.org/10.1007/s00467-016-3487-1.
71. Neu AM, Warady BA, Lederman HM, Furth SL, Fivush BA. Hypogammaglobulinemia in infants and young children maintained on peritoneal dialysis. Pediatric Dialysis Study Consortium. Perit Dial Int. 1998;18(4):440–3.
72. Sethna CB, Bryant K, Munshi R, Warady BA, Richardson T, Lawlor J, Newland JG, Neu A, SCOPE Investigators. Risk factors for and outcomes of catheter-associated peritonitis in children: the SCOPE collaborative. Clin J Am Soc Nephrol. 2016;11(9):1590–6. https://doi.org/10.2215/CJN.02540316.
73. Redpath Mahon A, Neu AM. A contemporary approach to the prevention of peritoneal dialysis-related peritonitis in children: the role of improvement science. Pediatr Nephrol. 2017;32(8):1331–41. https://doi.org/10.1007/s00467-016-3531-1.
74. Lofaro D, Vogelzang JL, van Stralen KJ, Jager KJ, Groothoff JW. Infection-related hospitalizations over 30 years of follow-up in patients starting renal replacement therapy at pediatric age. Pediatr Nephrol. 2016;31(2):315–23.
75. Shroff R, Rees L, Trompeter R, Hutchinson C, Ledermann S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2006;21(2):257–64.
76. Wood EG, Hand M, Briscoe DM, Donaldson LA, Yiu V, Harley FL, Warady BA, Ellis EN, North American Pediatric Renal Transplant Cooperative Study. Risk factors for mortality in infants and young children on dialysis. Am J Kidney Dis. 2001;37(3):573–9.
77. Ledermann SE, Scanes ME, Fernando ON, Duffy PG, Madden SJ, Trompeter RS. Long-term outcome of peritoneal dialysis in infants. J Pediatr. 2000;136(1):24–9.
78. Neu AM, Richardson T, Lawlor J, Stuart J, Newland J, McAfee N, Warady BA, SCOPE Collaborative Participants. Implementation of standardized follow-up care significantly reduces peritonitis in children on chronic peritoneal dialysis. Kidney Int. 2016;89(6):1346–54. https://doi.org/10.1016/j.kint.2016.02.015.

Infectious Complications of Peritoneal Dialysis in Children

16

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Introduction

Home peritoneal dialysis (PD) is often the chronic dialysis modality of choice for children with end-stage kidney disease (ESKD), as the inherent flexibility of this modality places fewer restrictions on school and other activities and its daily delivery minimizes dietary and fluid restrictions. Although recent data suggests that hemodialysis is increasingly used at dialysis initiation in children with ESKD in the United States (US), especially in the adolescent population, PD remains the most common dialysis modality utilized worldwide, and its usage is expanding rapidly on a global scale [1–4]. Unfortunately, PD-related infections, which include PD catheter-related infections (infections of the catheter exit-site and tunnel) and peritonitis, remain a frequent and significant complication of PD in children. Data from the United States Renal Data System (USRDS), the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), the International Pediatric Peritoneal Dialysis Network (IPPN) registry of the International Pediatric Dialysis Network (IPDN), and the European Society of Pediatric Nephrology/European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) registry reveal that infectious complications, primarily peritonitis, remain the most frequent cause for hospitalization of children receiving PD, and recurrent peritonitis is a significant reason for technique failure [1–5]. In addition, infection is a leading cause of death in children on PD [1, 2, 5].

Given the high clinical relevance of PD-related infectious complications, pediatric PD specialists around the globe have long collaborated to evaluate the causes, management, and outcomes of PD-related infections by systematically collecting and analyzing clinical information. In 2000, the first guidelines for the prevention and treatment of PD-related infections specifically for children were published by the International Society for Peritoneal Dialysis (ISPD) [6]. Following publication of these largely opinion-based guidelines, the International Pediatric Peritonitis Registry (IPPR) collected detailed data on 501 peritonitis episodes in children from 47 pediatric dialysis centers in Europe, Turkey, Asia, and America between 2001 to 2004 [7, 8].

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This effort was initiated to assess the efficacy and validity of the pediatric guidelines and to enhance existing knowledge regarding the global variability of bacteriology and antibiotic susceptibilities associated with peritonitis in children on PD [7, 8]. Data from that study, and the subsequent IPPN/IPDN Registry, informed the development of updated clinical practice guidelines for the prevention and treatment of PD-related infections in children and adolescents on PD, which were published in 2012 [9]. Those guidelines, and the studies used to develop them, form the basis for much of this chapter.

In 2011, the Standardizing Care to Improve Outcomes in Pediatric End-Stage Renal Disease (SCOPE) collaborative, a quality transformation network of nearly 50 pediatric dialysis centers in the United States, was launched with the goal of reducing PD-related infections by increasing implementation of standardized PD catheter care practices [10]. The care practices, or bundles, included in the SCOPE collaborative were largely derived from the ISPD pediatric guidelines [9, 10]. Data from the SCOPE collaborative, which has demonstrated a significant reduction in peritonitis rates among participating centers, support much of the information included in this chapter's discussion of risk factors and infection prevention [11, 12].

Incidence of PD-Related Infections

Peritonitis rates among children on chronic PD have improved substantially over the past few decades, likely related to technical improvements in connectology, and increased emphasis on training and patient education [13–16]. According to the NAPRTCS 2011 Dialysis Report, the annualized peritonitis rate among children enrolled in that registry decreased from 0.79 episodes per patient year in children who initiated PD between 1992 and 1996 to 0.44 in those children who initiated PD between 2007 and 2010 [1]. Among children participating in the IPPN registry between 2007 and 2018, the annualized rate of peritonitis was 0.44 [17]. Of note, IPPN data did not demonstrate any variation in infection rates between high- and low-resourced regions [8, 17]. Despite these improvements, these peritonitis rates still exceed the rate of 0.17 episodes per patient year reported among 130 Japanese children maintained on chronic PD between 1999 and 2003 [18].

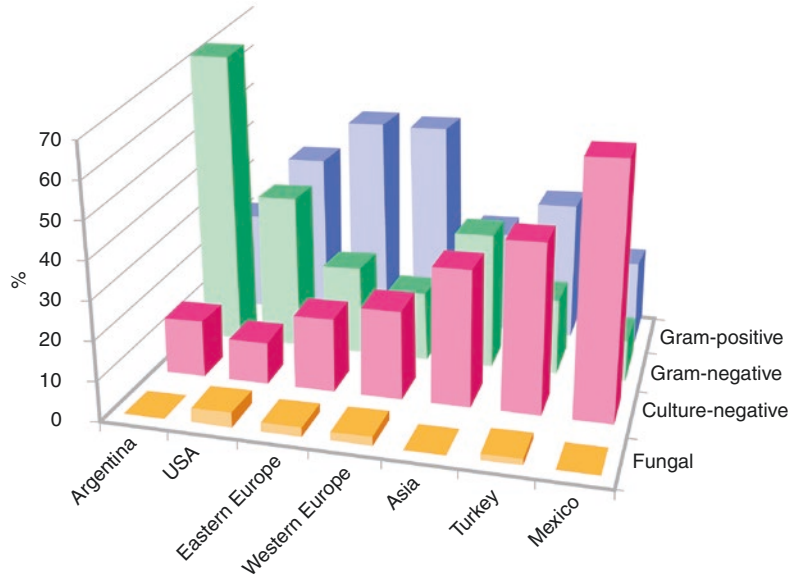
Rates of PD catheter-related infections are less often cited, but data from the IPPN revealed an exit-site/tunnel infection rate of 0.13 infections per patient year among patients enrolled in that registry between 2011 and 2014 [19]. The exit-site/tunnel infection rate among SCOPE participating centers was 0.25 episodes per catheter year during the same period (2011–2014) [20].

To guide quality improvement efforts aimed at reducing PD-related infections, both pediatric and adult ISPD peritonitis guidelines suggest that centers monitor their PD-related infection rates on a regular basis [9, 21, 22]. Organism-specific rates should be monitored as well, as the various organisms may direct improvement efforts to specific aspects of care [9, 21, 22]. For example, an increase in peritonitis rates with skin flora may prompt efforts to increase recognition and appropriate treatment for touch contamination [9, 21–23]. In addition, the antibiotic susceptibilities of the organisms should be monitored, which will allow the development of center-specific empiric antibiotic regimens [9, 21–23]. Population-based peritonitis rates can be misleading, because peritonitis risk is not evenly distributed across the PD population – some patients have few, if any, infections while others experience many. The 4248 episodes of peritonitis reported to the NAPRTCS registry between 1992 and 2001 occurred in fewer than half of the 4430 PD patients enrolled during this period, with 877 patients experiencing only 1 peritonitis episode, 432 experiencing 2 infections, 482 experiencing 3–7 infections, and 53 patients with 8 or more peritonitis episodes [1]. These data emphasize the potential value of expressing the average risk of peritonitis for a dialysis unit as the median of patient-specific peritonitis rates [24].

Microbiology of PD-Related Infections

Peritonitis

The majority of peritonitis episodes in children on PD are caused by bacteria, and historically the percentage of infections caused by fungi has been less than 5% [25]. This trend was confirmed by data from the IPPR, where only 10 of 501 (2%) episodes of peritonitis were due to fungi [26]. Of the remaining episodes, gram-positive organisms were cultured in 44% and gram-negative in 25%, while 31% of peritonitis episodes were associated with a negative bacterial culture [26]. These distributions were confirmed by data from the IPPN/IPDN, which revealed that among the 1456 peritonitis episodes reported to that registry between 2007 and 2014, the culture-negative rate was 33% [19]. Of the culture-positive cases, 63% were caused by gram-positive, 33% by gram-negative and 4% by fungal organisms [19]. The most common causative organisms were coagulase-negative *Staphylococci* (24.7%), *Staphylococcus aureus* (*S. aureus*) (22.2%), *Escherichia coli* (7.7%), *Streptococci* (6.9%), *Pseudomonas* species (6.3%), and *Enterococci* (5.5%) [19]. There was, however, significant regional variability in the distribution of organisms with gram-positive infections predominant in Europe, coagulase-negative *Staphylococci* most common in Eastern Europe, *S. aureus* predominant in Western Europe, and *Enterococci* in Turkey (Fig. 16.1) [8]. Conversely, gram-negative organisms were predominant in Argentina and the United States, where they accounted for 70% and 46% of culture-positive infections, respectively [8]. *Pseudomonas* species were the most common gram-negative organism cultured in the United States, while other gram-negative organisms were more common in Argentina [8]. *S. aureus* and *Staphylococcus epidermidis* (*S. epi*)



Data:							
	Argentina	USA	Eastern Europe	Western Europe	Asia	Turkey	Mexico
Fungal	0	3.61	1.92	2.45	0	1.23	0
Culture-negative	14.81	10.84	19.23	23.31	36	44.37	66
Gram-negative	59.3	40.96	23.1	18.41	36	20.25	11.1
Gram-positive	25.9	44	55.8	55.8	28.6	37.4	22.2

Fig. 16.1 Distribution of causative organisms according to regions among 501 episodes peritonitis reported by the IPPR. (Adapted from Ref. [8])

remain the most frequently isolated organisms in a more recent analysis of more than 2000 episodes of peritonitis reported to the IPPN, with culture-negative peritonitis most common in Turkey and Latin America [17]. This analysis also noted significant regional variation in antibiotic susceptibility for aminoglycosides and methicillin [17]. The SCOPE collaborative reported that among 389 episodes of peritonitis for which culture results were available, 37.8% were due to gram-positive organisms and 19.5% to gram-negative organisms [12]. Thirty (7.7%) fungal infections were reported, while 10.3% of cultures were polymicrobial, and 24.7% of the cultures were negative [12]. *S. epi.* was the most common gram-positive organism, while *Pseudomonas* species were the most common gram-negative organisms identified [12]. It has been proposed that this geographic variability in causative organisms is likely multifactorial in origin and factors may include environmental influences, such as climate and humidity, and variability in PD practices, including exit-site care and the routine use of topical antibiotic prophylaxis [27].

The IPPR discovered not only a wide regional variability in causative organisms but also in the rate of culture-negative peritonitis in their participating sites, representing from 11% to 67% of all center episodes [8]. A survey of the laboratory procedures among the participating centers did not reveal systematic differences in culture technique to explain this variability, but it was hypothesized that issues such as incubation of insufficient effluent volumes, long sample transport times in rural areas, and extreme ambient temperatures may have adversely affected culture results [8]. Similarly, the culture-negative peritonitis rate among SCOPE centers is quite high, at 24.7% [12]. A recent analysis of the data showed a significant center-to-center variability in culture-negative rates, ranging from 7.1% to 61.1%, as well as a significant variability in the culture techniques among the centers [28]. Since culture technique may influence the likelihood of isolating an organism from peritoneal effluent, the SCOPE collaborative has developed a standardized protocol for obtaining a culture from peritoneal dialysis effluent and processing the sample, based on the procedure recommended in the ISPD guidelines. Compliance with this culture "bundle" and the associated rates of culture-negative peritonitis will be tracked following implementation of this bundle [9].

As mentioned above, fungi account for a minority of peritonitis episodes and represent just 2% of episodes in the IPPR report and 4% among episodes reported to IPPN, with a slightly higher rate seen in the SCOPE collaborative [12, 19, 26]. Candida species are the most common fungal organisms implicated. In the largest pediatric report addressing this infection, *Candida* species accounted for 79% of all fungal infections, with nearly 24% due to *Candida albicans* and more than 26% secondary to *Candida parapsilosis* [29–31].

PD Catheter-Related Infections

PD catheter exit-site and tunnel infections may be caused by many organisms, including normal skin flora such as *Corynebacteria* [24, 32]. *S. aureus* infections are the most common, with or without *S. aureus* nasal carriage [20, 33, 34]. PD catheter-related infections due to gram-negative organisms, especially *Pseudomonas* species, are increasingly common [8, 35].

Risk Factors and Prevention

Analyses of data from large pediatric dialysis registries have revealed associations between many factors and the risk for PD-related infections, primarily peritonitis, in children on PD. Recognition of these risk factors is important, as they may prompt modification of care practices, which, in turn, may lower infection rates.

Patient Age

Data from the NAPRTCS has long revealed that peritonitis rates increase with decreasing age at dialysis initiation [1]. Data from the IPPR

confirmed a statistical association between young age and gram-negative peritonitis, and patients 2 years and under at dialysis initiation had the highest rates of peritonitis among children enrolled in the SCOPE collaborative [12, 36, 37]. An additional analysis of data from 156 infants enrolled in SCOPE, including neonates on chronic PD who had not yet been discharged from the hospital, revealed a peritonitis rate of 1.73 episodes per patient year, among those infants who remained hospitalized, and an overall annualized rate of 0.76 [38]. Multivariable regression models demonstrated that nephrectomy prior to or at the time of PD catheter placement and gastrostomy tube placement after PD catheter placement were associated with a significantly increased risk of peritonitis in this group of infants [38]. It seems intuitive that the relatively close proximity of the PD catheter to the diaper region or urinary or gastrointestinal ostomy sites in a small infant would increase the risk for bacterial contamination and subsequent infection, in fact, some centers have reported improvement in the infection rates of such patients, by placing the PD catheter exit-site in a presternal location [39, 40].

PD Catheter Design, Insertion, and Postoperative Exit-Site Care

Early data from the NAPRTCS suggested that a catheter with two subcutaneous cuffs rather than one; a swan-neck tunnel; and a downward or lateral directed exit-site orientation rather than upward, were associated with lower peritonitis rates and longer time to the first peritonitis episode [41]. A subsequent analysis revealed a significant increase in the use of this catheter configuration among NAPRTCS centers, and, associated with this trend, tunnel type (swan-neck versus straight), number of cuffs, and exit-site orientation were no longer associated with the risk for peritonitis in patients who initiated PD between 1997 and 2000, compared to those who initiated dialysis between 1992 and 1996 [42]. In a multivariate analysis performed on 490 non-fungal episodes of peritonitis reported by the IPPR, a single-cuff catheter and a downward orientation of the exit-site were independent risk factors for relapsing peritonitis [43]. Data from the IPPR also revealed a nearly 13 times increased risk for gram-negative peritonitis associated with a single-cuff catheter [36]. In the recent IPPN analysis, an upward pointing exit-site continued to be associated with an increased risk for peritonitis (OR 1.26, $p < 0.001$) [17]. A univariate analysis of catheter characteristics in patients with and without a history of peritonitis in the SCOPE collaborative revealed no difference in the percentage of patients with a swan-neck tunnel or with two subcutaneous cuffs, but subgroup analysis by organism was not performed [12]. Upward orientation of the exit-site was associated with a higher risk for peritonitis in multivariable analysis [12]. Current guidelines recommend the use of a double-cuff catheter with a downward- or lateral-oriented exit-site [9].

Other efforts to minimize the risk for peritonitis at the time of catheter placement include the provision of antibiotics prior to surgical incision, in order to reduce the risk for wound infection and peritonitis in the postoperative period [9, 44, 45]. Although vancomycin may be slightly more effective than a first-generation cephalosporin in the prevention of postoperative peritonitis, the use of the latter is recommended, because of concern for the generation of vancomycin resistance as a result of repeated usage [9, 21, 45, 46]. The ultimate choice of antibiotic for perioperative prophylaxis should be influenced by the PD unit's antibiotic susceptibility patterns [9, 21].

Placement of the PD catheter using a laparoscopic technique, rather than an open surgical procedure, has become increasingly common in pediatric centers, and among patients enrolled in the SCOPE collaborative more than 60% of catheters are placed using this technique [47]. Retrospective single-center studies have not demonstrated a difference in infection rates between catheters placed laparoscopically versus an open surgical insertion [48, 49]. More recently, the analysis of data from the SCOPE collaborative showed no difference in the percentage of patients undergoing laparoscopic versus open PD catheter placement among those patients with

and without early peritonitis, defined as infection within 60 days of catheter placement [47]. Once the catheter is inserted, sutures should be avoided at the catheter exit-site, as they may increase the risk of bacterial colonization and subsequent infection [50, 51].

In the immediate postoperative period, PD catheter and exit-site care are aimed at optimizing healing and minimizing bacterial colonization [52]. Current guidelines suggest that the sterile dressing placed in the operating room following PD catheter placement remain in place for at least 1 week. Subsequent dressing changes should be performed by a trained staff, using aseptic technique, and should occur no more frequently than weekly until the exit-site is healed [9, 53]. More frequent dressing changes should be performed only if the dressing becomes loose, damp, or soiled [9]. The catheter should be immobilized to optimize healing and minimize trauma [54]. Immobilization with tape or a dressing is usually sufficient, although commercially available immobilization devices may also be used [9]. It is generally recommended that initiation of dialysis be delayed for at least 2 weeks following catheter placement to minimize risk of leak at the peritoneal insertion site, although exit-site healing may take as long as 6 weeks. The care practices described here, and included in the most current ISPD guidelines for children, are derived primarily from the work done by Prowant and Twardowski over 20 years ago [52–54].

The care practices monitored by the SCOPE collaborative include a PD catheter insertion bundle [10]. The elements of this bundle, which address PD catheter insertion and the immediate postoperative care, were derived largely from the ISPD guidelines [9, 10]. The required care elements include the provision of an intravenous antibiotic prior to skin incision at the time of PD catheter placement, avoidance of sutures at the exit-site, no dressing change for at least 7 days following catheter placement unless soiled, loose or damp, sterile dressing changes performed by a healthcare professional until the exit-site is healed, and no use of the catheter for dialysis until at least 14 days following placement [9, 10]. In the first 3 years of the collaborative, compliance with the majority of these care practices has been high (80–90%), highlighting the capacity to incorporate these practices into clinical care [11]. The one exception is the requirement to avoid the use of the catheter for dialysis within the first 14 postoperative days, for which compliance across the collaborative has been between 50% and 60%, largely as a result of patients requiring prompt initiation of dialysis [11]. Whereas an early analysis of SCOPE data failed to detect an association between compliance with the PD catheter insertion bundle and risk for peritonitis at the patient level, a more recent analysis, which focused on peritonitis episodes in the first 60 days following catheter insertion, revealed a significant association between the risk for early peritonitis and initiation of dialysis within 14 days of catheter placement [47]. While there was no association found between compliance with the other bundle elements and the risk for early peritonitis, the high rate of compliance with these other care practices across the collaborative may have limited the ability to detect an association between compliance and infection risk [47].

Training

Because PD is a home dialysis therapy, appropriate training of patients and caregivers is essential to minimize the risk for peritonitis. Unfortunately, there are no randomized controlled trials to evaluate the relationship between various training elements or the training process itself and patient outcomes [55–57]. There are, however, several observational studies, which have sought associations between variations in timing of training, training content, training duration, nurse-to-patient ratios, and experience of the trainer and risk for peritonitis in both adult and pediatric settings [55–59]. In recent analyses of data from Brazil, shorter training time (<15 h), training in the 10 days after catheter insertion, and small center size were associated with increased risk for peritonitis [60]. In a survey of pediatric dialysis units, center size (≥15 patients) and longer training time dedicated to theory and practical/technical skills were associated with lower

peritonitis rates [58]. In agreement with the suggestions of the ISPD Nursing Liaison Committee, current pediatric guidelines suggest that PD training should use a formalized teaching program that has clear objectives and criteria, with the incorporation of adult learning principles [9, 55]. The training should be performed by an experienced PD nurse with pediatric training and should include core topics, including those related to infection prevention such as hand hygiene, aseptic technique, exit-site care, and appropriate treatment for contamination [9, 55]. It is suggested that PD training should include no more than one patient/family simultaneously [9, 55]. More recently, the ISPD published a syllabus for teaching PD to patients and caregivers, which includes a checklist for PD assessment and another for PD training [61]. It remains to be determined if widespread use of this syllabus and the associated tools leads to a decrease in the rate of infection.

The SCOPE collaborative monitors compliance with a training bundle, the elements of which were derived from the ISPD guidelines [9, 10]. The required elements include the following: (1) training must be performed by a registered nurse; (2) there should be only one patient/family per training session; (3) all of the elements recommended by the ISPD guidelines for training must be included in the training, and specific protocols for hand hygiene, aseptic technique, and exit-site care must be taught; (4) verification of competence at the end of training must be assessed, using both a written and a demonstration test; and (5) a home visit must be performed [9, 10, 55]. An analysis of the first 3 years of SCOPE data revealed that compliance with most of these bundle elements was high (90%) across the collaborative, except for the requirement to perform a home visit, which only occurred in 65–80% of cases as a result of various logistical issues [11]. No association between compliance with the overall training bundle and risk for peritonitis was demonstrated, either across the collaborative sites or when evaluated at the patient level [12], possibly as a result of the relatively high compliance with most bundle elements (vide infra) [11, 12].

Current guidelines suggest periodic retraining of patients/caregivers, particularly after a peritonitis episode [9, 55]. The Trial on Education and Clinical outcomes for Home PD patients (TEACH), a multicenter, open-labeled, randomized, controlled trial, compared PD-related infections in adult PD patients randomized to receive home visits for retraining every 1–3 months over a 24-month period compared to no retraining [62]. Both groups received the same initial training and two home visits in the first 2 months after starting PD [62]. The study failed to demonstrate a significant difference in peritonitis rates between the two groups, although a sub-analysis demonstrated a significantly lower risk for the first peritonitis episode in patients older than 60 years of age who received frequent home visits [62]. The SCOPE collaborative includes a "follow-up" care bundle, which consists of a review of key aspects of hand hygiene, exit-site care, and aseptic technique at each monthly follow-up visit in the clinic [10]. Competency with these procedures is also demonstrated by the patient/caregiver, using both a concept and a demonstration test, every 6 months [10]. Finally, the follow-up bundle requires that the appearance of the PD catheter exit-site be scored, using an objective storing tool developed by the Mid-European Pediatric Peritoneal Dialysis Study Group, and that touch contaminations be treated according to the ISPD guidelines (Table 16.1) [9, 10, 63]. Using a quality improvement methodology, SCOPE centers were able to demonstrate a significant increase in compliance with this care bundle over the first 3 years of the collaborative, accompanied by a significant reduction in peritonitis rates, from a pre-launch mean monthly peritonitis rate of 0.63 episodes per patient year

Table 16.1 Catheter exit-site scoring system [63]

	0 Points	1 Point	2 Points
Swelling	No	Exit only (<0.5 cm)	Including part of or entire tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

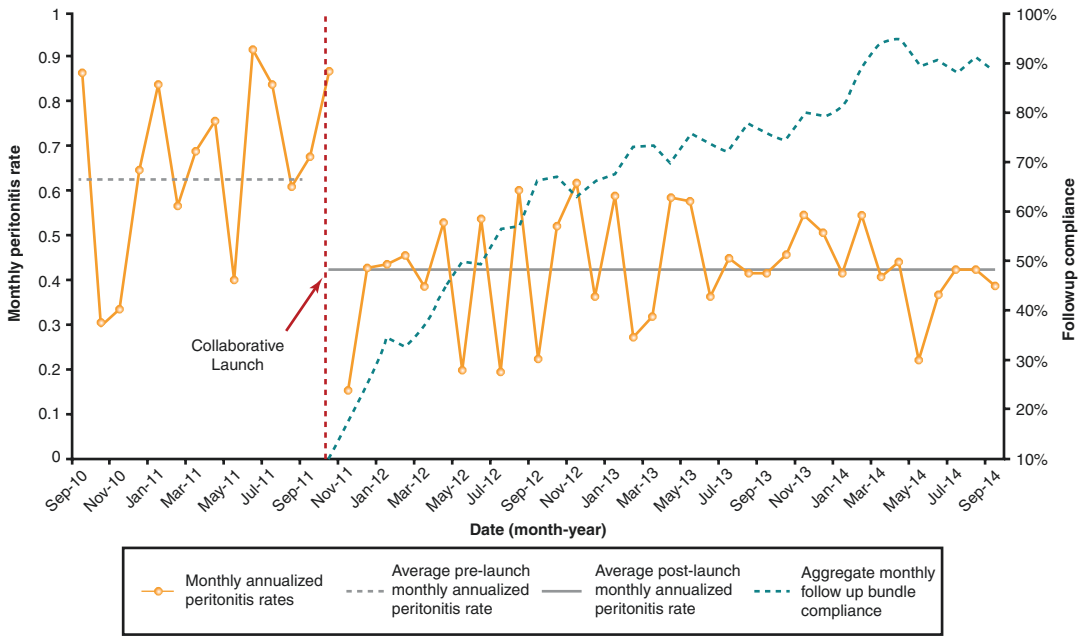


Fig. 16.2 Average monthly peritonitis rates, expressed as annual rates, among 24 SCOPE centers for whom "baseline" infection rates were available for the 13 months prior to the collaborative launch on October 1, 2011, revealing a significant reduction in the average monthly peritonitis rates from 0.63 (95% CI 0.43, 0.92) pre-launch to 0.42 (95% CI 0.31, 0.57) at 36 months postlaunch, $p = 0.026$. The figure also shows observed monthly compliance with the follow-up bundle, suggesting that as compliance with the follow-up bundle increased, the month-to-month variability in peritonitis rates decreased. (Adapted from Ref. [11])

to 0.42 episodes per patient year at 36 months postlaunch (Fig. 16.2) [11]. A subsequent analysis of SCOPE data at the patient level demonstrated that compliance with the follow-up care bundle was significantly associated with a lower rate of peritonitis [12]. Finally, compliance with the specific recommendation to review exit-site care at each visit was associated with lower exit-site infection rates among SCOPE participants [20]. These data suggest that in addition to comprehensive training at the initiation of dialysis, the ongoing review with regular testing of competency of PD catheter care and the dialysis procedure may minimize the risk for peritonitis.

Chronic Exit-Site Care

Once the catheter exit-site has healed, regular exit-site care is vital to minimize the risk for PD catheter-related infection, i.e., exit-site and tunnel infection. PD catheter-related infections are associated with an increased risk for peritonitis. However, even without subsequent peritonitis, treatment of exit-site and tunnel infections requires exposure to antibiotics, with the subsequent risk for fungal infection and drug-resistant organisms, and may require catheter removal [20, 64–66]. Current guidelines recommend regular cleansing of the exit-site with a sterile antiseptic solution and sterile gauze [9, 22]. Several cleansing agents are available, including povidone iodine, chlorhexidine, hydrogen peroxide, betaoctenidine, and sodium hypochlorite. Although many of these agents have been tested in both pediatric and adult PD patients, head-to-head comparisons have been conflicting or inconclusive, and both the current adult and pediatric guidelines suggest that no cleansing agent has been shown to be superior in the prevention of catheter-related infection [9, 22]. In addition, there is no clear guidance for the optimal frequency of exit-site care, e.g., daily, every other day, or weekly [9, 22]. Not surprisingly, the data

from the IPPR reveals significant variability in exit-site practices around the globe, including the frequency of exit-site care as well as the type of antiseptic agent used [8]. IPPR data also revealed that peritonitis due to *Pseudomonas* species was significantly more common at centers where exit-site care was performed more than twice weekly and where non-sterile cleansing agents (e.g., saline, soap) were used [8].

In addition to regular exit-site cleaning, current guidelines recommend application of a topical antibiotic during routine care, in an effort to minimize colonization of the exit-site with *Pseudomonas aeruginosa* and *S. aureus*, both of which are widely accepted as risk factors for exit-site infection and subsequent peritonitis [9, 22, 67–70]. A number of observational studies, randomized controlled trials, and meta-analyses have demonstrated that mupirocin applied to the skin around the exit-site reduces the risk for exit-site infection [9, 22, 45, 71–75]. However, there is concern that routine use of mupirocin may be associated with an increased risk for gram-negative infections, and data from the IPPR demonstrated an association between the use of mupirocin at the exit-site and an increased risk for *Pseudomonas* peritonitis [8, 35]. In addition, there are reports of increasing rates of mupirocin resistance in *Staphylococcus* species with widespread use of mupirocin [76]. Topical gentamicin is an alternative therapy, and a randomized trial in adults showed that daily application of gentamicin cream to the exit-site was not only effective in reducing exit-site infections caused by *Pseudomonas* species, but it was also as effective as topical mupirocin in reducing *S. aureus* infections [74]. There are concerns, however, about the possible development of gentamicin-resistant organisms and an increased risk of fungal infection with this therapy.

In a randomized study among adult PD patients, antibacterial honey applied daily to the catheter exit-site care resulted in infection rates that were similar to those experienced with intranasal mupirocin [77]. However, a subgroup analysis suggested an increased risk for exit-site and tunnel infections as well as peritonitis in diabetic patients using antibacterial honey [77]. The study also did not directly compare mupirocin applied to the exit-site with topical antibacterial honey [77]. The authors of the study concluded that antibacterial honey could not be recommended for the prevention of PD-related infections [78].

Current guidelines suggest that the exit-site be routinely monitored for signs and symptoms of infection, to allow prompt diagnosis and treatment [9]. The use of an objective scoring tool has been advocated, and previous studies using this tool supported that an exit-site score of 2 or greater in the presence of a pathogenic organism, and 4 or greater regardless of culture results, was consistent with the diagnosis of an exit-site infection (Table 16.1) [9, 63]. Routine use of this tool to score the exit-site at each monthly PD visit is included in the SCOPE care bundles, and a recent analysis revealed that any score greater than 0 was associated with a significant increase in the risk for an exit-site infection in the following month [20].

Touch Contamination

Accidental contamination of the sterile portions of the PD catheter transfer set or dialysis tubing, or touch contamination, is the leading cause of peritonitis [12, 26, 79]. Current guidelines recommend that a contamination prior to the infusion of dialysis fluid into the peritoneal cavity be treated with a sterile transfer set change alone, without antibiotics [9]. Unfortunately, this approach may require that the patient present to the dialysis unit or an outside facility for a transfer set change. An alternate approach implemented by some pediatric centers is to have the patient/caregiver soak the end of the transfer set in a disinfecting agent, although the efficacy of this practice has not been established. A recent study did establish that following inoculation of a loosened transfer set with *S. aureus*, effective disinfection was achieved by performing a 1-min scrub of the external surfaces of the catheter and transfer set connection followed by a 5-min soak of the open catheter end in either 10% povidone iodine or 0.55% sodium hypochlorite [80].

If the contaminating event occurs after dialysis solution has been infused into the peritoneal cavity, both a sterile transfer set change and antibiotic prophylaxis is recommended [9, 59]. Intraperitoneal administration of a first-generation cephalosporin for 1–3 days is typically recommended, unless the patient has a history of methicillin-resistant *S. aureus* (MRSA), in which case a glycopeptide should be used [9, 59]. Gram-negative coverage may be appropriate, if the contamination may have included enteric organisms, e.g., from stool in a diapered infant [9]. An effluent sample should be obtained prior to delivery of antibiotics, if possible, and culture results and susceptibility testing used to guide any subsequent antibiotic usage [9].

Ostomies

Ostomy sites, including gastrostomy, ureterostomy, nephrostomy, and colostomy, may increase the risk of bacterial contamination of an adjacent PD catheter. In fact, a recent analysis of data from the IPPN demonstrated an increased risk for peritonitis in the presence of any ostomy [17]. It is, therefore, reasonable to locate the PD catheter exit-site as far as possible from an ostomy site. A single-center retrospective study suggested an increased risk for peritonitis in the presence of a gastrostomy tube and data from the IPPR found an association, although not statistically significant, between the presence of a gastrostomy tube and gram-negative peritonitis [26, 81]. The percentage of patients with a gastrostomy tube was not significantly different among those with and without a history of peritonitis in the SCOPE collaborative as a whole, but a subsequent analysis did reveal an association between placement of a gastrostomy after PD catheter placement and risk for peritonitis among infants [12, 38]. Early reports of an association between the presence of a gastrostomy tube and the risk for a fungal infection were not supported by a subsequent study of NAPRTCS patients [31, 82]. In addition, an analysis of data from the SCOPE collaborative did not reveal a significant difference in the percentage of patients with a gastrostomy tube in those patients with and without fungal peritonitis [83]. Although data on the subject is limited, current guidelines suggest that an open procedure should be used to place a gastrostomy tube in patients who are already receiving PD, while either open or laparoscopic placement may be used if the gastrostomy is placed prior to initiating PD [9, 84]. Prophylactic antibiotics, typically with a first-generation cephalosporin, and antifungal therapy should be provided during gastrostomy tube placement [9].

The presence of a colostomy in children on PD is associated with an inherent risk for infection, but a single center reported a low rate of peritonitis in two infants on PD in the presence of a colostomy, by utilizing a swan-neck catheter with a presternal exit-site location [40]. In an analysis of SCOPE data, the presence of a colostomy was not associated with an increased risk for peritonitis, although there were only 14 patients with colostomies among the 857 children included in that analysis [12].

Antibiotic and Antifungal Prophylaxis

Although fungal peritonitis is relatively uncommon in children on PD, it is associated with an increased risk for significant morbidity and mortality [30, 83, 85]. Observational data suggests that risk factors for fungal peritonitis include prior treatment with antibiotics, recurrent peritonitis, and immunosuppression [29, 31, 83, 86–88]. Antifungal prophylaxis with either oral nystatin or fluconazole is currently recommended whenever antibiotics are administered to pediatric PD patients, based on a number of studies that have suggested a reduction in fungal peritonitis with this practice [9, 89–95]. Despite these recommendations, data from the SCOPE collaborative revealed that in 34 children diagnosed with fungal peritonitis, 61.8% had been prescribed antibiotics in the month preceding the fungal peritonitis episode, but only half of those patients had received antifungal prophylaxis [83]. Of note, a significant percentage of preceding antibi-

otic courses were for infections other than bacterial peritonitis, supporting the recommendation for antifungal prophylaxis when antibiotics are prescribed, regardless of the indication [83].

The ISPD guidelines recommend that prophylactic antibiotic therapy be provided when pediatric PD patients undergo invasive procedures, including gastrostomy tube placement, as previously discussed [9]. Additional procedures during which prophylaxis should be considered include invasive dental procedures, i.e., those that involve manipulation of the gingival tissue or periapical region of the teeth, or perforation of the oral mucosa, and those with significant bleeding risk, such as dental extractions, periodontal surgery, and professional scaling or tooth cleaning [9]. These recommendations are consistent with the guidelines from the American Heart Association for the prevention of subacute bacterial endocarditis [96, 97]. Antibiotic prophylaxis is also recommended for high-risk gastrointestinal procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), and any invasive gastrointestinal or genitourinary procedure [9].

Other Factors

The risk factors listed in this section were largely derived from observational studies that identified associations between various factors and risk for infection among a cohort of children on PD. There are clearly many other factors that may impact the risk for infection in individual patients. The dialysis unit should perform a formal review, or apparent cause analysis (ACA), of each infection in search of causation [9, 58, 59]. A tool to help carry out an ACA has been developed by the SCOPE collaborative (Fig. 16.3). This review should include nurses and physicians at a minimum. Inclusion of the patient and family, social worker, infection preventionist, and infectious diseases specialist is encouraged. Identification of causation will allow appropriate intervention for the individual patient, and potentially other patients in the unit.

Diagnosis and Management of Peritonitis

Diagnosis

PD patients with peritonitis typically present with cloudy effluent and abdominal pain but may also have fever, chills and rigors, emesis, anorexia, and abdominal distention [9]. Cloudy effluent without symptoms should also prompt an evaluation [9]. Cloudy fluid almost always indicates infectious peritonitis, but other causes include chemical peritonitis, eosinophilic peritonitis, fluid obtained from a "dry" abdomen, chylous effluent, and malignancy, although the last two are relatively rare [9, 98]. Peritonitis should also be considered in patients who present with abdominal pain without cloudy dialysis effluent [9, 26]. The abdominal pain associated with peritonitis is typically generalized, but the severity of the pain can be quite variable. Data from the IPPR suggests that symptoms of *S. aureus*, *Streptococcus*, and gram-negative peritonitis are often more severe at presentation than with coagulase-negative *Staphylococcus* peritonitis, as demonstrated by a disease severity score [26, 63]. Enterococcal peritonitis has also been reported to be associated with severe symptoms; however, among patients experiencing enterococcal peritonitis in the IPPR registry, the disease severity scores at presentation were no different than in other patients in that registry [37]. Localized pain and tenderness may warrant evaluation for appendicitis, and if subsequent cultures from the peritoneal dialysate effluent grow multiple organisms, intra-abdominal sources, such as a viscus perforation, must be considered [9].

The evaluation for peritonitis should include a cell count, differential, gram stain, and culture from the dialysis effluent, and an empiric diagnosis of peritonitis should be made if the white blood cell count (WBC) is greater than 100/mm^3 and at least 50% of the white blood cells are polymorphonuclear neutrophils (PMN) [9]. The effluent sample should be obtained from the first cloudy bag or the initial drain for patients on continuous ambulatory peritoneal dialysis (CAPD) or

SCOPE Collaborative **Exit Site/Peritonitis Apparent Cause Analysis Tool**

Patient Information

Place Patient Sticker Here:	Name: DOB: MRN:

Surgical PD Catheter Placement Information *(complete this section if infection occurs w/i 60 days of catheter insertion)*

MRSA nares culture obtained? ☐Yes ☐ No Date: ___/___/____ Results: ☐ Positive ☐ Negative

- If positive, was it treated prior to O.R? ☐ Yes ☐ No If yes, antibiotic used:_____

Date Catheter Inserted: ___/___/____ Surgeon:_____

Pre-op CHG Wipes or CHG bath? ☐Yes ☐No

Pre-op Antibiotic Given? ☐ Yes ☐ No If yes, antibiotic used:_____

Catheter Type: ☐Flex-Neck ☐Tenckhoff ☐ Laparoscopic ☐ Open surgical

No. of Catheter Cuffs: ☐ 1 ☐ 2

Exit site: ☐Up ☐ Lateral ☐Downward Sutures at exit site? ☐Yes ☐ No

Were other procedures done at time of PD catheter placement? ☐ Yes ☐ No If yes: check all that apply

☐G-tube ☐ Vesicostomy ☐ Urinary Stoma ☐ Colostomy ☐ Nephrectomy ☐ Other:_____

Problems with operative procedure? ☐ Yes ☐ No

Post-Op Catheter/Exit Site Care *(complete this section if infection occurs w/i 60 days of catheter insertion)*

Dressing change: Was full sterile procedure (sterile gloves, sterile drapes and mask) used for dressing changes until exit-site was well healed? ☐Yes ☐No

Was catheter immobilized at exit-site until exit-site well healed? ☐Yes ☐No

Did dressing changes occur within 7 days of insertion? ☐Yes ☐ No

a. Specify # of days post-op when dressing first changed: _____Days post-op

b. Specify reason for dressing change: ☐Soiled ☐ Loose ☐Damp ☐Other:_____

c. Was dressing change performed by dialysis nurse? ☐Yes ☐ No

Was catheter used for dialysis within 14 days of insertion? ☐Yes ☐ No

a. Specify # of days post-op when dialysis was initiated: _____Days post-op

Was catheter flushed prior to the day dialysis was initiated? ☐Yes ☐ No

a. Provide number of days post-op when first flushed: _____Days post-op

Peritonitis ☐ N/A

Date of Infection: ___/____/____

Occurred: ☐NICU ☐PICU/CICU ☐Other inpatient unit ☐ Home (Note: check "Home" if initial symptoms occurred before admission or on hospital day 1 or 2 (with day 1 being day of admission)

Signs/Symptoms: ☐ Fever ☐ Abdominal Pain ☐ Cloudy Effluent ☐ Vomiting ☐ Other

Fig. 16.3 An example of an Apparent Cause Analysis Tool, developed by the SCOPE collaborative, which may be used to identify factors contributing to the development of a PD-Related Infection

SCOPE Collaborative **Exit Site/ Peritonitis Apparent Cause Analysis Tool**

Cell count #1 Date: ____/_____/_____

Collected by: ☐Caregiver ☐ Patient ☐Staff ☐ Other:_____

Effluent Color: ☐ Clear ☐Cloudy ☐Bloody ☐Milky ☐ Other:_____

Effluent Volume: _____mL

Cell Count Results: Total Nucleated Cells (WBC):_____ Neutrophils:_____% Eos:_____%

Empiric (Initial) Antibiotic Therapy: ☐Cefazolin ☐Vancomycin ☐Clindamycin ☐Cefepime ☐ Ceftazidime

☐Other:_____

Antifungal therapy started? ☐Yes ☐ No ☐Already On

If yes, what was used: ☐ Nystatin ☐ Fluconazole ☐ Other:_____

Other Positive Cultures: ☐ MRSA nares Cx (obtain with peritonitis ☐Pos ☐ Neg ☐ Not done)

☐Urine_____ ☐Blood_____ ☐ Respiratory_____ ☐Other_____ ☐N/A

PD Fluid Culture Result: ☐ Staph Aureus ☐ Staph Epi ☐ Pseudomonas ☐ E. Coli ☐ Fungus ☐ Klebsiella

☐ Streptococcus ☐ Proteus species ☐ No Growth ☐Other_____

Maintenance (Treatment) Antibiotic Therapy: ☐Cefazolin ☐Vancomycin ☐Clindamycin ☐Cefepime
Other:_____

Duration of Therapy: ☐7days ☐10 days ☐14 Days ☐21 Days ☐Other:_____

Cell count #2 (if needed) ☐N/A Date: ____/_____/_____

Effluent Color: ☐ Clear ☐Cloudy ☐Bloody ☐Milky ☐ Other:_____
Cell Count Results: Total Nucleated Cells (WBC): _____ Neutrophils:_____% Eos_____%

Peritonitis Outcome: ☐ Resolution of infection ☐ Temporary Catheter Removal ☐ Permanent Catheter Removal

☐ Hemodialysis ☐ Other:_____

Exit Site/Tunnel Infection ☐ N/A

Exit Site Score (see Scoring Table at top of page 3):_____
Check symptoms below that contributed to Score:

☐ Swelling ☐ Crust ☐ Redness at Exit Site ☐ Painful to Touch ☐ Secretion

Did patient have fever? ☐Yes ☐ No
Date of most recent dressing change prior to infection: ___/_____/____
Culture Date: ___/_____/____

Culture Results: ☐ Staph aureus MSSA (not MRSA) ☐ Staph aureus (MRSA) ☐Pseudomonas ☐No Growth

☐Other organism(s):_____
Empiric (Initial) Antibiotic Therapy:_____
Maintenance (Treatment) Antibiotic Therapy:_____

Antifungal therapy started? ☐Yes ☐ No ☐Already On

If yes, what was used? ☐ Nystatin ☐ Fluconazole ☐ Other:_____

Exit site inf Outcome: ☐ Resolution of infection ☐Temporary Catheter Removal ☐Peritonitis ☐ Other:_____

Fig. 16.3 (continued)

SCOPE Collaborative Exit Site/ Peritonitis Apparent Cause Analysis Tool

SCOPE Exit Site Scoring System:

	0 Points	1 Point	2 Points
Swelling	No	Exit only <0.5cm	>0.5cm including tunnel
Crust	No	<0.5cm	>0.5cm
Redness at Exit Site	No	<0.5cm	>0.5cm
Painful to Touch	No	Slight	Severe
Secretion	No	Serous	Purulent

Infection should be assumed with an exit site score of 4 or greater. Purulent drainage, even if alone, is sufficient to indicate infection. A score of less than 4 may not represent infection.

Potential Contributing Factors (within 30 days)

Catheter Care/Patient Factors:

Catheter Coiled Under Dressing? ☐Yes ☐No Catheter Immobilized: ☐Yes ☐No

Recent contamination? ☐Yes ☐No

If yes, what type: ☐Hole in catheter ☐Accidental disconnection at transfer set or patient line

☐Mini cap fell off ☐Contamination at time of connection ☐Catheter cuff exposed

☐Other _____

Treatment for contamination (check all that apply): ☐ IP Antibiotic for 3 days (specify):_____;

Soak end in: ☐ Alcavis ☐ Betadine, or ☐ Other; ☐ Transfer set change; ☐ Other intervention; ☐None

Recent catheter malfunction: ☐Yes ☐No If yes, interventions? ☐IP Heparin ☐TPA Other:_____

Leakage or drainage from the catheter exit site? ☐Yes ☐No

Recent transfer set change? ☐Yes ☐No If yes, when: _____

Has patient recently had any viral infections? ☐Yes; if yes, describe:_____ ☐No

Any patient bacterial or fungal infections at another site? ☐Yes; if yes, describe:_____ ☐No

If yes, were antibiotics or antifungals prescribed? ☐Yes ☐No

Has anyone in the home recently been sick? ☐Yes; if yes, describe:_____ ☐No

Date of last menstruation: ___/____/____ ☐ N/A

Recent (last 30 days) vascular port infections? ☐Yes ☐No ☐N/A If yes, treatment: _____

Recent (last 30 days) dental visit? ☐Yes ☐No If yes, antibiotic taken one hour prior? ☐Yes ☐No

Any recent (last 30 days) surgeries? ☐Yes ☐No If yes, what kind: _____

Patient currently constipated? ☐Yes ☐No Incontinent of stool or diapered? ☐Yes ☐No

Incontinent of urine? ☐Yes ☐No Does the patient have an ostomy? ☐Yes ☐No

Fig. 16.3 (continued)

SCOPE Collaborative **Exit Site/ Peritonitis Apparent Cause Analysis Tool**

Catheter Care/Environmental Factors:

Person(s) who routinely changes dressing: ☐Patient ☐Parent ☐Home Health RN ☐Other_____

Was the above person(s) trained by a healthcare provider? ☐Yes ☐No
When did they last perform dressing care?_____

Mask worn during dressing change by caregiver? ☐Always ☐Sometimes ☐Never

Mask (or face protection) used during dressing change by patient? ☐Yes ☐No

How often is dressing changed? _____ times/wk and where:_____

Does caregiver apply antibiotic ointment routinely to exit site? ☐Yes; if yes, describe_____ ☐No

Have caregivers had a recent review of PD learning at a clinic visit? ☐Yes ☐No If yes, date: ___/_____/____

Door open or closed during dressing change? ☐Open ☐Closed

Ceiling/Standing Fan On or Off during dressing change? ☐On ☐Off ☐NA

Heater turned off and vents covered during dressing change? ☐Yes ☐No

Ointment used at exit site?: ☐Yes ☐No

If yes, which ointment was used? ☐Gentamicin ☐Mupirocin ☐Other:_____ ☐None

Skin antiseptic used? ☐Yes ☐No

Who connects/disconnects dialysis tubing? ☐Patient ☐Parent ☐Home Health RN ☐Other_____

Was the above person(s) trained by a healthcare provider? ☐Yes ☐No
When did they last connect/disconnect the patient? _____

Mask worn during connection/disconnection by caregiver? ☐Always ☐Sometimes ☐Never

Mask worn during connection/disconnection by patient? ☐Always ☐Sometimes ☐Never

For inpatient infection, # of hospital staff that cared for line in past 96 hours: _____ ☐NA

Hand Hygiene (at home): ☐ N/A, patient acquired infection while hospitalized

Hand hygiene performed before dressing change? ☐Always ☐Sometimes ☐Never

Hand hygiene performed before connecting/disconnection? ☐Always ☐Sometimes ☐Never

Method of hand hygiene: ☐Waterless hand sanitizer ☐Antibacterial soap ☐Bar soap ☐None

Hand drying: ☐Paper towels ☐ Cloth Towel ☐ None

If cloth towel, how often is it changed? ☐ Daily ☐ Other:_____

Nails: Does person doing cares have artificial nails, gels, extended wear polish, chipped nail polish, extensions, and/or nail jewelry? ☐Yes ☐No Rash on hands? ☐ Yes ☐ No

Water source: Does home water come from a well? ☐Yes ☐No

If yes, has it been tested? ☐Yes ☐No ☐ Unknown If yes, testing date (month/year): ___/____

Did results meet EPA Drinking Water Standards for Coliforms & E. coli? *(refer to pg. 6)* ☐Yes ☐No ☐ Unknown

Fig. 16.3 (continued)

SCOPE Collaborative **Exit Site/ Peritonitis Apparent Cause Analysis Tool**

Bathing/Swimming:

Method of bathing: ☐Tub Bath ☐Shower ☐Sponge bath With Dressing: ☐ On ☐ Off

Frequency of bathing: ☐Daily ☐ Every other day ☐Other (specify): _____

Dressing changed immediately after bathing? ☐Yes ☐No

Recent swimming in the past 30 days? ☐Yes ☐No If yes: ☐Own pool ☐Public pool ☐Hot tub

☐Lake/creek ☐ Ocean ☐ Other_____

Miscellaneous:

Housing: Has there been a recent change in housing or place where home dialysis is performed? ☐Yes ☐No

Pets: Are there Pets in the home? ☐Yes ☐No

If yes, what kind?_____ Are any of the pets allowed in treatment area? ☐Yes ☐No

Are any of the pets allowed to sleep with patient while on PD? ☐Yes ☐No

Supplies: How are supplies delivered? ☐ Open-air truck ☐ Closed truck ☐ Unknown

Where are supplies stored? ☐ Closed container/cupboard ☐ Clean Closet ☐ Unfinished Basement

☐Bathroom or near sink ☐ Other:_____

Complete the following after team review ***(for internal use only)****:*
Potential contributing factors:
Lessons learned:
Action Plan:

Fig. 16.3 (continued)

automated peritoneal dialysis (APD) with a daytime exchange, respectively [9]. For children on APD without a daytime dwell, the fill volume should be allowed to dwell for at least 1–2 h prior to specimen collection [9]. In specimens collected in this manner, peritonitis should be diagnosed if the percentage of PMNs exceeds 50%, even if the total WBC does not exceed 100/mm^3 [9]. Among the clinical peritonitis episodes reported to the IPPR, a WBC of less than 100/m^3 was present in 2.8% and the percentage of PMNs lower than 50% in 8.5% of episodes [31]. Although the sensitivity of gram stain of the dialysis effluent is low, the presence of organisms, particularly budding yeast, may guide empiric therapy [9].

Whereas bacterial or fungal growth in a culture obtained from effluent typically confirms the diagnosis of peritonitis, a negative culture does not rule out infectious peritonitis. It has been suggested that the center-specific culture-negative rate should not exceed 20% and, ideally, should be lower than 10%. However, and as mentioned previously, data from the IPPR and SCOPE reveal that this goal is not routinely achieved at pediatric centers [8, 9, 12, 99]. Efforts to optimize culture yields include prompt delivery of the specimen to the laboratory, ideally within 6 h of collection, with refrigeration (4 °C) of samples that are not immediately delivered to a lab [99, 100]. Centrifugation of at least 50 mL of effluent, with resuspension of the sediment for inoculation onto solid-culture media and into blood culture media, is recommended [101, 102]. Alternatively, 20–30 mL of effluent may be injected directly into 3–4 blood culture bottles [99]. In the majority of cases, cultures will be positive within 72 h. If cultures remain negative after 3–5 days, repeat cell count, differential, culture, as well as fungal and mycobacterial culture should be obtained from dialysis effluent, with an additional subculture on media with aerobic, anaerobic, and microaerophilic incubation conditions to identify fastidious bacteria and yeasts [9, 21].

Empiric Therapy

To optimize treatment outcomes, empiric antibiotics should be delivered in suspected cases of peritonitis as soon as a dialysis effluent sample for cell count, differential, gram stain, and culture is obtained. Intraperitoneal instillation, if possible, is the preferred method of antibiotic delivery, and antibiotics may be given continuously, as recommended for beta-lactam antibiotics, or intermittently [9, 103]. Continuous dosing typically begins with a higher antibiotic concentration (loading dose) delivered with an extended-dwell cycle, followed by a lower maintenance dose [9]. Current guidelines suggest that intermittent dosing with glycopeptide antibiotics (vancomycin or teicoplanin) may be considered, but the dose in this case should be provided using an extended dwell (6–8 h), and antibiotic blood levels should be monitored, particularly in non-anuric patients for whom the frequency of dosing may need to be increased [9, 99]. The dosing recommendations for the various antibiotics and antifungals used to treat children with peritonitis are shown in Table 16.2 [9].

Antibiotics selected for empiric treatment should cover both gram-positive and gram-negative organisms [9, 21]. Given the significant variability in both causative organisms and antibiotic susceptibility seen around the globe, center-specific antibiotic susceptibility patterns should influence empiric antibiotic selection [8, 9, 21]. Current pediatric guidelines recommend either monotherapy with cefepime for empiric coverage or a first-generation cephalosporin or a glycopeptide in combination with ceftazidime or an aminoglycoside, if cefepime is not available [9]. The empiric use of a glycopeptide, either in addition to cefepime or as a substitute for a first-generation cephalosporin, is recommended if the center-specific resistance rate of MRSA exceeds 10% or the patient has a history of MRSA [9].

Table 16.2 Dosing recommendations for the treatment of peritonitis

	Continuous therapy[a]		
	Loading dose	Maintenance dose	Intermittent therapy
Aminoglycosides[b]			
Gentamicin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg
			Non-anuric: 0.75 mg/kg
Netilmicin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg
			Non-anuric: 0.75 mg/kg
Tobramycin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg
			Non-anuric: 0.75 mg/kg
Amikacin	25 mg/L	12 mg/L	2 mg/kg
Cephalosporins			
Cefazolin	500 mg/L	125 mg/L	20 mg/kg
Cefepime	500 mg/L	125 mg/L	15 mg/kg
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg
Ceftazidime	500 mg/L	125 mg/L	20 mg/kg
Glycopeptides[c]			
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg; repeat dosing 15 mg/kg q 3–5 days
Teicoplanin	400 mg/L	20 mg/L	15 mg/kg q 5–7 days
Penicillins[b]			
Ampicillin	–	125 mg/L	–
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	–
Others			
Aztreonam	1000 mg/L	250 mg/L	–
Clindamycin	300 mg/L	150 mg/L	–
Imipenem/ cilastatin	250 mg/L	50 mg/L	–
Linezolid (oral)	<5 years, 30 mg/kg/day divided TID; 5–11 years, 20 mg/kg/day divided BID; ≥12 years, 600 mg/dose BID		
Metronidazole (oral)	30 mg/kg/day divided TID (max daily dose 1.2 g)		
Rifampin (oral)	10–20 mg/kg/day divided BID (max daily dose 600 mg)		
Antifungals			
Fluconazole	6–12 mg/kg **IP**, **IV**, or **PO** q 24–48 h (max daily dose 400 mg)		
Caspofungin	IV only: initial dose 70 mg/m^2 on day 1 (max daily dose 70 mg); subsequent dosing 50 mg/m^2 daily (max daily dose 50 mg)		

Used with permission from Ref. [9]
Administration should be via intraperitoneal route unless specified otherwise
Intermittent doses should be applied once daily unless specified otherwise
[a]For continuous therapy, the exchange with the loading dose of antibiotics should dwell for 3–6 h, followed by the use of the maintenance dose for all subsequent exchanges
[b]Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation
[c]Accelerated glycopeptide elimination may occur in patients with residual renal function. If intermittent therapy is used in this setting, the second dose of antibiotic should be time-based on a blood level obtained 2–4 days after the initial dose. Redosing should occur when the blood level is <15 mg/L for vancomycin or 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum drug levels can be monitored in a timely manner

Subsequent Treatment of Peritonitis

Gram-Positive Peritonitis

Empiric antibiotics should be modified once culture results are available. As stated previously, the most common gram-positive organisms cultured among children with PD-related peritonitis are coagulase-negative *Staphylococcus* and *S. aureus* [8, 26]. Coagulase-negative *Staphylococcus* characteristically infects the peritoneum following touch contamination [104]. *S. aureus* infections are commonly associated with a PD catheter-related infection [33, 34]. *Streptococci* and *Enterococci* are relatively less frequent causes of PD-related infections [19, 26]. *Streptococci* often cause peritonitis by hematogenous spread, either following a dental procedure or possibly originating from the respiratory tract, the skin, or the bowel. *Enterococci* are fecal in origin, and infection may occur via transmural migration or by contamination of the PD catheter by stool in incontinent patients.

The recommended modifications of therapy for gram-positive organisms are shown in Fig. 16.4, but antibiotic selection should be guided by the antibiotic susceptibilities of the organism cultured [9]. In general, gram-negative coverage should be discontinued once a gram-positive organism is identified, although continued use of an aminoglycoside may be considered for synergy in infections with susceptible *Enterococcus* species [9]. However, data from the IPPR revealed clinical improvement in all patients with enterococcal peritonitis, despite the fact that no patient received combined treatment with an aminoglycoside [37]. It should also be recognized that because of incompatibility, aminoglycosides should not be combined in the same exchange with a penicillin [9]. Treatment for gram-positive peritonitis should be continued for 2–3 weeks, depending on the organism cultured [9].

Gram-Negative Peritonitis

The recommendations for treatment modification for gram-negative infections are shown in Fig. 16.5, but antibiotic selection should be guided by the antibiotic susceptibilities of the cultured organism [9]. As stated previously, among peritonitis episodes reported to the IPPR, *E. coli and Pseudomonas* were the most common

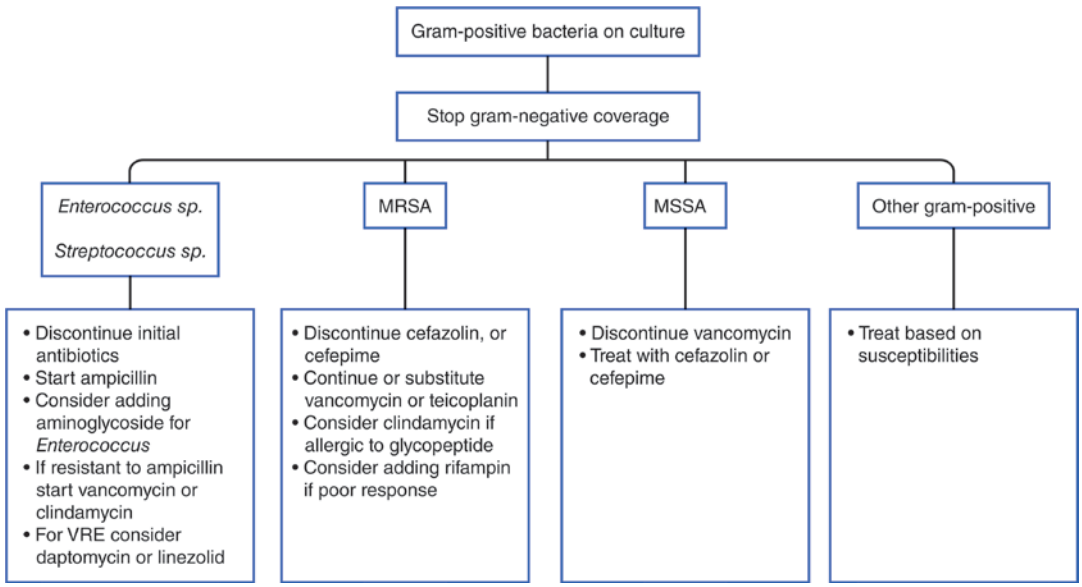


Fig. 16.4 Recommended modification of empiric therapy for gram-positive organism on culture. MRSA methicillin-resistant *S. aureus*, MSSA methicillin-sensitive *S. aureus*, VRE vancomycin-resistant *Enterococci*. (Adapted from Ref. [9])

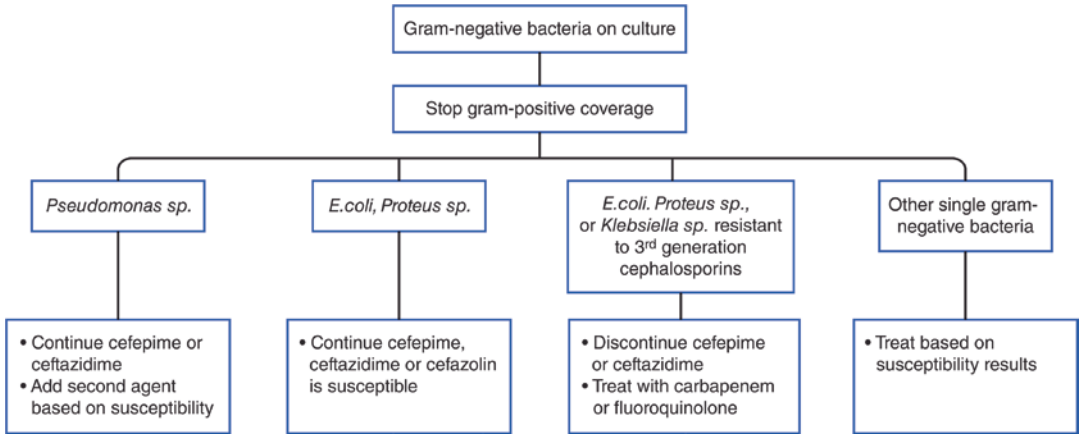


Fig. 16.5 Recommended modification of empiric therapy for gram-negative organism on culture. (Adapted from Ref. [9])

gram-negative species cultured [9, 36]. However, there was significant global variability in causative organisms, and in the United States, *Pseudomonas* species were dominant, a fact recently confirmed by the SCOPE collaborative [8]. Infections due to *Pseudomonas* species may be particularly difficult to treat, given the organism's capacity to generate a biofilm, and successful eradication often requires catheter removal [9]. In light of this, combination therapy with cefepime or ceftazidime and a second agent, which has a different mechanism of action, such as a fluoroquinolone or aminoglycoside, is recommended [9, 105]. The typical duration of treatment for gram-negative peritonitis is 2–3 weeks, depending on the cultured organism [9].

Culture-Negative Peritonitis

In the setting of culture-negative peritonitis, empiric therapy should be continued for 14 days, provided that the patient has demonstrated clinical improvement [9]. These recommendations are supported by data from the IPPR, where 97% of the patients with culture-negative peritonitis showed good primary response to empiric antibiotic therapy at 72 h and full functional recovery was seen in 97% of patients in whom empiric treatment was continued for 14 days [9, 26]. If an aminoglycoside was included in the empiric treatment and the patient has shown clinical improvement within 72 h, the aminoglycoside may be discontinued [9]. This recommendation seeks to minimize unnecessary prolonged exposure to an aminoglycoside, which is associated with ototoxicity and nephrotoxicity, and is supported by the facts that gram-negative organisms typically grow well in culture, and gram-negative peritonitis is typically associated with more severe and prolonged symptoms than seen with gram-positive infections [9, 36]. Thus, clinical improvement in the setting of a negative culture argues against a gram-negative pathogen. Patients who fail to demonstrate clinical improvement after 72 h should have a repeat cell count, differential, and culture (vide infra), while failure to improve after 5 days should prompt catheter removal (vide infra) [9].

Fungal Peritonitis

As stated previously, fungal peritonitis is a potentially serious infection and is associated with a significant risk for hospitalization, change in modality, and mortality [30, 83, 85]. Prompt therapy, consisting of treatment with an antifungal agent, and early catheter removal are recommended [9, 21]. Amphotericin B causes significant irritation when delivered via the intraperitoneal route and has poor penetration of the peritoneal cavity when given intravenously [106]. Therefore, current pediatric guidelines suggest the use of fluconazole as the treatment of choice for peritonitis due to most *Candida* spe-

cies, as this agent has an excellent bioavailability and peritoneal penetration (Table 16.2) [9, 106]. Unfortunately, the prevalence of azole resistance is increasing [107]. Alternate treatments include the echinocandins (e.g., caspofungin, micafungin, and anidulafungin), which have activity against *Aspergillus* species and non-albicans *Candida* species [9, 108–110]. It is currently recommended that antifungal therapy be provided for 2 weeks or longer after catheter removal and complete resolution of symptoms [9, 21].

Relapsing Peritonitis

Relapsing peritonitis is diagnosed when peritonitis recurs with the same organism, including similar/identical antibiotic susceptibilities, within 4 weeks of completion of antibiotics. Retrospective data in adult and pediatric PD patients suggests that relapsing peritonitis is associated with a worse prognosis than non-relapsing infections [21, 43, 111]. Current pediatric guidelines suggest that the empiric treatment of relapsing peritonitis be based on the antibiotic susceptibilities of the organism cultured with the first episode, but that post-empiric antibiotic therapy be guided by in vitro susceptibility testing results from the organism cultured from the relapsing episode [9]. Data from the IPPR suggested an increased risk for relapse with first-generation cephalosporin monotherapy, and so current guidelines recommend avoiding this treatment in relapsing peritonitis [9, 43]. Instillation of a fibrinolytic agent may be considered as an adjuvant to antibiotic therapy [9]. Catheter removal is recommended if the relapse is associated with a persistent or recurrent PD catheter-related infection or in the setting of a second relapse [9].

Refractory Peritonitis

As mentioned previously, the majority of children with PD-related peritonitis demonstrate prompt clinical improvement, with a significant reduction in symptoms and a decrease in dialysis effluent cloudiness by 72 h after initiation of antibiotic therapy [8, 63]. Failure to demonstrate improvement should prompt reevaluation, including repeat effluent cell count, differential, gram stain, and culture; additional subculture on media with aerobic, anaerobic, and microaerophilic incubation conditions to identify fastidious bacteria and yeasts should be considered [9, 21]. Refractory peritonitis, defined as a failure to show improvement in PD effluent cell count and/or symptoms after 5 days of appropriate antibiotics, should prompt catheter removal to help eradicate the infection and preserve peritoneal membrane function [9, 21].

Diagnosis and Management of PD Catheter-Related Infections

Diagnosis

PD catheter-related infections include exit-site and tunnel infections. An exit-site infection should be considered in the presence of pericatheter swelling, redness, and tenderness and/or purulent drainage [9]. Guidelines for adult PD patients recommend diagnosis of an exit-site infection based on the presence of purulent drainage, with or without other symptoms [22]. The use of an objective scoring tool developed in pediatric PD patients has been recommended as a complement to clinical judgment in the diagnosis of exit-site infections [9, 60]. Previous studies using this tool supported that exit-site scores of 2 or greater in the presence of pathogenic organism and 4 or greater regardless of culture results were consistent with the diagnosis of an exit-site infection (Table 16.1).

A tunnel infection is defined by the presence of erythema, edema, and tenderness along the subcutaneous portion of the catheter, with or without purulent drainage from the exit-site [9]. Ultrasound may be helpful in identifying an occult tunnel infection [9, 22].

As stated previously, a variety of skin flora are implicated in PD catheter-related infections, but *S. aureus* is the most common causative organism for PD catheter-related infections, followed by *Pseudomonas* species [8, 20, 33–35]. While a positive culture is not required for the diagnosis of a PD catheter-related infection, it can guide therapy. A positive culture from the exit-site without evidence of inflammation should be considered colonization, rather than infection [9, 22].

Treatment of PD Catheter-Related Infections

Oral antibiotics can be used to treat uncomplicated catheter exit-site infections, with the specific agent chosen according to culture results and susceptibilities [9]. Empiric oral, intraperitoneal, or intravenous antibiotic therapy is indicated for tunnel infections, particularly if there are signs of severe infection and/or a history of *S. aureus* or *Pseudomonas aeruginosa* [9]. Treatment with a first-generation cephalosporin or a penicillinase-resistant penicillin is indicated for infections due to gram-positive organisms, with intraperitoneal or intravenous glycopeptide therapy prescribed only if MRSA is cultured [9]. The use of oral ciprofloxacin for infections due to *Pseudomonas aeruginosa* had previously been recommended, with the addition of a second antibiotic, such as cefepime, piperacillin, or a carbapenem if resolution of the infection is slow or there is recurrence [9]. However, recent reports from observational studies have suggested an increased risk for aortic aneurysm or dissection associated with fluoroquinolone use, particularly in the setting of other risk factors such as hypertension, which led the United States' Food and Drug Administration to issue a safety announcement (https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm) [112–115].

Treatment duration for PD catheter-related infections is typically for at least 2 weeks and should continue for at least 7 days after complete resolution of the infection [9]. Treatment for 3 weeks is recommended for infections caused by *S. aureus* or *Pseudomonas aeruginosa* [9]. Failure to achieve a complete resolution in this time frame and the development of peritonitis due to the same organism are indications for catheter removal [9].

Outcome

Data from the IPPR revealed that peritonitis outcomes vary by causative organism and by global region, although more recent data from the IPPN found no differences in outcome by region in more than 2000 episodes of peritonitis reported to that registry [8, 17, 26]. Among the peritonitis episodes captured by the IPPR, 89% achieved full functional recovery and 8.1% experienced technique failure [26]. The response by causative organism among the cases of bacterial peritonitis is shown in Fig. 16.6 and demonstrates that gram-

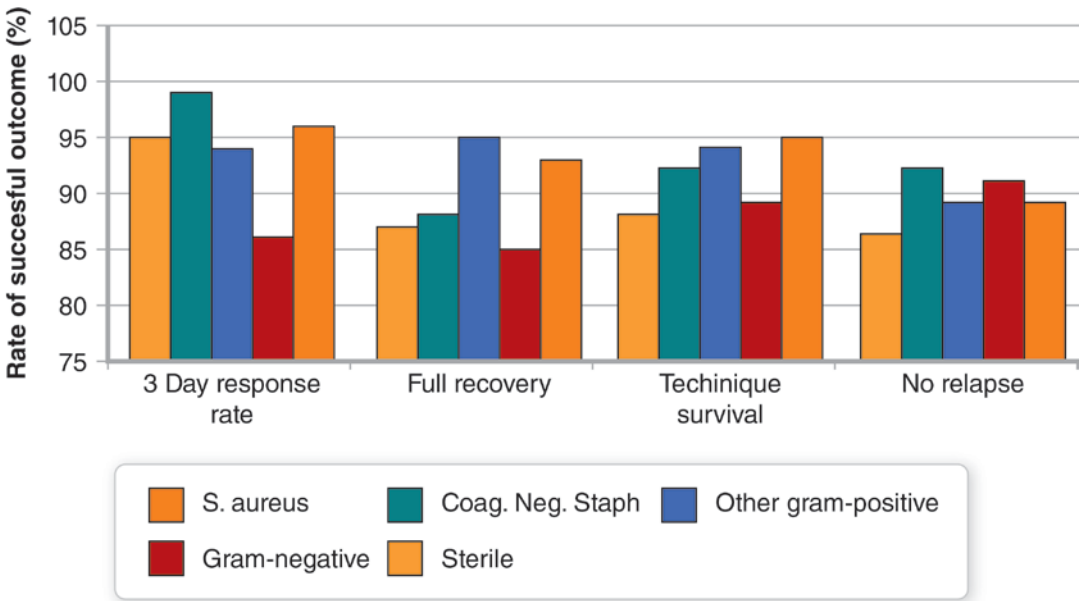


Fig. 16.6 Peritonitis outcome by organisms as reported by the International Pediatric Peritonitis Registry (IPPR). (Adapted from Ref. [26])

negative peritonitis is associated with lower rates of full recovery [26]. Initial response rates were not different among the various regions included in the IPPR, but technique failure was highest in Eastern Europe, occurring in 20% of patients [8].

Data from the SCOPE collaborative revealed that nearly 60% of the peritonitis episodes required hospitalization for treatment of the infection [12]. Hospitalization rates varied by organism and were higher for treatment of gram-negative and fungal infections, than for gram-positive and culture-negative infections [12]. More than two thirds of the peritonitis episodes resolved with antimicrobial therapy alone, while 6% required catheter removal [12]. Twelve percent of episodes were associated with technique failure, similar to the rate of 10% reported among US centers in the IPPR [8, 12].

With regard to peritonitis-related mortality, 6 deaths were reported by the IPPR, representing 1.2% of the peritonitis episodes [36]. Three of these deaths were in patients with gram-negative peritonitis [36].

In summary, peritonitis remains a significant complication of PD in children. New technologies, a better understanding of the epidemiology of the infections, individualized antibiotic therapy, and ongoing efforts to increase implementation of standardized care practices should result in ongoing improvements in infection rates and overall outcomes for these vulnerable children.

References

1. NAPRTCS. NAPRTCS 2011 annual dialysis report. 2011 [cited 2018]. Available from: https://naprtcs.org.
2. United States Renal Data System. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.
3. Chesnaye N, et al. Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA-EDTA registry. Pediatr Nephrol. 2014;29(12):2403–10.
4. Schaefer F, et al. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry. Perit Dial Int. 2012;32(4):399–409.
5. Chesnaye NC, et al. Mortality risk in European children with end-stage renal disease on dialysis. Kidney Int. 2016;89(6):1355–62.
6. Warady BA, et al. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int. 2000;20(6):610–24.
7. Feneberg R, et al. The international pediatric peritonitis registry: a global internet-based initiative in pediatric dialysis. Perit Dial Int. 2005;25(Suppl 3):S130–4.
8. Schaefer F, et al. Worldwide variation of dialysis-associated peritonitis in children. Kidney Int. 2007;72(11):1374–9.
9. Warady BA, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
10. Neu AM, et al. Design of the standardizing care to improve outcomes in pediatric end stage renal disease collaborative. Pediatr Nephrol. 2014;29(9):1477–84.
11. Neu AM, et al. Implementation of standardized follow-up care significantly reduces peritonitis in children on chronic peritoneal dialysis. Kidney Int. 2016;89(6):1346–54.
12. Sethna CB, et al. Risk factors for and outcomes of catheter-associated peritonitis in children: the SCOPE collaborative. Clin J Am Soc Nephrol. 2016;11(9):1590–6.
13. Burkart JM, et al. Comparison of peritonitis rates during long-term use of standard spike versus Ultraset in continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int. 1990;10(1):41–3.
14. Burkart JM, et al. Comparison of exit-site infections in disconnect versus nondisconnect systems for peritoneal dialysis. Perit Dial Int. 1992;12(3):317–20.
15. Valeri A, et al. The epidemiology of peritonitis in acute peritoneal dialysis: a comparison between open- and closed-drainage systems. Am J Kidney Dis. 1993;21(3):300–9.
16. Monteon F, et al. Prevention of peritonitis with disconnect systems in CAPD: a randomized controlled trial. The Mexican Nephrology Collaborative Study Group. Kidney Int. 1998;54(6):2123–8.
17. Warady BB-DDSF. World wide experience with peritonitis in children: a report from the International Pediatric Peritoneal Dialysis Network (IPPN). Perit Dial Int. 2019;39(Supplement 1):S10–4.
18. Hoshii S, Wada N, Honda M. A survey of peritonitis and exit-site and/or tunnel infections in Japanese children on PD. Pediatr Nephrol. 2006;21(6):828–34.
19. Neu A, Schaefer F. Chronic PD in children: prescription, management, and complications. In: Geary DF, Schaefer F, editors. Pediatric kidney disease. Berlin: Springer-Verlag; 2016. p. 1675–3.
20. Swartz SJ, et al. Exit site and tunnel infections in children on chronic peritoneal dialysis: findings from the Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative. Pediatr Nephrol. 2018;33(6):1029–35.

21. Li PK, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2016;36(5):481–508.
22. Szeto CC, et al. ISPD catheter-related infection recommendations: 2017 update. Perit Dial Int. 2017;37(2):141–54.
23. Piraino B, Bernardini J, Bender FH. An analysis of methods to prevent peritoneal dialysis catheter infections. Perit Dial Int. 2008;28(5):437–43.
24. Schaefer F, Kandert M, Feneberg R. Methodological issues in assessing the incidence of peritoneal dialysis-associated peritonitis in children. Perit Dial Int. 2002;22(2):234–8.
25. Vas S, Oreopoulos DG. Infections in patients undergoing peritoneal dialysis. Infect Dis Clin N Am. 2001;15(3):743–74.
26. Warady BA, et al. Peritonitis in children who receive long-term peritoneal dialysis: a prospective evaluation of therapeutic guidelines. J Am Soc Nephrol. 2007;18(7):2172–9.
27. Szeto CC, et al. Influence of climate on the incidence of peritoneal dialysis-related peritonitis. Perit Dial Int. 2003;23(6):580–6.
28. Davis TK, Bryant KA, Rodean J, Richardson T, Selvarangan R, Qin X, Neu A, Warady BA: Variability in culture-negative peritonitis rates in pediatric peritoneal dialysis programs in the United States. Clin J Am Soc Nephrol. 2021. In Press.
29. Goldie SJ, et al. Fungal peritonitis in a large chronic peritoneal dialysis population: a report of 55 episodes. Am J Kidney Dis. 1996;28(1):86–91.
30. Wang AY, et al. Factors predicting outcome of fungal peritonitis in peritoneal dialysis: analysis of a 9-year experience of fungal peritonitis in a single center. Am J Kidney Dis. 2000;36(6):1183–92.
31. Warady BA, Bashir M, Donaldson LA. Fungal peritonitis in children receiving peritoneal dialysis: a report of the NAPRTCS. Kidney Int. 2000;58(1):384–9.
32. Keane WF, et al. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. Perit Dial Int. 2000;20(4):396–411.
33. Piraino B. Peritoneal infections. Adv Ren Replace Ther. 2000;7(4):280–8.
34. Zelenitsky S, et al. Analysis of microbiological trends in peritoneal dialysis-related peritonitis from 1991 to 1998. Am J Kidney Dis. 2000;36(5):1009–13.
35. Piraino B, et al. Staphylococcus aureus prophylaxis and trends in gram-negative infections in peritoneal dialysis patients. Perit Dial Int. 2003;23(5):456–9.
36. Zurowska A, et al. Gram-negative peritonitis in children undergoing long-term peritoneal dialysis. Am J Kidney Dis. 2008;51(3):455–62.
37. Sutherland SM, et al. Enterococcal peritonitis in children receiving chronic peritoneal dialysis. Nephrol Dial Transplant. 2010;25(12):4048–54.
38. Zaritsky JJ, et al. Epidemiology of peritonitis following maintenance peritoneal dialysis catheter placement during infancy: a report of the SCOPE collaborative. Pediatr Nephrol. 2018;33(4):713–22.
39. Warchol S, Roszkowska-Blaim M, Sieniawska M. Swan neck presternal peritoneal dialysis catheter: five-year experience in children. Perit Dial Int. 1998;18(2):183–7.
40. Chadha V, et al. Chest wall peritoneal dialysis catheter placement in infants with a colostomy. Adv Perit Dial. 2000;16:318–20.
41. Furth SL, et al. Peritoneal dialysis catheter infections and peritonitis in children: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 2000;15(3–4):179–82.
42. Neu AM, et al. Chronic dialysis in children and adolescents. The 2001 NAPRTCS annual report. Pediatr Nephrol. 2002;17(8):656–63.
43. Lane JC, et al. Relapsing peritonitis in children who undergo chronic peritoneal dialysis: a prospective study of the international pediatric peritonitis registry. Clin J Am Soc Nephrol. 2010;5(6):1041–6.
44. Sardegna KM, Beck AM, Strife CF. Evaluation of perioperative antibiotics at the time of dialysis catheter placement. Pediatr Nephrol. 1998;12(2):149–52.
45. Strippoli GF, et al. Antimicrobial agents to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. Am J Kidney Dis. 2004;44(4):591–603.
46. Berns JS. Infection with antimicrobial-resistant microorganisms in dialysis patients. Semin Dial. 2003;16(1):30–7.
47. Keswami M, Mahon ACR, Richardson T, Rodean J, Couloures O, Martin A, Blaszak RT, Warady BA, Neu A. Risk factors for early onset peritonitis: the SCOPE collaborative. Pediatr Nephrol. 2019;34(8):1387–94.
48. Mattioli G, et al. Laparoscopic-assisted peritoneal dialysis catheter implantation in pediatric patients. Urology. 2007;69(6):1185–9.
49. Copeland DR, et al. Laparoscopic Tenckhoff catheter placement in children using a securing suture in the pelvis: comparison to the open approach. J Pediatr Surg. 2008;43(12):2256–9.
50. Bakkaloglu SA. Prevention of peritonitis in children: emerging concepts. Perit Dial Int. 2009;29(Suppl 2):S186–9.
51. Twardowski ZJ, Nichols WK. Peritoneal dialysis access and exit site care including surgical aspects. In: Khanna R, Gokal R, Krediet R, Nolph KD, editors. Peritoneal dialysis. Dordrecht: Kluwer Academic Publishers; 2000. p. 307–61.
52. Prowant BF, Twardowski ZJ. Recommendations for exit care. Perit Dial Int. 1996;16(Suppl 3):S94–s99.
53. Prowant BF, Warady BA, Nolph KD. Peritoneal dialysis catheter exit-site care: results of an international survey. Perit Dial Int. 1993;13(2):149–54.
54. Twardowski ZJ, Prowant BF. Exit-site healing post catheter implantation. Perit Dial Int. 1996;16(Suppl 3):S51–s70.
55. Bernardini J, Price V, Figueiredo A. Peritoneal dialysis patient training, 2006. Perit Dial Int. 2006;26(6):625–32.

56. Bernardini J, et al. International survey of peritoneal dialysis training programs. Perit Dial Int. 2006;26(6):658–63.
57. Campbell DJ, et al. Prevention of peritoneal dialysis-related infections. Nephrol Dial Transplant. 2015;30(9):1461–72.
58. Holloway M, et al. Pediatric peritoneal dialysis training: characteristics and impact on peritonitis rates. Perit Dial Int. 2001;21(4):401–4.
59. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. Kidney Int Suppl. 2006;103:S44–54.
60. Figueiredo AE, et al. Impact of patient training patterns on peritonitis rates in a large national cohort study. Nephrol Dial Transplant. 2015;30(1):137–42.
61. Figueiredo AE, et al. A syllabus for teaching peritoneal dialysis to patients and caregivers. Perit Dial Int. 2016;36(6):592–605.
62. Chang JH, et al. Frequent patient retraining at home reduces the risks of peritoneal dialysis-related infections: a randomised study. Sci Rep. 2018;8(1):12919.
63. Schaefer F, et al. Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). J Am Soc Nephrol. 1999;10(1):136–45.
64. van Diepen AT, Tomlinson GA, Jassal SV. The association between exit site infection and subsequent peritonitis among peritoneal dialysis patients. Clin J Am Soc Nephrol. 2012;7(8):1266–71.
65. van Diepen AT, Jassal SV. A qualitative systematic review of the literature supporting a causal relationship between exit-site infection and subsequent peritonitis in patients with end-stage renal disease treated with peritoneal dialysis. Perit Dial Int. 2013;33(6):604–10.
66. Lloyd A, et al. The risk of peritonitis after an exit site infection: a time-matched, case-control study. Nephrol Dial Transplant. 2013;28(7):1915–21.
67. Piraino B. Staphylococcus aureus infections in dialysis patients: focus on prevention. ASAIO J. 2000;46(6):S13–7.
68. Blowey DL, Warady BA, McFarland KS. The treatment of Staphylococcus aureus nasal carriage in pediatric peritoneal dialysis patients. Adv Perit Dial. 1994;10:297–9.
69. Kingwatanakul P, Warady BA. Staphylococcus aureus nasal carriage in children receiving long-term peritoneal dialysis. Adv Perit Dial. 1997;13:281–4.
70. Gupta B, Bernardini J, Piraino B. Peritonitis associated with exit site and tunnel infections. Am J Kidney Dis. 1996;28(3):415–9.
71. Strippoli GF, et al. Catheter-related interventions to prevent peritonitis in peritoneal dialysis: a systematic review of randomized, controlled trials. J Am Soc Nephrol. 2004;15(10):2735–46.
72. Tacconelli E, et al. Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. Clin Infect Dis. 2003;37(12):1629–38.
73. Bernardini J, et al. A randomized trial of Staphylococcus aureus prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. Am J Kidney Dis. 1996;27(5):695–700.
74. Chu KH, et al. A prospective study of the efficacy of local application of gentamicin versus mupirocin in the prevention of peritoneal dialysis catheter-related infections. Perit Dial Int. 2008;28(5):505–8.
75. Xu G, Tu W, Xu C. Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. Nephrol Dial Transplant. 2010;25(2):587–92.
76. Kavitha E, Srikumar R. High-level mupirocin resistance in Staphylococcus spp. among health care workers in a Tertiary Care Hospital. Pharmacology. 2019;103(5–6):320–3.
77. Johnson DW, et al. Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. Lancet Infect Dis. 2014;14(1):23–30.
78. SPRINT Research Group, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
79. Piraino B, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int. 2011;31(6):614–30.
80. Firanek C, et al. Comparison of disinfection procedures on the catheter adapter-transfer set junction. Perit Dial Int. 2016;36(2):225–7.
81. Ramage IJ, et al. Complications of gastrostomy feeding in children receiving peritoneal dialysis. Pediatr Nephrol. 1999;13(3):249–52.
82. Murugasu B, et al. Fungal peritonitis in children treated with peritoneal dialysis and gastrostomy feeding. Pediatr Nephrol. 1991;5(5):620–1.
83. Munshi R, et al. Fungal peritonitis in the standardizing care to improve outcomes in pediatric end stage renal disease (SCOPE) collaborative. Pediatr Nephrol. 2018;33(5):873–80.
84. Ledermann SE, et al. Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol. 2002;17(4):246–50.
85. Miles R, et al. Predictors and outcomes of fungal peritonitis in peritoneal dialysis patients. Kidney Int. 2009;76(6):622–8.
86. Raaijmakers R, et al. Fungal peritonitis in children on peritoneal dialysis. Pediatr Nephrol. 2007;22(2):288–93.
87. Michel C, et al. Fungal peritonitis in patients on peritoneal dialysis. Am J Nephrol. 1994;14(2):113–20.
88. Bren A. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Eur J Clin Microbiol Infect Dis. 1998;17(12):839–43.

89. Prasad KN, et al. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single centre Indian experience. J Infect. 2004;48(1):96–101.
90. Lo WK, et al. A prospective randomized control study of oral nystatin prophylaxis for Candida peritonitis complicating continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1996;28(4):549–52.
91. Zaruba K, Peters J, Jungbluth H. Successful prophylaxis for fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: six years' experience. Am J Kidney Dis. 1991;17(1):43–6.
92. Robitaille P, et al. Successful antifungal prophylaxis in chronic peritoneal dialysis: a pediatric experience. Perit Dial Int. 1995;15(1):77–9.
93. Wadhwa NK, Suh H, Cabralda T. Antifungal prophylaxis for secondary fungal peritonitis in peritoneal dialysis patients. Adv Perit Dial. 1996;12:189–91.
94. Moreiras-Plaza M, et al. Ten years without fungal peritonitis: a single center's experience. Perit Dial Int. 2007;27(4):460–3.
95. Restrepo C, Chacon J, Manjarres G. Fungal peritonitis in peritoneal dialysis patients: successful prophylaxis with fluconazole, as demonstrated by prospective randomized control trial. Perit Dial Int. 2010;30(6):619–25.
96. Dajani AS, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. J Am Dent Assoc. 1997;128(8):1142–51.
97. Wilson W, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736–54.
98. Rocklin MA, Teitelbaum I. Noninfectious causes of cloudy peritoneal dialysate. Semin Dial. 2001;14(1):37–40.
99. Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005;25(2):107–31.
100. von Graevenitz A, Amsterdam D. Microbiological aspects of peritonitis associated with continuous ambulatory peritoneal dialysis. Clin Microbiol Rev. 1992;5(1):36–48.
101. Lye WC, et al. Isolation of organisms in CAPD peritonitis: a comparison of two techniques. Adv Perit Dial. 1994;10:166–8.
102. Sewell DL, et al. Comparison of large volume culture to other methods for isolation of microorganisms from dialysate. Perit Dial Int. 1990;10(1):49–52.
103. Sisterhen LL, et al. Disposition of ceftazidime after intraperitoneal administration in adolescent patients receiving continuous cycling peritoneal dialysis. Am J Kidney Dis. 2006;47(3):503–8.
104. Kim DK, et al. Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: a single center's experience over one decade. Perit Dial Int. 2004;24(5):424–32.
105. Burgess DS, Nathisuwan S. Cefepime, piperacillin/tazobactam, gentamicin, ciprofloxacin, and levofloxacin alone and in combination against Pseudomonas aeruginosa. Diagn Microbiol Infect Dis. 2002;44(1):35–41.
106. Blowey DL, et al. Peritoneal penetration of amphotericin B lipid complex and fluconazole in a pediatric patient with fungal peritonitis. Adv Perit Dial. 1998;14:247–50.
107. Levallois J, et al. Ten-year experience with fungal peritonitis in peritoneal dialysis patients: antifungal susceptibility patterns in a North-American center. Int J Infect Dis. 2012;16(1):e41–3.
108. Madariaga MG, Tenorio A, Proia L. Trichosporon inkin peritonitis treated with caspofungin. J Clin Microbiol. 2003;41(12):5827–9.
109. Fourtounas C, et al. Treatment of peritoneal dialysis related fungal peritonitis with caspofungin plus amphotericin B combination therapy. Nephrol Dial Transplant. 2006;21(1):236–7.
110. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. Perit Dial Int. 2009;29(Suppl 2):S161–5.
111. Szeto CC, et al. Recurrent and relapsing peritonitis: causative organisms and response to treatment. Am J Kidney Dis. 2009;54(4):702–10.
112. Lee CC, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med. 2015;175(11):1839–47.
113. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ. 2018;360:k678.
114. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open. 2015;5(11):e010077.
115. Lee CC, et al. Oral fluoroquinolone and the risk of aortic dissection. J Am Coll Cardiol. 2018;72(12):1369–78.

17 Noninfectious Complications of Peritoneal Dialysis in Children

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Noninfectious (NI) complications, mainly related to the dialysis catheter, are the major causes of peritoneal dialysis (PD) technique failure and patient morbidity. These complications can be categorized into mechanical (catheter-related and related to intra-abdominal pressure) and technique-related (ultrafiltration problems and metabolic effects of the absorption of glucose and its degradation products) (Table 17.1) [1–4]. Membrane failure, characterized by ultrafiltration failure and inadequate solute removal, was responsible for 8–27% of cases of chronic PD (CPD) termination in pediatric series [5–7]. Additionally, adverse metabolic effects of PD may further exacerbate the increased cardiovascular risk in end-stage kidney disease (ESKD).

Mechanical Complications of PD

Long-term catheter survival rates seem to be improved over time [8–10]; however, in reality it is highly variable in different registries; at 4 years, it was reported to be 73% in a recent report of the International Pediatric Peritoneal Dialysis Network (IPPN; based on the date from 2007 to 2014) [9] and 75% in an earlier Turkish registry (1989–2002) [11], but 35% in a national registry from Italy [8]. In line with this, while two large retrospective studies from Germany [12] and from the USA [13] showed catheter exchange rates of 34%, other studies and registry reports revealed lower catheter replacement rates (7–17%), due to noninfectious complications [7–9, 14].

Data from 2453 patients enrolled in the IPPN between 2007 and 2015 showed that mechanical catheter-related problems (malfunction and leakage) doubled the risk of technique failure compared with infectious causes (peritonitis and exit-site infection – 28%) [9].

The most common mechanical complications associated with PD catheters in children are inflow/outflow problems, catheter malposition, pericatheter leak, and hernia. Children under 2 years of age or weighing less than 10 kg are at a higher risk of these complications [12–16].

Pain is another important complication of PD for children. It may occur during infusion – possibly related to the jet of fluid – or at the end of draining [3]. This discomfort is frequently transient, resolving shortly after PD is initiated. Coiled catheter design [17], usage of warm, biocompatible fluids, slowing the rate of infusion, and tidal dialysis may minimize infusion and pressure pain.

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Table 17.1 Noninfectious complications of peritoneal dialysis [1–4]

Mechanical complications
Catheter-related
Perioperative (perforation of viscus or hemorrhage)
Obstruction to flow
Inflow problems Catheter kinking
Outflow failure Constipation Catheter malposition, kinking Catheter occlusion (internal by fibrin or external by omentum)
Leakage (exit-site or concealed)
Pain (on infusion or drainage)
Catheter cuff extrusion, tunnel erosion
Related to increased intra-abdominal pressure
Hernia
Pleural leak (hydrothorax)
Back pain
Gastroesophageal reflux and delayed gastric emptying
Technique-related complications
Adequacy and ultrafiltration problems
Inadequate solute clearance
Poor compliance
Decreased peritoneal permeability
Inadequate ultrafiltration
Fast transport status Encapsulated peritoneal sclerosis
Metabolic complications
Hyperglycemia
Hyperinsulinemia
Hypertriglyceridemia
Hypokalemia
Magnesium alterations
Other complications
Hemoperitoneum
Pneumoperitoneum
Pancreatitis
Ischemic colitis and necrotizing enterocolitis
Subcapsular steatosis

Obstruction of PD Fluid Flow

Inflow obstruction suggests intraluminal blockage with fibrin or blood and may be due to kinking of the catheter (Fig. 17.1a). It usually becomes obvious soon after catheter placement. Outflow failure, which is defined as incomplete drain of instilled dialysate, most commonly occurs because of constipation, catheter malposition, intraluminal catheter occlusion (often by thrombus and fibrin), extraluminal catheter occlusion (by omentum, adhesions, epiploid fat appendices, fallopian tubes), and catheter kinking [1, 2].

Migration of the catheter out of the pelvic cavity (Fig. 17.1b) usually causes poor drainage and sometimes poor inflow of the dialysate, which is usually evident within days of placement. Omental occlusion is commonly observed within several weeks of catheter implantation and may also cause migration. Large side holes on the intraperitoneal portion of PD catheter may cause omental entrapment [15]. Large pediatric series showed the rate of malfunction/obstruction between 5% and 36% (Table 17.1) [7–10, 12–16, 18–20]. Age less than 1–2 years is a significant risk factor for dislocation [13] and malfunction [16]. A recent retrospective report analyzing infants only (n = 25, median: 18 months) demonstrated that malfunction and malposition of the catheters were seen in 44% of the cases [18].

Prevention Strategies

A simple strategy against malfunctioning migrated catheters is avoiding constipation. In addition to spontaneous repositioning, saline flushing into the peritoneal cavity, enema administration, and modification of the patient's position are conservative methods used by clinicians to reposition a migrated catheter. Liberal use of laxatives or enemas is an underappreciated strategy to promote good catheter function via inducing bowel peristalsis, since fecal impaction can cause catheter migration and external compression of the lumen by the bowel [1].

Other strategies to prevent early catheter malfunction include appropriate catheter selection, optimal surgical technique by center's best experience, good postimplantation care, and education of patients and caregivers. Insertion of catheters by experienced and dedicated physicians is advised [1, 15]. A number of modifications of PD catheter design have been proposed; however, overall, the intraperitoneal configuration, straight vs coiled, or tunnel configuration,

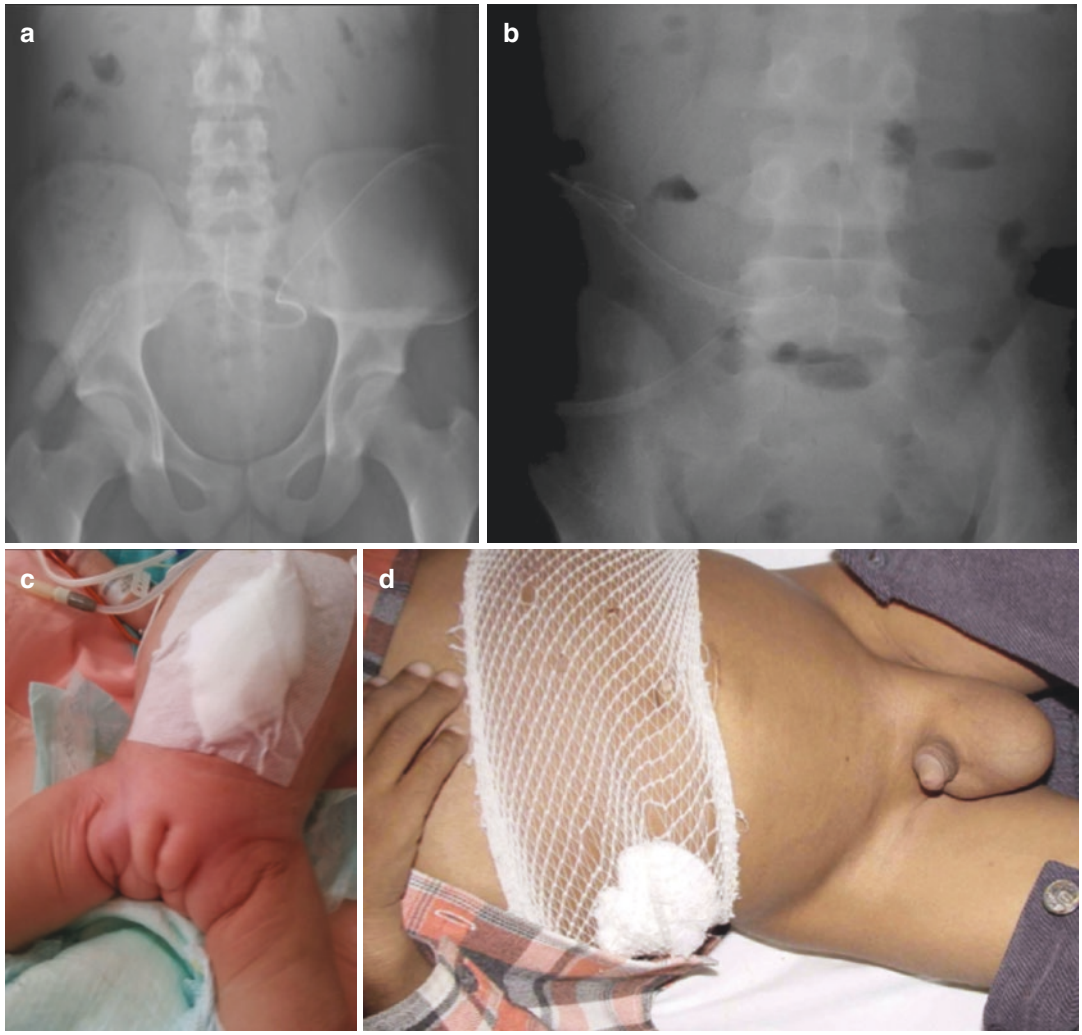

Fig. 17.1 (**a**) Catheter kinking, (**b**) catheter migration out of the pelvic cavity, (**c**) genital swelling due to leakage in an infant on chronic peritoneal dialysis, (**d**) inguinal hernia in a child on nightly intermittent peritoneal dialysis. (With permission of Sevcan A. Bakkaloglu, MD)

swan-neck vs straight, does not seem to modify this risk [1, 2, 9, 14, 17]. In the experience of the International Pediatric Peritonitis Registry (IPPR), the use of Tenckhoff catheters with a straight ending was associated with an increased rate of post-peritonitis technique failure [8]; however, in the IPPN registry, swan-neck tunnel with a curled intraperitoneal portion had a significantly higher percentage of catheter revisions secondary to mechanical dysfunction and peritonitis compared with other catheter types [9]. On the other hand, a recent cohort from the USA reported that lateral exit-site was associated with catheter migration in small infants with single-cuff catheters [14]. A single cuff may act as a fulcrum about which the catheter may rotate and cause malfunction. Tunneling these catheters straight superiorly is suggested [14]. In line with this, a recent RCT demonstrated that a new open surgical technique, involving catheter fixation to the lower abdominal wall combined with a straight upward tunnel configuration and low implant position (i.e., a shorter intra-abdominal catheter section), was successful in reducing

catheter malfunction, due to migration and omental entrapment [21]. Straight upward tunnel configuration for preventing catheter malfunction should be evaluated in pediatric RCTs.

There is a controversial data about the effect of omentectomy on catheter patency [13–16, 19]. Some studies showed 2–3 times reduced catheter replacement rate in patients undergoing an omentectomy (7–15% vs 23–27%) [14, 16, 19]. On the other hand, recent retrospective studies suggested that omentectomy did not change early or late mechanical complications and the reoperation rate [13, 15]. Therefore, omentectomy is left to physician's discretion in the current practice.

The catheter tip should sit deep in the pelvis. Selection of a catheter that is too short will result in poor drainage because the catheter will sit higher in the abdomen, where it is vulnerable to interference with omentum. Compared with other methods of PD catheter placement, positioning of the catheter can be done more accurately with laparoscopy [22]. However, studies and meta-analyses have yielded conflicting results; some are in favor of laparoscopic placement [13, 23] in terms of long-term catheter complications, while others are not [24–26]. Advanced laparoscopic techniques might further improve clinical outcome. Crabtree et al. have described advanced laparoscopic management with rectus sheath tunneling, prophylactic adhesiolysis, and prophylactic omentopexy (fixing the redundant omentum to the upper abdomen by means of a suture) and reported a reduction in the rate of catheter flow complications to <1% compared with 12% with standard laparoscopic technique [27]. In adults, nephroscope-assisted laparoscopic technique may also provide additional advantages over standard laparoscopy, including a single port entry and less leakage, less surgical time, and lower cost [28]. Particularly for patients at higher risk for catheter malfunction as a result of previous complicated abdominal surgery, advanced laparoscopic techniques provide good results in experienced hands. In children, the reported frequencies of flow problems are similar with both implantation techniques, varying between 5% and 36% [8, 10, 19, 22, 29–31]. Furthermore, recent studies in infants/neonates who had their catheters implanted mainly laparoscopically observed 2–3 times more noninfectious complications compared to those implanted open surgically in different centers [7, 18]. While awaiting convincing data from pediatric RCTs, it should be realized that the frequency of complications decreases as the experience gained by the operator increases [15], regardless of the surgical technique.

Treatment Options

Guidewire manipulation should be considered when poor drainage persists, despite an adequate trial of conservative methods. This treatment is usually reserved for catheters with radiographic evidence of migration to the hypochondriac region, although malfunctioning catheters that are properly positioned in the true pelvis may be entrapped in an adhesion and benefit from guidewire manipulation. Using a stiff rod and a stiff wire under fluoroscopy guidance, catheters can be drawn back into the rectovesical pouch with a promising long-term patency [32]. In an analysis of CPD outcomes in infants reported to the Italian registry, a successful catheter reposition rate of 25% was noted [7]. If fluoroscopically guided manipulations fail, open or laparoscopic surgery is necessary to reposition the catheter. In omental trapping, laparoscopic mobilization of the catheter can also be possible [33].

Intraluminal instillation of thrombolytics is helpful if intraluminal obstruction persists after vigorous flushing and results in a high rate of restoration of flow. Administration of tissue plasminogen activator (tPA, 8 mg in 10 mL of sterile water injected into the catheter and allowed to dwell for 1 h) in 29 cases of catheter obstruction resulted in restored patency in 24 instances with no adverse effects [34]. In children, empirically and partly based on patient and catheter size, 2.5–5 mg of tPA (1 mg/mL) in 10–20 mL saline may be used [35]. Pure tPA at a volume of 4 mL (4 mg) was shown to be effective in a newborn [36]. The reusability of tPA due to its nonallergenic properties makes it an attractive option, preventing unnecessary replacement of PD catheters.

Outcome

Although catheter patency can be sustained by conservative or interventional manipulations, obstruction to flow is still an important cause of catheter removal up to the rate of 22% in different single-center retrospective series (Table 17.2). There were no significant differences between early and delayed catheter use groups in terms of mechanical catheter problems [9, 10, 20]. However, newborns and small infants should be accepted as exception. In a study from the USA, usage of catheter within 3 days postimplantation resulted in catheter removal in 72% of these babies (median age 18 days, 60% neonates), and obstruction was the second most common cause following leakage [18].

Dialysate Leakage

An exit-site leak refers to the appearance of any moisture around the PD catheter identified as dialysate; however, the spectrum of dialysate leaks also includes any dialysate loss from the peritoneal cavity other than via the lumen of the catheter. Early leaks occur within 30 days of PD catheter insertion, and late leaks occur after this period. Early leakage most often manifests as a pericatheter leak and most commonly in newborns and infants [12, 14–16, 18]. Abdominal weakness appears to predispose mostly to late leaks, which may present more subtly with subcutaneous swelling and edema, weight gain, peripheral or genital edema, and apparent ultrafiltration failure. This reduced dialysate drainage may easily be mistaken for ultrafiltration failure at the peritoneal membrane level. Additionally, it is important to be aware that mechanical damage to the catheter will produce identical symptoms. A catheter puncture during suturing will be followed by leakage of dialysis fluid at the exit-site [33].

Risk Factors and Prevention

Leakage of dialysate at the pericatheter site tends to occur early after catheter placement, in association with high dialysate volumes, and in those with a weak abdominal wall (such as those with a history of multiple surgeries or newborns/small infants) or loose purse-string suture on the peritoneum and improperly sutured fascia [14, 33]. Intra-abdominal pressure increases linearly with the volume of dialysate infused and exponentially when abdominal compliance is exhausted. So, initiating PD with low dialysate volume (300 mL/m^2 body surface area) has been recommended as a good practice measure [37]. In addition, leaks frequently occur only after a patient becomes physically active and are less common in those who undergo dialysate exchanges when supine. Adult reports indicate that the incidence of dialysate leakage is seen in slightly more than 5% of CAPD patients [37]. The reported incidence of pericatheter leak is widely variable (3–41.5%) in different pediatric series [8, 10, 12–16, 18–20, 22, 29–31, 38] (Table 17.2). Infants with a body weight of <10 kg have 3–5 times higher risk of leakage compared to the older children [14, 15, 18]. Frequency of leakage can be as high as 71% in newborns [18]. So, the increased likelihood of leakage may be explained by patient size and delayed healing due to decreased subcutaneous tissue [18]. Although higher incidence of leakage may in part be attributed to surgical catheter placement in adult studies, the implantation method, either open surgical or percutaneous or laparoscopic, did not appear to make significant difference in pediatric series [8, 10, 18, 22].

Other factors suggested as potentially related to dialysate leak include the immediate initiation of PD [18] and median PD catheter insertion [37]. In a retrospective pediatric study, the delayed use of peritoneal catheter after its implantation (>14 days) was associated with a lower incidence of dialysate leak [29]. In line with this, the use of PD catheters within 3 days of placement was associated with catheter failure in newborns and infants [18]. Recent, large retrospective studies confirmed the impact of small age on leakage [12, 13, 15, 18]. On the other hand, the incidence of dialysate leakage in the IPPN cohort including 2453 patients with a median age of 10.5 (IQR, 3.4–14.2) years was similar for early (<7 days) and late (>7 days) PD start [9].

Table 17.2 Noninfectious complications of peritoneal dialysis: summary of pediatric studies from different countries

	Rinaldi [8]	Rahim [29]	Donmez [30]	Macchini [31]	Aksu [10]	Stringel [22]	Hooman [38]	Ladd [19]	Vidal [7]	Phan [16]
Publication year	2004, Italy	2004, USA	2005, Turkey	2006, Italy	2007, Turkey	2008, USA	2009, Iran	2011, USA	2012, Italy	2013, USA
Study period	1986–2000	1990–2000	1997–2004	1986–2002	1995–2005	–	1993–2006	1986–2008 Retrospective, single center	1995–2007 Registry data	1994–2009 Retrospective, single center
Number of patients	363 (503 catheters)	90 (127 catheters)	53 (72 catheters)	78 (89 catheters)	93 (108 catheters)	21	122	163	84	207
Age	<15 years	0–21 years	3 days–19 years		3 months–16 years	3 months–16 years	<14 years	Mean: 6.25 ± 5.58 years	All are infants started dx <1 years	Median: 12 (range: 0–21) years
Insertion technique	Surgical, omentectomy in 82.4%		Percutaneous Surgical laparoscopic	Open surgical + omentectomy in 70%	Percutaneous	Laparoscopic + omentectomy	Surgical	All open but 1% laparoscopic, 53% partial omentectomy	Open surgical + omentectomy (97%)	Mainly open, (laparoscopic in 9%) + partial or total omentectomy in 75%
PD modality		CCPD	CAPD	CAPD/CCPD	CAPD/CCPD	–	CAPD	CPD and acute (15% idiopathic acute renal failure)	CPD (70% APD 30% CAPD then APD)	CPD
Catheter type	Mainly double-cuff straight		Mainly double-cuff swan-neck curled and straight	Mainly double-cuff straight	Double-cuff swan-neck curled	Single-cuff curled, downward or lateral exit-site	Double-cuff straight or swan-neck curled	Curl or straight Quinton catheters	Mainly double cuffed, curled, downward-pointing exit-site	Mostly curled
Timing of catheter use		Early vs late	Early vs late		Early vs late	After 1 week	Early vs late	–		
Hernia			15.1%	1.5%	No		20%			33% for patients <1 year vs 10% for those >1 year

Leak	5.8%	14.2%	41.5%	2.5%	No	Several minor leaks	15%	13%	3	18% for patients <1 year vs 3% for those >1 year
Kink					7%					
Dislocation	5.8%			3.5%	12%			11%	6	
Malfunction (obstruction, drainage problems)	5.3%	21.3%	20.8%	5%	7%	7 catheters		36%	9	
Cuff extrusion	4.8%		5.7%						3	
Catheter exchange	7.6% (38 catheters (17 obstruction, 14 dislocation, 4 cuff extrusion, 3 leakage))	Catheter malfunction in 11.8% of the patients, leak with infection in 1.6%	39.6% (21 catheters from 20 patients, malfunction in 11 patients and leak in 9 patients)	7.9% (7 catheters (6 dislocation, 1 obstruction))	12% (13 catheters from 11 patients (malfunction in 6, dislocation in 3, omental capture in 2, kink in 2))	7 interventions in 5 patients (24%) due to adhesions	Catheter obstruction in 8.7% of the patients	63 (39%) underwent catheter revision (obstruction in 23, leak in 8, malposition in 7)	Catheter replacement in 15% of cases, all mechanical complications. 21 catheters were repositioned, due to NI complication	46 (22%) catheters were removed for malfunction 34% adhesions, 24% leak, 17% fibrin plugs, 17% migration, and 8% other reasons

(continued)

Table 17.2 (continued)

	Kim[a] [3]	Carpenter [13]	Radtke [12]	Borzych-Duzalka [9]	LaPlant [14]	Radtke [15]	Imani [18]	Nikibakhsh [20]
Publication year	2015, Korea	2016; USA	2016, Germany	2017, international	2018, USA	2018, Germany	2018, USA	2018, Iran
Study period	1986–2012 Retrospective, single center	2002–2014 Retrospective, single center	2009–2014 Retrospective, single center	2007–2015 Registry data International	2005–2017 Retrospective Two centers	2009–2015 Retrospective Two centers	Retrospective, single center, 2002–2015	2005–2011 Retrospective, single center
Number of patients	60 patients (70 catheters)	116 patients, 173 catheters	60 (71 catheters)	2453 (824 incident, 1629 prevalent)	130 patients, 157 catheters	122 patients, 154 catheters	25 catheters, only <2 years	56
Age at dialysis initiation	9.9 ± 5.5 (at dx initiation)	9.7 ± 6.3 years (2 days to 22 years)	Median: 3.3 (0.01–15.5) years	Median 10.5 (IQR: 3.4–14.2) years	4 ± 5.3 years (1 day to 23 years) – 46% infants	Median: 3.0 (0.01–17.1) years	Median: 18 (7–121) days, 60% neonate	Median: 6.5 y (1 month – 14 years)
Insertion technique	–	Open (122) and laparoscopic (51) ± partial omentectomy (34%)	Open surgical	All	Mainly open and laparoscopic (*n* = 20, 13%) + omentectomy	Open ± partial omentectomy	Laparoscopic (84%) ± omentectomy (40%)	Open surgical ± omentectomy
PD modality	CAPD	All CPD	33 CPD, 37 acute	Chronic PD	Acute and CPD	89 catheters for CPD, remaining for acute use	CPD	Acute (21) and CPD (35) (>3 weeks on PD)
Catheter type	Two-cuffed straight Tenckhoff, downward-pointing ES	Double cuffed catheters	One cuffed	All types	Argyle curl catheters (no straight tunnel) upward-pointing ES	One-/double-cuffed curled and straight catheters in small children (*n* = 19), downward ES	One/double (29%)-cuffed curled (48%) and straight catheters	Swan-neck coil two cuff
Timing of catheter use				Immediately, <7 day, ≥7 day	Same day and later on – 22% delayed use		Use within 3 days (48%)	Immediate use
Hernia	Hernia (8.6%)				10% 15% in infants, and 5% in older children		20% hernia at catheter insertion (60% of newborns)	

Leak	Leakage (10.0%)		7.1% (only in <10 kg)	29 (%1)	14% 21% leakage for infants vs 8% for others	18 (11.7% of catheters) (25.5% for pts. < 10 kg vs 5.6% for pts. > 10 kg)	32% (71% of newborns)	5.35%
Dislocation	Catheter tip migration (2.9%)	7% (15% for pts. < 2 years vs 5% for those >2 years)	10%		6%	16 (10.4% of the catheters)	18%	
Malfunction (obstruction, drainage problems)	Outflow failure (14.3%)	24% (including leak and kink)	12.9%	270 (%11)	6% – adhesion	31 (20.1% of catheters) (15 – omental trapping)	26%	21.4%
Catheter exchange	Catheter malfunction, injury, and oozing resulted in catheter removal in 7 (11.6%) patients – catheter exchange rate is 7.1% (n = 5)	34% of the patients had their catheter exchanged due to NI causes (dysfunction more in children <2 years)	17 out of 70 catheters (24.3%) needed a surgical revision within 6 months after implantation	Catheter malfunction and leakage resulted in catheter exchange in 7.8% of the pts. (n = 192)[b]	17% of the patients had their catheter exchanged (8 for leakage, 3 migration, 1 adhesion, 1 hernia)	53 (34.4%) catheters underwent revision	18 new catheters (72%) were inserted within 12-month follow-up	8.3% of CPD patients transferred to HD NI complications are same with immediate use.

CPD chronic peritoneal dialysis, *ES* exit-site, *IQR* interquartile range, *NI* non-infectious, *y* years, *d* days, *pts*. patients

[a]Other noninfectious complications: peritoneal bleeding (7.1%), inflow or outflow pain (4.3%), catheter injury by patient or caregiver (2.9%), and abdominal distension (1.4%); metabolic complications: 5% of the patients

[b]Access revision: 13% of all patients and 23% of incident patients required one or more access revisions

A decreasing overall incidence of leakage was reported by the Italian registry, possibly related to improved surgical experience [8]. In a prospective, open-label randomized study performed in a single pediatric center, the application of fibrin glue to the peritoneal cuff suture prevented early dialysate leakage [39]. Overall, the surgical approach, the number of cuffs, and the primary renal diagnosis were not predictors of initial catheter complications [18]; however, omentectomy may be a risk factor for leakage by recognizing the rate of leakage as 25% vs 5% in patients with or without omentectomy [19].

Diagnosis

The presence of fluid around a peritoneal catheter may be due to leakage of dialysate or to serosanguineous fluid extruding from the subcutaneous tissue. If the etiology of the fluid is unclear, a dialysate leak can be confirmed by checking the glucose concentration of the leaking fluid.

Fluid infiltration of the abdominal wall is easily overlooked, particularly in obese patients. Reduced drain volumes may occur because a substantial portion of the dialysate leaks into the abdominal wall and once a steady state is achieved is absorbed at a rate equal to the leakage rate. Normal solute equilibration in the PET, with apparently lacking ultrafiltration, suggests the diagnosis of "internal" leakage. The most widely used approach to confirm the diagnosis and to determine the exact site of fluid leaking into the abdominal subcutaneous tissue and/or intermuscular layers is T2-weighted MRI with an empty and filled abdominal cavity or CT with contrast agent-added PD fluid [33, 37].

Groin or genital swelling caused by leaks (Fig. 17.1c) is usually related to underlying hernias (which are often palpable), with a patent processus vaginalis, or a peritoneal membrane defect along the catheter tract. Scrotal swelling is much more common than labial swelling; it is generally bilateral. Leakage into the pleural space will be discussed separately below.

Management

Successful management of pericatheter leaks can usually be accomplished by decreasing the dialysate volume. Occasionally, converting the patient to continuous peritoneal modalities in which exchanges occur when supine or application of temporary hemodialysis may resolve dialysate leakage. Leaks that do not respond to conservative management may require minor surgical repair of the deep cuff or rarely catheter replacement. Surgical repair has been strongly suggested for leakage causing genital swelling [33, 37].

Hernia

Hernia is a common complication in children on PD, with a reported incidence up to 30% across pediatric series (Table 17.2). Several different types of hernias have been described in PD patients. The sites of anatomic weakness that predispose to hernia formation include the inguinal canals with or without patent processus vaginalis, the umbilicus, the linea alba, the exit site, and any sites of prior surgical incision (Fig. 17.1d).

Risk Factors

The risk of PD-associated hernia in children is affected by the intraperitoneal pressure (IPP), the patient age [14, 16, 18, 40–42], and the presence of anatomically weak sites in the abdominal wall [40]. Infants compared to older children had a three times higher risk of hernia development (15% vs 5% and 33% vs 11%, in different series) [14, 16]. In a study from the USA, 20% of 25 infants starting CPD during the first 2 years of life had hernia at catheter insertion; 60% of those cases were newborns, and presence of a hernia was one of the main predictors of initial PD catheter failure in small infants [18]. Therefore, the risk of hernia seems to be confined to neonates and infants [14, 16, 18], due to their high incidence of patent

processus vaginalis and, possibly, higher intra-abdominal pressure. These findings support the concept of prophylactic closure of the processus vaginalis at the time of catheter insertion in neonates and young infants. Recently in adults, combined hernia repair and PD catheter placement has been shown as a safe procedure [43]. However, the presence of a hernia at PD catheter placement with or without repair was associated with dialysate leak in neonates and infants [18].

Abdominal wall hernias are not uncommon in patients on CAPD, and some risk factors have been identified in adult patients. These include female gender, increasing age, longer time on peritoneal dialysis, increasing number of laparotomies, and multiparity [44]. However, there is no clear data in children.

Clinical Features

The most common presentation of the hernia is a painless swelling. Other symptoms associated with abdominal hernia in PD patients include discomfort or disfigurement and problems related to a complication from the hernia. Complicated hernias present as a tender lump, recurrent gram-negative peritonitis, bowel obstruction, and perforation, if there is strangulation or incarceration of the bowel. An umbilical hernia has a special predilection for strangulation. Catheter and other incisional site hernias and least commonly inguinal hernias may lead to incarceration and strangulation of the bowel. These complications are also more likely when the hernia is small, preventing the free movement of bowel into and out of the hernia sac. The presence of genital swelling may suggest occult indirect inguinal hernias [2]. Additionally, hernias may be associated with poor PD outcomes because of ineffective dialysis from increases in hernia size with increasing dwell volumes.

Diagnosis

Patients can easily be diagnosed clinically. MRI or CT peritoneography is a useful confirmatory diagnostic procedure. Peritoneal scintigraphy is usually used in patients who are allergic to contrast dye and in centers where MR peritoneography is not available [2].

Prevention

There are several implantation best practice recommendations for preventing leakage and hernias. Two-cuff designs and placement of the deep cuff at an intramuscular location are preferred. Intramuscular cuff placement results in fewer pericatheter leaks and hernias. In infants and children, a paramedian fascial incision is usually preferred in order to avoid herniation or dialysate leakage [8]. However, surprisingly, the number of catheter cuffs was not significantly associated with catheter outcomes in a recent cohort of infant PD [18]. Laparoscopic catheter placement is an attractive alternative to open surgical insertion, since it allows complete visualization of the peritoneal cavity, including inspection of the inner inguinal ring and prophylactic closure of patent processus vaginalis in infants [22]. A recent paper from the USA reported that three umbilical hernias, three bilateral inguinal hernias, and two ventral hernias were successfully repaired in 8 of 21 pediatric patients during laparoscopic PD catheter placement [22].

Intraperitoneal pressure (IPP) can be easily measured using a central venous pressure scale attached to the PD tubing system as the mean of inspiratory and expiratory pressure in the midaxillary line in the supine position. IPP in the empty abdominal cavity is 0.5–2.2 cmH_2O, increasing with rising amounts of fluid volume and change in posture. The supine position generates the lowest IPP for a given volume of IP fluid [2]. Biocompatible PD solutions reduce IPP by 15–20%. On the other hand, IPP increases with obesity and organomegaly, for example, autosomal recessive polycystic kidney disease. Likewise, abdominal pain and constipation increase IPP [45]. IPP monitoring may be used as an objective measure to guide fill volume prescription by determining how much intraperitoneal volume is tolerated and potentially lower the risk of mechanical complications such as hernia and leakage [40, 41, 45], although the concept has not been verified in RCTs. In children, IPP is usually acceptable up to 13–14 cmH_2O, which corresponds to a mean fill volume of 1400 mL/m^2. Abdominal pain is not reported below 12 cmH_2O. Below 2 years of age, IPP should not be above 8–10 cmH_2O, that is,

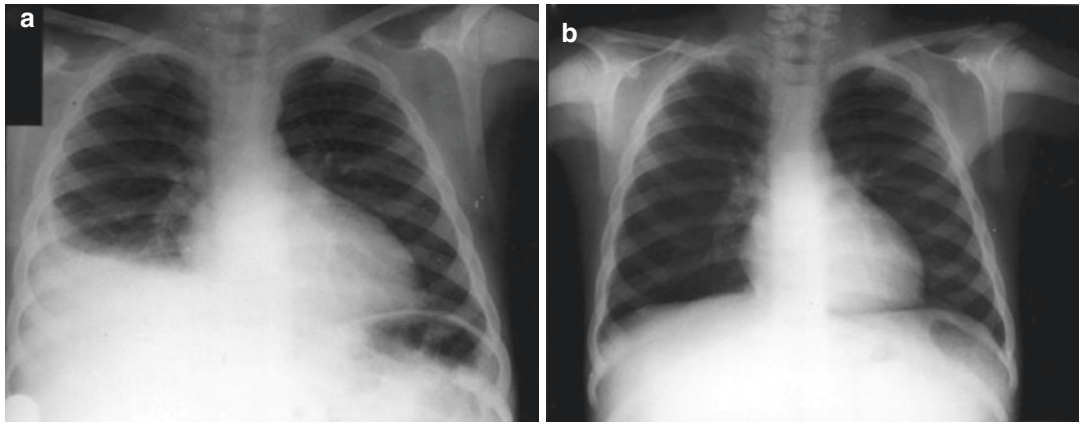

Fig. 17.2 (**a**) Right-sided massive pleural effusion. (**b**) Complete resolution of pleural effusion after pleurodesis with tetracycline. (With permission of Sevcan A. Bakkaloglu, MD)

in most cases fill volume not above 800 mL/m^2. Otherwise, the risk of hernia and leakage increases considerably in infants [45].

Treatment

Most hernias need surgical repair [33]. Repair of preexisting hernias and delaying PD catheter use to allow for a longer period of healing reduces the risk of complications and improves the overall catheter survival [18]. If immediate use of PD catheter is necessary, patients should be maintained on low-volume nocturnal cyclic PD, with an empty or small-volume dwell during daytime.

Hydrothorax

Hydrothorax is an uncommon but well-recognized complication of peritoneal dialysis. The reported incidence of hydrothorax varies from 1.6% to 10%. It can present as an asymptomatic effusion found on a chest radiograph ([46], Fig. 17.2a), or it can be massive, causing major respiratory symptoms. Hydrothorax can follow the first few dialysate exchanges or occur after years of uneventful PD [37]. Increased intra-abdominal pressure after instillation of fluid into the peritoneal cavity can result in leakage of the PD solution from the peritoneal cavity into the pleural space across the diaphragm. The pleural to peritoneal connection is almost always on the right side. The presence of the heart and pericardium may prevent the leak of fluid across the left hemidiaphragm. The condition should be differentiated from other causes of transudative pleural effusion, such as congestive cardiac failure, hypoalbuminemia, or fluid overload for any reason [2, 37]. Spontaneous leakage of dialysate fluid from the peritoneal cavity into the pericardium via a pericardioperitoneal fistula, "hydropericardium," is an extremely rare, potentially life-threatening complication of PD [47].

Pathogenesis

The physiopathology of hydrothorax is not entirely clear. It is most commonly secondary to a pleuroperitoneal communication. Possible mechanisms include a disorder of lymphatic drainage, pleuroperitoneal pressure gradient, and congenital diaphragmatic defects. A disorder of lymphatic drainage was suggested by the finding of diaphragmatic lymphatic swelling after peritoneal fluid instillation during surgical exploration. In autopsy studies, discontinuities in the tendinous portions of the hemidiaphragms have been

observed, thereby supporting the presence of diaphragmatic defects. In addition, the negative intrathoracic pressure combined with an increased intra-abdominal pressure caused by dialysate instillation may open small defects in the diaphragm and promote the flow of dialysate into the pleural space [2, 37].

Clinical Features

The most common clinical symptom is shortness of breath, which can be mistaken for congestive heart failure. Patients may use more hypertonic dialysis solution to increase ultrafiltration; however, that will lead to a further increase in the intra-abdominal pressure and subsequently worsening of symptoms. Physical examination will reveal decreased or absent breath sounds and stony dullness on percussion.

Diagnosis

Chest X-ray may show right-sided pleural effusion (Fig. 17.2a). The presence of left-sided pleural effusion should prompt the clinician to evaluate for other secondary causes of hydrothorax. Thoracocentesis with biochemical analysis of pleural fluid is the first-line investigation. A transudative effusion with high glucose content (>300–400 mg/dL or pleural fluid to serum glucose concentration gradient >50 mg/dL) proves the peritoneal origin of the pleural fluid. In patients with icodextrin solution, iodine mixed with the effluent results in a bluish-black discoloration, which is diagnostic for PD-induced hydrothorax [48]. In uncertain cases, or when there is a clinical need to demonstrate the anatomy of the communication, an imaging approach such as MRI or CT peritoneography can also be used [2, 49].

Treatment

Once hydrothorax secondary to pleuroperitoneal communication is confirmed, temporary cessation of PD remains the first-line treatment. Frequent small-volume exchanges can be a feasible alternative in children. In case of acute shortness of breath, discontinuation of PD and immediate thoracocentesis are indicated. PD can often be resumed after temporary cessation, presumably because of spontaneous resolution of the leakage.

Current evidence in adults shows that video-assisted thoracoscopic pleurodesis or diaphragmatic repair should be the treatment of choice in patients who failed conservative management [49]. Chemical pleurodesis has been performed with talc, autologous blood, and tetracycline ([46], Fig. 17.2b), with uneventful recovery both in children and adults [2, 46, 49]. There is no evidence to suggest that one agent is superior to another. The main side effect of these sclerosing agents is pain. Open surgical treatment is the last option for recurrent hydrothorax [2, 49].

Technique-Related Complications

Peritoneal Membrane Failure

Peritoneal membrane failure is an important complication of PD characterized by ultrafiltration failure (UFF) and/or inadequate solute removal. It ensues due mainly to structural and functional changes in the peritoneal membrane attributable to severe, persistent, and/or relapsing intraperitoneal infection and the use of conventional bio-incompatible PD solutions, which are hyperosmolar, acidic, has lactate buffer and contains high concentrations of glucose and glucose degradation products (GDPs) (see Chap. 12).

Pathogenesis

Continuous exposure to bio-incompatible PD solutions and bacterial infection triggers inflammation of the peritoneal membrane, which leads to the release of endogenous cellular compo-

nents and matrix degradation products that cause progressive fibrosis, neoangiogenesis, vasculopathy, epithelial-to-mesenchymal transition (EMT) of mesothelial cells, collagen deposition in the sub-mesothelial compact zone and, ultimately, UFF. A peritoneal biopsy study clearly showed that PD treatment per se had a strong impact on peritoneal fibrosis and vasculopathy. The thickness of the sub-mesothelial zone and the extent of vasculopathy were positively correlated with the duration of PD, and inversely with UF capacity [50].

There is emerging evidence that toll-like receptor (TLR) activation of peritoneal mesothelial cells is linked to fibrosis of the membrane; thus, TLRs may be a potential therapeutic target for preventing fibrosis and membrane failure [51]. EMT of peritoneal mesothelial cells is also an important mechanism involved in the process of peritoneal membrane failure. EMT is induced by multiple stimuli, which include GDPs and advanced glycation end products and inflammatory cytokines, such as TGF-beta. Mesothelial cells that undergo EMT promote neoangiogenesis through VEGF expression. Dysfunctional aquaporin 1 (AQP1) in peritoneal endothelial cells is another putative mechanism of UFF. Peritoneal neoangiogenesis is probably the main effector of increased solute transport and UFF in long-term PD. In addition, mast cells and various genetic factors controlling angiogenesis and fibrosis and effects of medications may modulate the rate at which UFF develops. However, the relative roles of fluid components, bacterial inflammation, genetic disposition, drugs and other factors, and the precise sequence of the pathophysiologic events, initiating and propagating peritoneal fibrosis and angiogenesis, remain elusive [50].

Differential Diagnosis

The ability to evaluate for UFF is of major clinical importance. In the case of low drain volumes, a distinction must be made between catheter dysfunction, leakage of fluid either externally through the catheter tunnel or internally from the peritoneal cavity to the pleural space, and impairment of the peritoneal membrane. In fact, multiple membrane-related causes should be considered, which include the following:

1. Large functional peritoneal surface area relative to the size of the fill volume, the result of either too low a prescribed fill volume or too large a vascular surface area secondary to hyperperfusion (e.g., GDP-induced neoangiogenesis)
2. Impaired free-water transport as a result of aquaporin dysfunction
3. High lymphatic absorption associated with a marked elevation of IPP
4. Limited peritoneal surface area available for exchange, as might occur with postinfectious or postsurgical adhesions, peritoneal fibrosis, or peritoneal sclerosis [41]

The causes of membrane failure can be distinguished in part by the peritoneal equilibration test (PET, see Chap. 11). The peritoneal membranes can be classified according to PET results into high, high-average, low-average, and low transporter categories. The high transporter status is associated with a poor technique and even patient survival in adults, probably due to increased glucose resorption, leading to UFF, fluid overload, hypertension and left ventricular hypertrophy, increased atherogenesis, and malnutrition related to increased peritoneal protein losses [52, 53]. Children with high transporter status are at risk for poor longitudinal growth [54].

Management

The traditional method to treat membrane failure is to use short exchanges with hypertonic dialysate. However, exposure to the high glucose concentration in hypertonic dialysate can accelerate the process of peritoneal inflammation and neoangiogenesis, thereby further aggravating UFF. Therefore, the protection of the peritoneal membrane from the long-term toxic and metabolic effects of conventional high GDP-containing, glucose-based solutions would be ideal [53, 55]. More biocompatible PD solutions may preserve peritoneal membrane function and

promote ultrafiltration (see Chap. 12 for details). In children with established UFF, PD fluids containing icodextrin as osmotic agent may be of some value, both by their greater efficacy in inducing ultrafiltration [55, 56] and by minimizing peritoneal glucose exposure (see Chap. 12 for details). However, the level of evidence to support the use of biocompatible fluid to prevent or treat peritoneal membrane failure is not adequate. In a recent Cochrane review of 42 studies including adults and children, due to the inconsistency of reporting and low methodologic quality of studies, the impact of biocompatible solutions on long-term peritoneal membrane function was determined to be uncertain [57].

Prognosis

Membrane failure is responsible for up to 27% of CPD termination in different pediatric series [5, 6, 58]. Altered peritoneal membrane function over time has a significant impact on both technique and patient survival. As the prevalence of UF failure increases, it becomes the predominant reason for dropout in long-term PD, particularly in anephric and oliguric patients. According to the Japanese long-term experience, the frequency of PD termination due to UFF steadily increases with time on PD, from 14% in the first 5 years of treatment to 33% thereafter [58]. In contrast, insufficient solute removal was a constant cause of technique failure in 13% of cases before and after 5 years on PD.

The prognosis of membrane failure is not unvariably poor and likely depends on the underlying mechanism of the high transporter phenotype. Recent classification attempts to differentiate the various types: "type 1," an early inherent type of membrane failure associated with increased mortality related to marked underlying comorbidity and inflammation; "type 2," an early inherent type with a large peritoneal surface area; and "type 3," a late-acquired type with peritoneal membrane changes which develop with time on PD. The latter two types have a good prognosis provided that fluid balance is controlled using APD and icodextrin-based PD solution [52].

Ultrafiltration failure due to an elevated peritoneal solute transport may be transient or sustained. Transient increases are seen during episodes of peritonitis. In some cases, repeated episodes of peritonitis lead to a sustained increase in solute transport and a persistent loss of ultrafiltration. Other factors like prolonged PD vintage, dialysate buffer, glucose and buffer byproducts used in the dialysate, and the use of beta-blockers may contribute to impaired ultrafiltration [53].

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare, but serious, complication of long-term PD, characterized by encasement of the bowel loops accompanied by extensive sclerotic thickening of the peritoneal membrane. Clinical features of EPS result from underlying pathogenic processes, particularly ileus, inflammation, and/or peritoneal adhesions. Signs and symptoms frequently include abdominal pain, nausea, vomiting, fatigue, loss of appetite, constipation, diarrhea, abdominal mass, ascites, weight loss, low-grade fever, and hemorrhagic effluent [59]. It is also typically associated with a progressive loss of ultrafiltration, resulting in fluid retention and edema. Unlike other causes associated with these clinical findings, EPS is an insidious, gradual, non-acute clinical syndrome [58]. It is important to recognize that EPS may also present long after the cessation of PD [60].

Pediatric registries from Japan, Italy, and the European Pediatric Dialysis Working Group (EPDWG) report an incidence of 1.5–2% for EPS in children on PD [61–63]. In the Japanese registry, all patients who developed EPS had received PD for longer than 5 years, with a mean PD duration of 10.3 years. The incidence of EPS was 6.6% among all patients on PD for longer than 5 years and 22% among those who had received PD for longer than 10 years [62]. Similar results were found in the Italian and EPDWG registries [61–63].

Pathogenesis

The etiology of EPS is believed to be multifactorial. Potential risk factors for the development of EPS include extended duration of PD; previous frequent severe peritonitis episodes; a reaction to other foreign agents, such as plasticizers from catheters; exit-site cleansing agents, such as povidone-iodine or chlorhexidine; and extended exposure to bio-incompatible dialysis solutions [58]. Of note, there was no difference reported in the incidence of EPS between biocompatible and standard PD solutions in the Italian and EPDWG registries [61–63].

Diagnosis

The diagnosis of EPS is suspected in the patient with a long history of PD, signs and symptoms consistent with SEP, and/or progression to a high peritoneal permeability state and is confirmed with radiographic or histological findings of bowel encapsulation. Imaging with computed tomographic (CT) scanning is recommended to evaluate for characteristic signs, such as peritoneal calcification, bowel thickening, bowel tethering, bowel dilatation, and localized ascites. (Fig. 17.3) [64, 65]. Peritoneal membrane thickening is common among long-term PD patients and without symptoms is not, in and of itself, diagnostic of EPS.

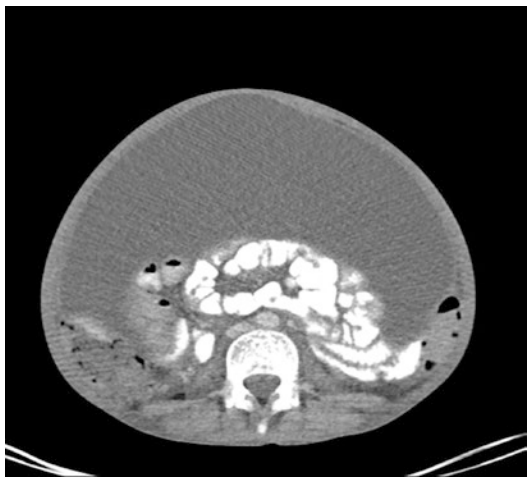

Fig. 17.3 Massive ascites secondary to EPS pushing stomach and intestinal loops posteriorly. (With permission of Sevcan A. Bakkaloglu, MD)

Treatment

Although frequently unsuccessful, the treatment of sclerosing peritonitis most commonly entails cessation of PD with transfer to hemodialysis and bowel rest with total parenteral nutrition (TPN). In addition, drug therapy with corticosteroids, tamoxifen (a selective estrogen receptor modulator that inhibits the production of TGF-β by fibroblasts), and other immunosuppressive agents including, azathioprine, sirolimus, and mycophenolate mofetil have been tried with variable results [58, 65]. There are no consensus guidelines for the use of drug therapy in EPS [61–63]. Surgery is indicated for bowel obstruction, bowel perforation, hemoperitoneum, or lack of improvement with drug therapy.

Prognosis

EPS is the most serious complication of long-term PD with a mortality ranging from 14% to 38% [61–63]. The major causes of death are almost invariably related to problems concerning bowel obstruction or complications of surgery, such as malnutrition or septicemia. Therefore, a high index of suspicion and elective discontinuation of PD in high-risk patients is of particular importance for the early diagnosis and prevention of potentially fatal outcome. The development of UFF, a high dialysate/plasma creatinine ratio, peritoneal calcification, a persistently elevated C-reactive protein level, and severe peritonitis in patients on PD for longer than 5 years are signals that should prompt the clinician to consider terminating PD as a possible means of preventing the development of EPS [58]. However, there is no evidence to support the benefit of routine transitioning to hemodialysis for all long-term PD patients as EPS is very rare.

Metabolic Complications

Dyslipidemia and Insulin Resistance

Disturbances of lipid and glucose metabolism are the common complications of chronic renal failure and persist or deteriorate during renal replacement therapy. The few reports available in

pediatric PD patients are consistent with findings of adult studies, indicating insulin resistance, hyperleptinemia, dyslipidemia, and an atherogenic lipid profile [4, 66–69]. The pathophysiology of these metabolic complications in PD patients is multifactorial, including the continuous administration of glucose in the dialysate, albumin and HDL losses into the peritoneal cavity, and reduced lipolytic enzyme activity.

Serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, apolipoprotein A, and lipoprotein (a) levels are elevated, and HDL lipoprotein levels are decreased in children on PD. The prevalence of dyslipidemia differs by dialysis modality, with PD conferring an increased risk for dyslipidemia compared to hemodialysis. Dyslipidemia was reported in 85.1% of PD patients and 76.1% of hemodialysis patients in the European ESPN/ERA-EDTA registry of 976 children with ESRD. Interestingly, younger age on PD was associated with a more adverse lipid profile. Monitoring for dyslipidemia with annual fasting lipid level measurements is recommended in children on chronic PD [70]. Therapeutic lifestyle modifications including moderate-to-vigorous exercise and reduction in sedentary activities and dietary fat are vital for primary prevention of dyslipidemia. There is currently a lack of evidence regarding the efficacy of pharmacological treatment of dyslipidemia in children, although statin therapy can be considered for children ≥10 years old that fail nonpharmacologic treatment [71]. The direct benefit of statin therapy in reducing the mortality from cardiovascular disease in children on dialysis is not yet proven.

As has been shown in adults, glucose intolerance and insulin resistance are of concern because they may be risk factors for cardiovascular disease in children on PD. In a study that included 31 pediatric PD patients, 54.8% demonstrated glucose intolerance, 25.8% had impaired fasting glucose, 22.6% had impaired glucose tolerance, 6.5% were diagnosed with diabetes mellitus, and 9.7% had insulin resistance. There were no differences in these parameters when compared to hemodialysis patients [69]. There are currently no pediatric specific guidelines for the monitoring of glucose metabolism. Minimization of glucose in the PD prescription and the use of icodextrin for the long-dwell dialysis solution are strategies that can be implemented in children with glucose abnormalities.

Hypokalemia

As compared with pediatric patients on hemodialysis, patients on PD are at increased risk of hypokalemia because of the greater cumulative clearance of potassium by PD [72]. Also, enhanced cellular uptake of potassium, prompted by the intraperitoneal glucose load with subsequent insulin release, and bowel losses may also play a role in the hypokalemia observed in PD patients. Furthermore, cultural dietary preferences are likely to affect the disposition to hypokalemia on PD. Kt/V urea, the etiology of renal failure, age, the peritoneal membrane transport type, and oral protein and caloric intake appear not to be related to hypokalemia [73].

Hypokalemic patients complain of weakness more often than those with normal potassium levels. For stable chronic outpatients, liberalization of dietary potassium restriction and, when needed, oral potassium replacement (based upon individual patient serum potassium determinations) are usually successful treatments for hypokalemia.

Hypermagnesemia

Hypermagnesemia, a common finding in PD patients, is due to positive magnesium balance, resulting from renal failure and the relatively high dialysate magnesium concentration. The typical serum magnesium level in patients with ESKD is 2.4–3.6 mg/dL (1.0–1.5 mmol/L), a value usually not associated with clinical symptoms. Serum magnesium levels are usually elevated in those dialyzed against solutions containing magnesium concentrations of 0.75 mmol/L (1.8 mg/dL) [74]. Since there is an inverse relationship between concentrations of magnesium and intact parathyroid hormone

(PTH), raising the possibility that hypermagnesemia may contribute to adynamic bone disease [75], the 0.50 mmol/L (1.2 mg/dL) concentration dialysate may generally be preferable. Hypomagnesemia may develop in patients utilizing 0.25 mmol/L (0.6 mg/dL) magnesium concentration [74].

Other Complications

Hemoperitoneum

The presence of blood in PD effluent is called hemoperitoneum. This is a benign complication of chronic PD. Only a very small amount of bleeding is required to make dialysate appear bloody. As little as 1 mL of whole blood injected into 2 L of an effluent bag can make the fluid readily blood tinged, and injection of 7 mL of blood can make the entire volume as red as fruit juice.

Pathogenesis

Hemoperitoneum has a wide differential diagnosis. Blood tinging of dialysate is commonly seen after PD catheter placement, as a result of direct vascular and visceral damage. It rapidly clears with a few in-and-out exchanges. The most common and benign cause of hemoperitoneum in adolescent girls is menstruation. Two theories are proposed to explain its mechanism. First, endometrial tissue, if present in the peritoneum, will shed simultaneously with uterine endometrium. Secondly, shed endometrial tissue and blood moves out of the cervix through the fallopian tubes in a retrograde fashion. Peritoneal bleeding starts a few days before vaginal menstrual flow. Other causes of hemoperitoneum in adolescent girls are ovulation (with a typical mid-cycle timing of occurrence) and ruptured ovarian cysts.

Trauma (including strenuous exercising), procedures to the abdominal area, bleeding disorders, or anticoagulation therapy can also predispose to hemoperitoneum. Bleeding into a hepatic or renal cyst with rupture into the peritoneal cavity, acute and chronic pancreatitis, sclerosing peritonitis, and peritoneal calcification in patients with severe CKD-associated mineral-bone disorder are further, less frequent causes of hemoperitoneum [2].

Diagnosis

The extent of bleeding and associated symptoms are of primary importance in determining further evaluation. If bleeding is very mild, self-limited, and not associated with other symptoms, the patient may not require further evaluation. This is especially likely if the patient is menstruating. If the bleeding is severe, recurrent, and/or associated with pain and fever, urgent evaluation is required to exclude underlying intra-abdominal pathology, such as cyst rupture or a vascular catastrophe. Findings on physical examination such as a rebound or guarding do not occur with benign intraperitoneal bleeding and should be treated as a surgical emergency. In this setting, peritoneal fluid cell count, culture and sensitivity, and peritoneal amylase level (>50 μU/L suggests an intra-abdominal process) should be obtained. Peritoneal dialysate hematocrit >2% suggests an intraperitoneal pathology. All of the possible disorders in this setting are cause for great concern, and merit surgical consultation and consideration of early laparoscopy or laparotomy [2].

Abdominal imaging by CT, ultrasound, or MRI may also be indicated. A CT scan of the abdomen and pelvis should be performed if ultrasound is negative or inconclusive. In patients with persistent bleeding, isotope-labeled RBC scan can be done to localize the site of bleeding, which can then be selectively embolized. Contrast agents should be avoided in patients with preserved residual function. Angiography is the last option that may be required for more definitive diagnosis [2].

Management

Treatment of the underlying cause is essential, and curative management may require emergent evaluation and care. Menstruating adolescent girls should be reassured that asymptomatic hemoperitoneum is benign and that it will likely resolve spontaneously. Rapid flushes and instillation of heparin in the dialysate to prevent catheter clotting are usually done. Infusing cool dialysate

(i.e., room temperature) may also be helpful. Most commonly, the hemoperitoneum will clear after one to three rapid flushes. In severe conditions, extensive diagnostic studies and required surgical interventions should be done as indicated [2, 76].

Acute Pancreatitis

Acute pancreatitis (AP) is characterized by inflammation of the pancreas, which presents with acute onset of epigastric abdominal pain accompanied by epigastric tenderness on physical exam. The incidence rate of AP in children on PD was reported to be 6.2 per 1000 person-years in the Italian Registry of Pediatric Chronic Dialysis [77]. The risk of AP is higher in hemodialysis patients compared to PD, and patients on dialysis appear to be at a higher risk for AP than the general population.

Pathogenesis

Patients with ESKD may be at increased risk for AP due to the decreased catabolism of gastric hormones that may lead to hypersecretion of the pancreatic enzyme trypsin. Trypsin hypersecretion is thought to induce morphologic changes in the pancreas that could make the pancreas more susceptible to inflammation. In addition, it has been hypothesized – but not proven – that PD may directly contribute to the risk for AP. Dialysate fluid containing glucose and calcium may theoretically irritate the pancreas. Hyperglycemia, hypercalcemia, as well as hypertriglyceridemia are known causes of AP in the general population. Furthermore, it has been suggested that repeated episodes of peritonitis may release enzymes that irritate and cause inflammation of the pancreas.

Diagnosis

The diagnosis of AP may be difficult to distinguish from peritonitis in children on PD. Patients with AP present with an acute onset of severe epigastric abdominal pain. Pain will often radiate to the back, which may be relieved by sitting forward. AP is usually accompanied by nausea and vomiting. On physical examination, there is tenderness to palpation in the epigastric region or there may be diffuse abdominal tenderness. Abdominal distension and hypoactive bowel signs may be present due to underlying ileus. Patients with severe AP often present with fever, dyspnea, tachypnea, and hypotension.

Diagnostic criteria for AP include two of the following: (1) characteristic epigastric pain or pain radiating to the back, (2) elevated serum lipase or amylase to three times the upper limit of normal, or (3) radiographic evidence of AP by CT, MRI, or ultrasound. Reliance on serum pancreatic marker criteria may not be possible in children on PD, since amylase and lipase are often elevated above three times the upper limit in asymptomatic patients. The elevation in pancreatic enzymes is due to decreased urinary excretion and the minimal clearance of the enzymes by PD [78]. In children treated with icodextrin, amylase may be reduced due to the competitive inhibition by icodextrin on the amylase assay [79]. Therefore, radiologic studies may be required to aid in the diagnosis of AP. Focal or diffuse enlargement of the pancreas is suggestive of AP. Imaging may also be required later in the clinical course to evaluate for necrotizing pancreatitis and other complications.

Management

Treatment of AP is mainly supportive with recommendations for bowel rest, intravenous fluids or parenteral nutrition, and pain control. Prophylactic antibiotics can be considered for prevention/treatment of necrotizing pancreatitis. Continuation of PD during AP is often possible. Surgical treatment may be necessary in cases of necrotizing pancreatitis or pseudocyst.

Prognosis

Most episodes of AP are mild and most patients recover without complications or recurrence; however, AP can be severe with complications. Complications include pancreatic pseudocyst, necrosis, systemic inflammatory response syndrome, and organ failure. Mortality reported among adult dialysis patients varies from 8% to 58%. A culmination of 32 children on dialysis

from pediatric series reported in the literature demonstrated the prevalence of mortality to be 22% [77].

References

1. McCormick BB, Bargman JM. Noninfectious complications of peritoneal dialysis: implications for patient and technique survival. J Am Soc Nephrol. 2007;18:3023–5.
2. Saha TC, Singh H. Noninfectious complications of peritoneal dialysis. South Med J. 2007;100:54–8.
3. Kim JE, Park SJ, Oh JY, Kim JH, Lee JS, Kim PK, Shin JI. Noninfectious complications of peritoneal dialysis in Korean children: a 26-year single-center study. Yonsei Med J. 2015;56:1359–64.
4. Bakkaloglu SA, Ekim M, Tumer N, Soylu K. The effect of CAPD on the lipid profile of pediatric patients. Perit Dial Int. 2000;20:568–71.
5. Verrina E, Edefonti A, Gianoglio B, Rinaldi S, Sorino P, Zacchello G, Lavoratti G, Maringhini S, Pecoraro C, Calevo MG, Turrini Dertenois L, Perfumo F. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
6. Honda M. The 1997 report of the Japanese National Registry data on pediatric peritoneal dialysis patients. Perit Dial Int. 1999;19(Suppl 2):S473–8.
7. Vidal E, Edefonti A, Murer L, Gianoglio B, Maringhini S, Pecoraro C, Sorino P, Leozappa G, Lavoratti G, Ratsch IM, Chimenz R, Verrina E, Italian Registry of Paediatric Chronic Dialysis. Peritoneal dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. Nephrol Dial Transplant. 2012;27:388–95.
8. Rinaldi S, Sera F, Verrina E, Edefonti A, Gianoglio B, Perfumo F, Sorino P, Zacchello G, Cutaia I, Lavoratti G, Leozappa G, Pecoraro C, Rizzoni G, Italian Registry of Pediatric Chronic Peritoneal Dialysis. Chronic peritoneal dialysis catheters in children: a fifteen-year experience of the Italian Registry of Pediatric Chronic Peritoneal Dialysis. Perit Dial Int. 2004;24:481–6.
9. Borzych-Duzalka D, Aki TF, Azocar M, White C, Harvey E, Mir S, Adragna M, Serdaroglu E, Sinha R, Samaille C, Vanegas JJ, Kari J, Barbosa L, Bagga A, Galanti M, Yavascan O, Leozappa G, Szczepanska M, Vondrak K, Tse KC, Schaefer F, Warady BA, International Pediatric Peritoneal Dialysis Network Registry. Peritoneal dialysis access revision in children: causes, interventions, and outcomes. Clin J Am Soc Nephrol. 2017;12:105–12.
10. Aksu N, Yavascan O, Anil M, Kara OD, Erdogan H, Bal A. A ten-year single-centre experience in children on chronic peritoneal dialysis – significance of percutaneous placement of peritoneal dialysis catheters. Nephrol Dial Transplant. 2007;22:2045–51.
11. Bakkaloglu SA, Ekim M, Sever L, Noyan A, Aksu N, Akman S, Elhan AH, Yalcinkaya F, Oner A, Kara OD, Caliskan S, Anarat A, Dusunsel R, Donmez O, Guven AG, Bakkaloglu A, Denizmen Y, Soylemezoglu O, Ozcelik G. Chronic peritoneal dialysis in Turkish children: a multicenter study. Pediatr Nephrol. 2005;20:644–51.
12. Radtke J, Lemke A, Kemper MJ, Nashan B, Koch M. Surgical complications after peritoneal dialysis catheter implantation depend on children's weight. J Pediatr Surg. 2016;51:1317–20.
13. Carpenter JL, Fallon SC, Swartz SJ, Minifee PK, Cass DL, Nuchtern JG, Pimpalwar AP, Brandt ML. Outcomes after peritoneal dialysis catheter placement. J Pediatr Surg. 2016;51:730–3.
14. LaPlant MB, Saltzman DA, Segura BJ, Acton RD, Feltis BA, Hess DJ. Peritoneal dialysis catheter placement, outcomes and complications. Pediatr Surg Int. 2018;34:1239–44.
15. Radtke J, Schild R, Reismann M, Ridwelski RR, Kempf C, Nashan B, Rothe K, Koch M. Obstruction of peritoneal dialysis catheter is associated with catheter type and independent of omentectomy: a comparative data analysis from a transplant surgical and a pediatric surgical department. J Pediatr Surg. 2018;53:640–3.
16. Phan J, Stanford S, Zaritsky JJ, DeUgarte DA. Risk factors for morbidity and mortality in pediatric patients with peritoneal dialysis catheters. J Pediatr Surg. 2013;48:197–202.
17. Hagen SM, Lafranca JA, IJzermans JN, Dor FJ. A systematic review and meta-analysis of the influence of peritoneal dialysis catheter type on complication rate and catheter survival. Kidney Int. 2014;85:920–32.
18. Imani PD, Carpenter JL, Bell CS, Brandt ML, Braun MC, Swartz SJ. Peritoneal dialysis catheter outcomes in infants initiating peritoneal dialysis for end-stage renal disease. BMC Nephrol. 2018;19:231.
19. Ladd AP, Breckler FD, Novotny NM. Impact of primary omentectomy on longevity of peritoneal dialysis catheters in children. Am J Surg. 2011;201:401–4; discussion 404–405.
20. Nikibakhsh AA, Mahmoodzadeh H, Vali M, Enashaei A, Asem A, Yekta Z. Outcome of immediate use of the permanent peritoneal dialysis catheter in children with acute and chronic renal failure. Iran J Pediatr. 2013;23:171–6.
21. Zhang Q, Jiang C, Zhu W, Sun C, Xia Y, Tang T, Wan C, Shao Q, Liu J, Jin B, Zhang M. Peritoneal catheter fixation combined with straight upward tunnel and low implant position to prevent catheter malfunction. Nephrology (Carlton). 2018;23:247–52.
22. Stringel G, McBride W, Weiss R. Laparoscopic placement of peritoneal dialysis catheters in children. J Pediatr Surg. 2008;43:857–60.
23. Chen Y, Shao Y, Xu J. The survival and complication rates of laparoscopic versus open catheter placement in peritoneal dialysis patients: a meta-analysis. Surg Laparosc Endosc Percutan Tech. 2015;25:440–3.

24. Xie H, Zhang W, Cheng J, He Q. Laparoscopic versus open catheter placement in peritoneal dialysis patients: a systematic review and meta-analysis. BMC Nephrol. 2012;13:69.
25. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Catheter type, placement and insertion techniques for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev. 2004;(4):CD004680.
26. van Laanen JHH, Cornelis T, Mees BM, Litjens EJ, van Loon MM, Tordoir JHM, Peppelenbosch AG. Randomized controlled trial comparing open versus laparoscopic placement of a peritoneal dialysis catheter and outcomes: the CAPD I trial. Perit Dial Int. 2018;38:104–12.
27. Crabtree JH, Fishman A. A laparoscopic method for optimal peritoneal dialysis access. Am Surg. 2005;71:135–43.
28. Hu JC, Chiu KY, Wang SS, Chen CS, Ho HC, Yang CK, Chen CC, Wang SC, Lin CY, Hung SC, Cheng CL, Li JR. A modified application of peritoneal dialysis catheter implantation: a revolution from the laparoscope- to the nephroscope-assisted surgery. J Endourol. 2018;32:502–8.
29. Rahim KA, Seidel K, McDonald RA. Risk factors for catheter-related complications in pediatric peritoneal dialysis. Pediatr Nephrol. 2004;19:1021–8.
30. Donmez O, Durmaz O, Ediz B, Cigerdelen N, Kocak S. Catheter-related complications in children on chronic peritoneal dialysis. Adv Perit Dial. 2005;21:200–3.
31. Macchini F, Valade A, Ardissino G, Testa S, Edefonti A, Torricelli M, Luzzani S. Chronic peritoneal dialysis in children: catheter related complications. A single centre experience. Pediatr Surg Int. 2006;22:524–8.
32. Ozyer U, Harman A, Aytekin C, Boyvat F, Ozdemir N. Correction of displaced peritoneal dialysis catheters with an angular stiff rod. Acta Radiol. 2009;50:139–43.
33. Ratajczak A, Lange-Ratajczak M, Bobkiewicz A, Studniarek A. Surgical management of complications with peritoneal dialysis. Semin Dial. 2017;30:63–8.
34. Zorzanello MM, Fleming WJ, Prowant BE. Use of tissue plasminogen activator in peritoneal dialysis catheters: a literature review and one center's experience. Nephrol Nurs J. 2004;31:534–7.
35. Krishnan RG, Moghal NE. Tissue plasminogen activator for blocked peritoneal dialysis catheters. Pediatr Nephrol. 2006;21:300.
36. Sakarcan A, Stallworth JR. Tissue plasminogen activator for occluded peritoneal dialysis catheter. Pediatr Nephrol. 2002;17:155–6.
37. Leblanc M, Ouimet D, Pichette V. Dialysate leaks in peritoneal dialysis. Semin Dial. 2001;14:50–4.
38. Hooman N, Esfahani ST, Mohkam M, Derakhshan A, Gheissari A, Vazirian S, Mortazavi F, Ghane-Sherbaff F, Falak-Aflaki B, Otoukesh H, Madani A, Sharifian-Dorcheh M, Mahdavi A, Esmaeile M, Naseri M, Azhir A, Merikhi A, Mohseni P, Ataei N, Fallahzadeh MH, Basiratnia M, Hosseini-Al-Hashemi G. The outcome of Iranian children on continuous ambulatory peritoneal dialysis: the first report of Iranian National Registry. Arch Iran Med. 2009;12:24–8.
39. Sojo ET, Grosman MD, Monteverde ML, Bailez MM, Delgado N. Fibrin glue is useful in preventing early dialysate leakage in children on chronic peritoneal dialysis. Perit Dial Int. 2004;24:186–90.
40. Aranda RA, Romao Junior JE, Kakehashi E, Domingos W, Sabbaga E, Marcondes M, Abensur H. Intraperitoneal pressure and hernias in children on peritoneal dialysis. Pediatr Nephrol. 2000;14:22–4.
41. Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24:1633–42; quiz 1640, 1642.
42. Jander A, Nowicki M, Tkaczyk M, Makulska I, Zwolinska D, Latoszynska J, Boguszewska-Baczkowska A, Grenda R, Balasz-Chmielewska I, Zagozdzon I, Zaluska-Lesniewska I, Zurowska A, Stefaniak E, Zachwieja J, Leszczynska B, Roszkowska-Blaim M, Zachwieja K, Pietrzyk JA, Wiercinski R, Zoch-Zwierz W, Stankiewicz R. Chronic peritoneal dialysis in infants – preliminary results of the multicenter survey. Przegl Lek. 2006;63(Suppl 3):72–4.
43. Tom CM, Dubina ED, Simms ER, de Virgilio C, Moazzez A. Outcomes of combined hernia repair and peritoneal dialysis catheter placement: a NSQIP analysis. Am Surg. 2018;84:1604–7.
44. Bargman JM. Complications of peritoneal dialysis related to increased intraabdominal pressure. Kidney Int Suppl. 1993;40:S75–80.
45. Schmitt CP, Zaloszyc A, Schaefer B, Fischbach M. Peritoneal dialysis tailored to pediatric needs. Int J Nephrol. 2011;2011:940267.
46. Bakkaloglu SA, Ekim M, Tumer N, Gungor A, Yilmaz S. Pleurodesis treatment with tetracycline in peritoneal dialysis-complicated hydrothorax. Pediatr Nephrol. 1999;13:637–8.
47. Borzych D, Ley S, Schaefer F, Billing H, Ley-Zaporozhan J, Schenk J, Schmitt CP. Dialysate leakage into pericardium in an infant on long-term peritoneal dialysis. Pediatr Nephrol. 2008;23:335–8.
48. Camilleri B, Glancey G, Pledger D, Williams P. The icodextrin black line sign to confirm a pleural leak in a patient on peritoneal dialysis. Perit Dial Int. 2004;24:197.
49. Szeto CC, Chow KM. Pathogenesis and management of hydrothorax complicating peritoneal dialysis. Curr Opin Pulm Med. 2004;10:315–9.
50. Kim YL. Update on mechanisms of ultrafiltration failure. Perit Dial Int. 2009;29(Suppl 2):S123–7.
51. Raby AC, Gonzalez-Mateo GT, Williams A, Topley N, Fraser D, Lopez-Cabrera M, Labeta MO. Targeting Toll-like receptors with soluble Toll-like receptor 2 prevents peritoneal dialysis solution-induced fibrosis. Kidney Int. 2018;94:346–62.
52. Chung SH, Heimburger O, Lindholm B. Poor outcomes for fast transporters on PD: the rise and fall of a clinical concern. Semin Dial. 2008;21:7–10.

53. Saxena R. Pathogenesis and treatment of peritoneal membrane failure. Pediatr Nephrol. 2008;23:695–703.
54. Schaefer F, Klaus G, Mehls O. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. Mid-European Pediatric Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1999;10:1786–92.
55. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int Suppl. 2008;(108):S137–44.
56. Michallat AC, Dheu C, Loichot C, Danner S, Fischbach M. Long daytime exchange in children on continuous cycling peritoneal dialysis: preservation of drained volume because of icodextrin use. Adv Perit Dial. 2005;21:195–9.
57. Htay H, Johnson DW, Wiggins KJ, Badve SV, Craig JC, Strippoli GF, Cho Y. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2018;10:CD007554.
58. Honda M, Warady BA. Long-term peritoneal dialysis and encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2010;25:75–81.
59. Stefanidis CJ, Shroff R. Encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2014;29:2093–103.
60. Brown EA, Bargman J, van Biesen W, Chang MY, Finkelstein FO, Hurst H, Johnson DW, Kawanishi H, Lambie M, de Moraes TP, Morelle J, Woodrow G. Length of time on peritoneal dialysis and encapsulating peritoneal sclerosis – position paper for ISPD: 2017 update. Perit Dial Int. 2017;37:362–74.
61. Vidal E, Edefonti A, Puteo F, Chimenz R, Gianoglio B, Lavoratti G, Leozappa G, Maringhini S, Mencarelli F, Pecoraro C, Ratsch IM, Cannavo R, De Palo T, Testa S, Murer L, Verrina E, Italian Registry of Pediatric Chronic Dialysis. Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients: the experience of the Italian Registry of Pediatric Chronic Dialysis. Nephrol Dial Transplant. 2013;28:1603–9.
62. Hoshii S, Honda M. High incidence of encapsulating peritoneal sclerosis in pediatric patients on peritoneal dialysis longer than 10 years. Perit Dial Int. 2002;22:730–1.
63. Shroff R, Stefanidis CJ, Askiti V, Edefonti A, Testa S, Ekim M, Kavaz A, Ariceta G, Bakkaloglu S, Fischbach M, Klaus G, Zurowska A, Holtta T, Jankauskiene A, Vondrak K, Vande Walle J, Schmitt CP, Watson AR, European Paediatric Dialysis Working Group. Encapsulating peritoneal sclerosis in children on chronic PD: a survey from the European Paediatric Dialysis Working Group. Nephrol Dial Transplant. 2013;28:1908–14.
64. Ekim M, Fitoz S, Yagmurlu A, Ensari A, Yuksel S, Acar B, Ozcakar ZB, Kendirli T, Bingoler B, Yalcinkaya F. Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients. Nephrology (Carlton). 2005;10:341–3.
65. Kawaguchi Y, Saito A, Kawanishi H, Nakayama M, Miyazaki M, Nakamoto H, Tranaeus A. Recommendations on the management of encapsulating peritoneal sclerosis in Japan, 2005: diagnosis, predictive markers, treatment, and preventive measures. Perit Dial Int. 2005;25(Suppl 4):S83–95.
66. Bakkaloglu SA, Saygili A, Sever L, Noyan A, Akman S, Ekim M, Aksu N, Doganay B, Yildiz N, Duzova A, Soylu A, Alpay H, Sonmez F, Civilibal M, Erdem S, Kardelen F. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report. Nephrol Dial Transplant. 2009;24:3525–32.
67. Bonthuis M, van Stralen KJ, Jager KJ, Baiko S, Jahnukainen T, Laube GF, Podracka L, Seeman T, Tyerman K, Ulinski T, Groothoff JW, Schaefer F, Verrina E. Dyslipidaemia in children on renal replacement therapy. Nephrol Dial Transplant. 2014;29:594–603.
68. Buyan N, Bideci A, Ozkaya O, Ortac E, Bakkaloglu S, Gonen S, Peru H, Soylemezoglu O, Cinaz P. Leptin and resistin levels and their relationships with glucose metabolism in children with chronic renal insufficiency and undergoing dialysis. Nephrology (Carlton). 2006;11:192–6.
69. Canpolat N, Caliskan S, Sever L, Guzeltas A, Kantarci F, Candan C, Civilibal M, Kasapcopur O, Arisoy N. Glucose intolerance: is it a risk factor for cardiovascular disease in children with chronic kidney disease? Pediatr Nephrol. 2012;27:627–35.
70. KDIGO. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3(3):259.
71. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J, American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. J Cardiovasc Nurs. 2007;22:218–53.
72. Factor KF. Potassium management in pediatric peritoneal dialysis patients: can a diet with increased potassium maintain a normal serum potassium without a potassium supplement? Adv Perit Dial. 2007;23:167–9.
73. Khan AN, Bernardini J, Johnston JR, Piraino B. Hypokalemia in peritoneal dialysis patients. Perit Dial Int. 1996;16:652.
74. Hutchinson AJ. Serum magnesium and end-stage renal disease. Perit Dial Int. 1997;17:327–9.

75. Wei M, Esbaei K, Bargman JM, Oreopoulos DG. Inverse correlation between serum magnesium and parathyroid hormone in peritoneal dialysis patients: a contributing factor to adynamic bone disease? Int Urol Nephrol. 2006;38:317–22.
76. Greenberg A, Bernardini J, Piraino BM, Johnston JR, Perlmutter JA. Hemoperitoneum complicating chronic peritoneal dialysis: single-center experience and literature review. Am J Kidney Dis. 1992;19:252–6.
77. Vidal E, Alberici I, Verrina E, Italian Registry of Pediatric Chronic Dialysis. Acute pancreatitis in children on chronic maintenance dialysis. Pediatr Nephrol. 2019;34(9):1501–12.
78. Bastani B, Mifflin TE, Lovell MA, Westervelt FB, Bruns DE. Serum amylases in chronic and end-stage renal failure: effects of mode of therapy, race, diabetes and peritonitis. Am J Nephrol. 1987;7:292–9.
79. Wang R, Leesch V, Turner P, Moberly JB, Martis L. Kinetic analysis of icodextrin interference with serum amylase assays. Adv Perit Dial. 2002;18:96–9.

18 Remote Patient Monitoring in Peritoneal Dialysis

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Introduction

Maintenance peritoneal dialysis (PD) is a cost-effective therapy which confers major psychosocial advantages as compared to in-center HD with a greater degree of freedom and infrequent hospital visits. It can be realized in any age group with permanent PD catheters being used even in newborns and young infants. On the other hand, home PD requires significant medical and technical knowledge and encumbers families with major responsibility, preventing PD treatment in some families and resulting in early PD technique failures in others [1]. About half of pediatric patients on maintenance PD have inadequately controlled salt and water homeostasis and increased left ventricular mass index [2]; CKD MBD disease is insufficiently controlled [3]. Nonadherence with the prescribed regime is common. In a cohort in Kansas City, 45% of 51 children exhibited some nonadherence to prescribed PD regimen [4]. One important strategy to improve the quality of care in PD is increasing surveillance and support of the families at home.

For many decades patients and their carers have been keeping paper-based records of their PD treatments at home to be reviewed at the next outpatient appointment and were in contact with their clinical teams mainly via phone. At the beginning of the twenty-first century, PD cyclers with integrated digital card systems were introduced. These give retrospective insight into PD performance, complications, and adherence. The rapidly evolving digital technology now opens the doors to numerous opportunities, altering the face of medicine as we currently practice it. Remote patient monitoring (RPM) through telemedicine offers heightened treatment surveillance and has the potential to reduce the burden felt by families delivering care at home, to improve treatment adherence, and through real-time feedback loops to improve knowledge through individualized education. The latest generations of PD cycler have been or are being equipped with online monitoring technology that allows for automated, online transfer of the PD regime, ultrafiltration volumes, and triggered alarms, together with manually entered data sets such as body weight and blood pressure to the dialysis center and respective data-based communication with the families. This should improve PD patient care and the families' confidence by sharing medical responsibility and in turn promote the use of PD. The large data sets

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created by RPM have to be processed, respective communication with the families has to be established, and the impact on present and future therapeutic standards requires careful consideration.

Definitions

Telemedicine comprises the use of information and (electronic) communication technologies between patient caregivers and healthcare providers to exchange information for diagnosis, treatment, and prevention of diseases and injuries (i.e., remote monitoring of patients) regardless of the physical location of the participants in order to advance the health of individuals. The broader term, telehealth, encompasses nonclinical services, i.e., education, and is often used interchangeably with telemedicine [5].

Remote Monitoring Techniques

At present remote patient monitoring of pediatric PD patients is mostly limited to phone calls, e-mails, fax, and regular mails. This type of communication limits data transfer and, except for phone calls, may be associated with a significant time lag. More recent cycler generations are equipped with card systems and reduce the burden of data collection and allow for retrospective but comprehensive analysis of the PD performance at follow-up visits, namely, UF rates per dwell, flow rate alarms, and adherence to the prescribed regimen. The card system requires regular use at home and must be brought along to the follow-up visits in the dialysis center.

Latest cyclers now provide integrated automated online data transfer technology. This system includes a home cycler which transfers the data to a secure storage place, i.e., cloud storage. The storage space has to be highly protected but accessible to various partners. The patient and the care takers should have access to the individual personal data, including the ability to scrutinize longitudinal data for optimal use. Authorized persons of the medical team in the dialysis center should have full access to all their patients. Healthcare authorities and administration may have access as appropriate according to national legislation, to help design and improve PD services for their local community and population wide [6]. Ideally, data collected online should automatically be integrated in existing electronic health records, to prevent data loss and needless duplication of data entry. Additional online functions that may be established are individual online communication portals between families and their clinical teams, remote reprograming of the cycler at home, and the ability to monitor and re-order dialysis consumables online. In parallel to analyzing longitudinal data from individuals, the wealth of knowledge and information contained within the collective dataset could form the basis of additional functions such as informing research and benchmarking. In the future we anticipate several digital devices being connected together to provide several parallel functions in unison for one patient clinical pathway. For example, we could see PD machines being used together with blood pressure monitors, scales, video systems, and oximetric devices to gain a comprehensive view on a patient's dialysis treatment (Fig. 18.1). This together with technologies such as voice recognition and Bluetooth connectivity should minimize or even eliminate the need of manual data entry and improve data quality, density, and reliability. Patients could be prompted to report on outcomes at regular intervals, e.g., by providing semi-quantitative assessments of well-being and individual patient symptoms over time. Finally, there is an opportunity to expedite and redesign education and training programs, combining face-to-face training with virtual and simulated learning modules. A virtual training program has recently been implemented in pediatric PD with success [7].

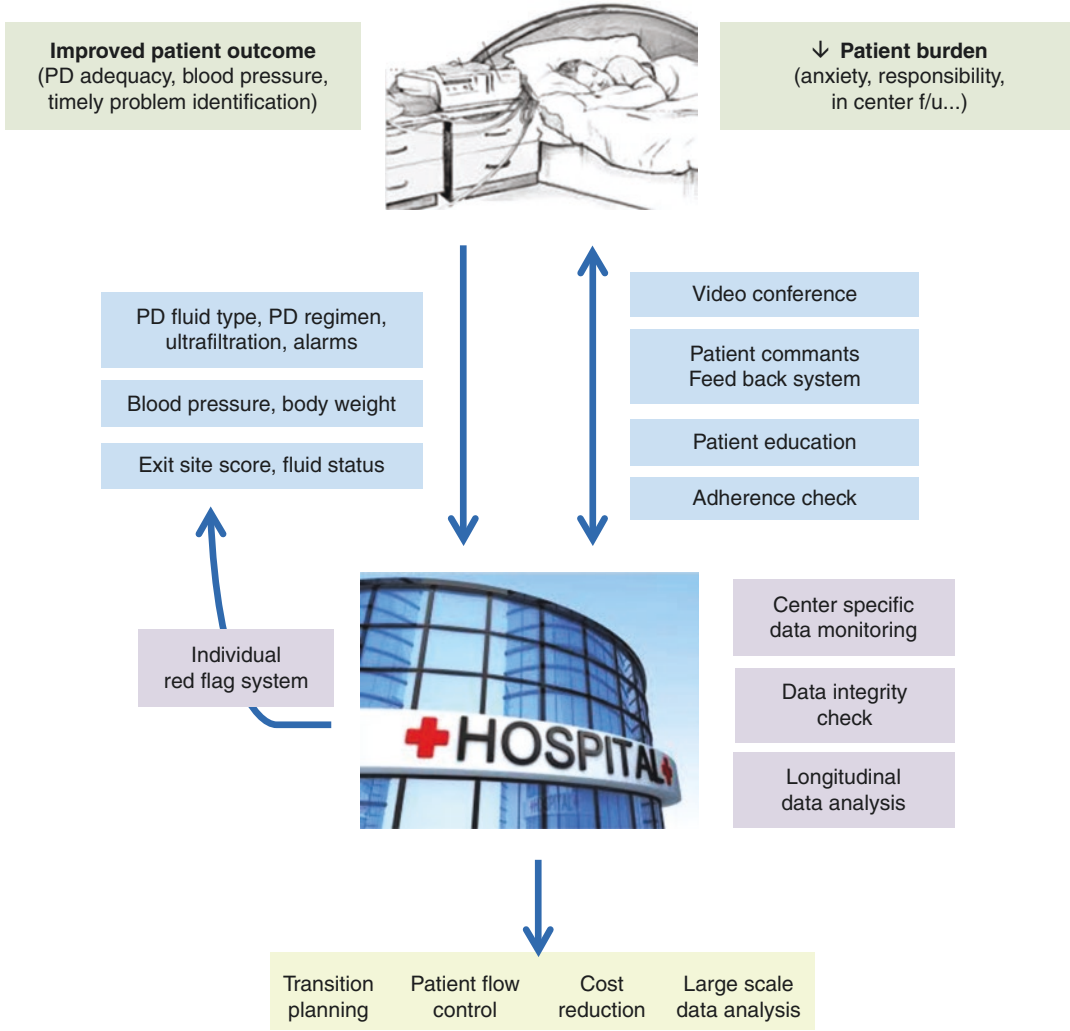

Fig. 18.1 Schematic presentation of advanced remote patient management with data transfer between the patient and his family at home and the dialysis center (blue squares), respective actions required at the dialysis center (purple squares), and expected patient benefits (green squares)

Benefits of RPM

The potential benefits of RPM depend on the technology implemented and the readiness of the operator. RPM allows real-time transfer of relevant treatment data between patient's homes and their clinical teams. Issues or emerging trends prompt conversations through different communication portals such as text messaging and audio and video conferencing and allow redefining or refining treatment parameters, including reprogramming of the cycler. This should provide an array of advantages, including the timely recognition of PD-associated problems, such as catheter dysfunction and peritonitis; inadequate treatment performance, e.g., with regard to PD fluid turnover and ultrafiltration; and monitoring of treatment adherence. Nonadherence has been shown to associate with peritonitis and PD technique failure rate. A single home visit can improve adherence and outcome [8]; thus similar effects may be achieved by means of RPM. With increased awareness, insight into trends and deviations, and earlier interventions, RPM should

significantly improve patient outcomes. The patient and families' treatment-related medical responsibility and perceived burden should decline with the online connection with the clinical teams. This should increase the recruitment of patients and their families into home PD and improve the experiences of managing PD at home and thus quality of life. Continuous training, counseling, and educational features should further improve treatment efficacy and safety and reduce the need for planned and unscheduled in-center assessments. The latter may counterbalance and potentially even exceed the costs of the technology. On a larger scale, the accumulating treatment data should provide significant information on technical shortcomings, PD efficacy, and complications and allow for targeting of future developments (Fig. 18.1).

To date, automated online data transfer of PD treatment data has only been realized in a few dialysis centers [6]. The burden of collecting and communicating treatment related data is reduced, but data such as blood pressure and body weight measurements still require manual data entry. Video conferencing in PD thus far has been reported from a single dialysis center only [9]. In this center 25 adult PD patients were remotely monitored for blood pressure, blood glucose, exit site and dialysate state, and medication for a total of 200 RPM months with 172 teleconsultations. These were compared to 32 non-remote-managed patients, of whom several had refused RPM. The number of emergency room visits and of hospitalizations and their duration declined with RPM; the associated costs were lower. The observed decline in patient contacts for technical and medical issues during the mean follow-up of 1 year may reflect RPM-related training effects and improved reassurance of both sides due to the higher degree of surveillance.

Published RPM experience in pediatric PD is thus far limited to few children. In these patients RPM appeared useful in detecting and solving clinical and technical problems of automated PD, reduced the number of shortened PD treatments [10], and improved fluid status [11]. In a pilot trial in Heidelberg, automated online transfer of body weight and blood pressure readings was established in 2005 [12]. Fourteen APD, five in-center HD, and one home-HD patients were followed for 2–5 weeks. This allowed for early detection of hypotensive and hypertensive blood pressure episodes and successful counteractions. Confidence increased in both the families and the medical team. At Great Ormond Street Hospital London, UK, 17 children switched from standard care to RPM using the web-based platform Sharesource™. Uptake was excellent, and pre-arranged patient appointments and number of dialysis-related hospital-based consultations decreased. The number of PD prescription changes increased substantially, mainly related to PD delivery alarms, indicating a more personalized dialysis prescription to patients with more timely adjustments. There was a shift toward greater virtual and remote care.

No randomized trial comparing standard care to RPM in PD has thus far been accomplished. An RCT in high-risk, nurse-supported HD patients yielded significant advantages with remote monitoring of blood pressure, blood glucose, heart rate, and O2 saturation and including video conferencing [13]. The number and duration of hospital admissions decreased in the 19 patients on RPM, and emergency room visits and costs were reduced as compared to standard of care.

Strong evidence in favor of RPM has been obtained in other disease conditions. RPM of patients with type 2 diabetes mellitus improved adherence [14]. A recent overview on systematic reviews on RPM in patients with heart failure provided grade 1A evidence for a reduction in hospitalizations and mortality. The impact of mobile phone-based monitoring and videoconferencing remains uncertain [15].

RPM Implementation and Data Handling

When implementing RPM in PD, benefits have to be carefully balanced against the limitations and potential drawbacks associated with data transfer. In contrast to conventional patient care with monthly in-center follow-up and commu-

nication by phone calls or fax, large-scale, continuous online data flow requires standardized procedures within the center and careful communication with the families, taking into account linguistic and intellectual barriers. The benefits of monitoring numerous parameters must be balanced against the risks of data overflow. Country-specific legal aspects regarding informed consent, storage, and access to the data need to be followed. Data governance and assurance processes need to be designed and implemented. Families need to be informed on what data is being collected and how the clinical teams monitor the data, how often by whom on which days of the week. The data surveillance procedures established should maximize the benefits such as reduced phone calls and timely (online) interventions and still be feasible within clinical routine, e.g., should be in line with clinicians' working hours. Families need assurance on how the personal information will be protected and confidentiality maintained and on how it may be used for present and future analyses. All this requires thorough information of patient and caregivers and also training of the clinical teams (Table 18.1). During the beginning phase of rolling out RPM, two parallel systems will be working together, the established clinical pathways and the digitally enhanced pathways. This may at least transiently increase the complexity and costs and thus resource pressure for the organization.

Table 18.1 Remote patient monitoring (RPM), step-by-step implementation and adaptation process

Choose technique and parameters to monitor; define data monitoring and action process
Verify alignment with law and regulations
Train staff (doctors and nurses)
Approach and train patients and carers
Set individual flags and alerts
Start RPM
Repeatedly review data sets and alerts, the analysis, and decisions taken based on RPM
Assess patient adherence to RPM
Refine individual and center RPM settings
Evaluate learning process
Reconsider standards of clinical practice established before RPM has been amended

Families and clinicians need to be trained using the RPM systems correctly and develop a solid understanding of the limitations of the system. Over-reliance in automated systems may result in adverse events and reduce situational awareness. In the PD treatment setting, there are acute and chronic communication needs. Availability of online communication does not necessarily provide adequate communication. Families have to be clear that they are still responsible for contacting the clinical team in case of acute problems. Real-time data assessment is not feasible 24/7 and unlikely to improve outcome [16]. Despite the online data transfer, a time lag still has to be considered, and urgent support will still need to be accessed through a phone call, even though communication platforms may allow the two-way exchange of information and immediate decision-making during office hours. RPM cannot delay or even replace emergency visits in case of urgent medical problems.

The monitoring functions require individual, patient-specific margin settings and respective alarm signals. UF range and blood pressure targets have to be defined, and potential technical pitfalls such as false readings must be considered. Regular readjustment, e.g., of target body weight, will be required. Thus, critical review of the pursued versus actual therapeutic success is essential at regular intervals during conventional face-to-face interactions between family and the clinical team. Setting rigorous alarm systems in RPM may result in unnecessary, frequent perturbations of domestic ambiance and possibly in mental and cognitive disconnection with the alarms. Conversely, liberalizing alarm limits may not sufficiently alert families and clinicians to a critical scenario and thus result in avoidable patient harm, e.g., regarding ultrafiltration and blood pressure control. The ambition to standardize and automate treatment practice with RPM needs to be balanced with the requirements for personalized care. RPM should be considered an adjunct in providing safe and effective clinical care but cannot replace human interactions and direct, face-to-face communication and training. Over-reliance on technology may result in failure

to seek help. In the limited publications to date, this, however, has not been reported to be a critical issue.

In the early phases of RPM, RPM provides support to established standards of care. As experience builds up, RPM may result in modifications of what is considered "good practice." For example, RPM may reduce the number of scheduled visits, e.g., reduce the face-to-face contacts. Optimized data presentation to easily visualize and track daily changes, e.g., of body weight, ultrafiltration, and blood pressure, against targets should facilitate data handling and optimize timely intervention. Interventional algorithms may evolve and improve the efficacy of decisions. Noteworthy, continuous comprehensive online data assessment may be perceived by some families as inappropriate surveillance and violation of privacy. Thus, the patient and families should have the right to opt out and discontinue online data transfer at all times. Centers performing RPM in PD thus far reported good overall acceptance with only occasional requests to discontinue RPM. The benefits of being supported at home obviously predominate over perceived disadvantages in the majority of families.

Regulatory Issues and Reimbursement

Local practices are legally obliged to establish and provide assurance on adequate risk management around the technical aspects of RPM and data protection, aligned with local/national laws and regulations. Protection of personal data is a critical issue and requires careful consideration by respective professionals. Adequate reimbursement is essential for sustainability of RPM. Telemedicine and RPM are increasingly acknowledged as part of medical care together with a comprehensive and online accessible electronic patient file. Reimbursement, however, varies between countries. Applying RPM in pediatric dialysis may shift patient care from a primarily center-based treatment with close follow-ups to a more virtual care. Virtual care without direct patient contact is associated with medical risk and requires time and careful consideration; adequate reimbursement of these activities needs to be achieved with insurance providers. Implementation of RPM should optimize patient care and not be considered a tool to reduce costs without significant improvements in patient outcome.

Conclusion

Telemedicine is a megatrend, with 29,000 publications in PubMed, of which 20,000 have been published the last 10 years. This interest is likely to continue and to multiply. In view of the widespread Internet access and greater adoption of digital devices in every aspect of our lives, the demand for telemedicine is rising. The expanding technical specification profiles, the growing functionality, and the user-friendly interfaces with ease of application of RPM place it at the heart of our promise to improve patient care. Within this context it is surprising that RPM has not yet been broadly established in (pediatric) PD and evaluated. At present, personal communications and small observational reports are positive; solid scientific evidence on the best mode of RPM, cost-effectiveness, the impact on family burden, quality of life, PD performance, and patient outcome, however, is scant. Vigorous research is required to understand the true impact of telehealth. An ongoing randomized PD trial in Canada (CONNECT trial) will provide significant information in adult patients. Large-scale prospective observational data from the International Pediatric Peritoneal Dialysis Network, IPPN, will provide pediatric evidence on the impact of RPM on PD and patient care modalities, biochemical and cardiovascular outcome, infectious and non-infectious complications, technique failure, modality switch, and death.

Next to scientific evidence, usage and success of RPM will depend on the feasibility of implementation in clinical routine and daily family life and on the interoperability with other data systems. A continued local and international surveillance of the RPM process regarding technical

aspects and the impact on clinical decision-making and targeted outcomes is required to provide the best outcome. In numerous countries with major limitations of healthcare budgets and inadequate or even missing dialysis options, in countries with shortage of medical staff, and in those where patients face very long distances to the dialysis centers, RPM should be an important mean to increase PD implementation.

Particular attention has to be paid on how virtual communication and RPM will transform patient care. Effective communication relies on the two-way exchange of information, verbal and non-verbal clues, and the ability to connect with people and gain their trust. Non-verbal clues apparent when communicating face to face may be missed; subtle signs of families not coping may be only detectable during personal communication. The human element, the "care" element of medicine, may be altered or even lost in digitally enhanced care pathways. This unintended consequence needs to be investigated and addressed. Until then RPM practices need to be adopted within clear boundaries interspersed with frequent opportunities of face-to-face interaction for scrutiny and reassurance. Up to now, RPM has mainly been used as an adjunct to established care. At present, the positive and sometimes even enthusiastic communications of the pediatric centers applying RPM in children on chronic PD are encouraging.

References

1. Jaar BG, Plantinga LC, Crews DC, Fink NE, Hebah N, Coresh J, Kliger AS, Powe NR. Timing, causes, predictors and prognosis of switching from peritoneal dialysis to hemodialysis: a prospective study. BMC Nephrol. 2009;10:3.
2. Bakkaloglu SA, Borzych D, Soo Ha I, Serdaroglu E, Büscher R, Salas P, Patel H, Drozdz D, Vondrak K, Watanabe A, Villagra J, Yavascan O, Valenzuela M, Gipson D, Ng KH, Warady BA, Schaefer F, International Pediatric Peritoneal Dialysis Network. Cardiac geometry in children receiving chronic peritoneal dialysis: findings from the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Clin J Am Soc Nephrol. 2011;6(8):1926–33.
3. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, Zambrano P, Ahlenstiel T, Bakkaloglu SA, Spizzirri AP, Lopez L, Ozaltin F, Printza N, Hari P, Klaus G, Bak M, Vogel A, Ariceta G, Yap HK, Warady BA, Schaefer F, International Pediatric PD Network (IPPN). The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78(12):1295–304.
4. Chua AN, Warady BA. Adherence of pediatric patients to automated peritoneal dialysis. Pediatr Nephrol. 2011;26(5):789–93.
5. Rosner MH, Lew SQ, Conway P, Ehrlich J, Jarrin R, Patel UD, Rheuban K, Robey RB, Sikka N, Wallace E, Brophy P, Sloand J. Perspectives from the kidney health initiative on advancing technologies to facilitate remote monitoring of patient self-care in RRT. Clin J Am Soc Nephrol. 2017;12(11):1900–9.
6. Wallace EL, Rosner MH, Alscher MD, Schmitt CP, Jain A, Tentori F, Firanek C, Rheuban KS, Florez-Arango J, Jha V, Foo M, de Blok K, Marshall MR, Sanabria M, Kudelka T, Sloand JA. Remote patient management for home dialysis patients. Kidney Int Rep. 2017;2(6):1009–17.
7. Olszewski AE, Daniel DA, Stein DR, McCulloch MI, Su SW, Hames DL, Wolbrink TA. Teaching pediatric peritoneal dialysis globally through virtual simulation. Clin J Am Soc Nephrol. 2018;13(6):900–6.
8. Bernardini J, Piraino B. Compliance in CAPD and CCPD patients as measured by supply inventories during home visits. Am J Kidney Dis. 1998;31(1):101–7.
9. Gallar P, Vigil A, Rodriguez I, Ortega O, Gutierrez M, Hurtado J, Oliet A, Ortiz M, Mon C, Herrero JC, Lentisco C. Two-year experience with telemedicine in the follow-up of patients in home peritoneal dialysis. J Telemed Telecare. 2007;13(6):288–92.
10. Edefonti A, Boccola S, Picca M, Paglialonga F, Ardissino G, Marra G, Ghio L, Parisotto MT. Treatment data during pediatric home peritoneal teledialysis. Pediatr Nephrol. 2003;18(6):560–4.
11. Chand DH, Bednarz D. Daily remote peritoneal dialysis monitoring: an adjunct to enhance patient care. Perit Dial Int. 2008;28(5):533–7.
12. Kirsch C, Mattingely-Scott M, Muszynski C, Schafer F, Weiss C. Monitoring chronically ill patients using mobile technologies. IBM Syst J. 2007;46(1):85–93.
13. Berman SJ, Wada C, Minatodani D, Halliday T, Miyamoto R, Lindo J, Jordan PJ. Home-based preventative care in high-risk dialysis patients: a pilot study. Telemed J E Health. 2011;17(4):283–7.
14. Farmer AJ, McSharry J, Rowbotham S, McGowan L, Ricci-Cabello I, French DP. Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with type 2 diabetes: a systematic review of randomized trials. Diabet Med. 2016;33(5):565–79.
15. Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote monitoring of patients with heart failure: an overview of systematic reviews. J Med Internet Res. 2017;19(1):e18.
16. Marshall MR, Pierratos A, Pauly RP. Delivering home hemodialysis: is there still a role for real-time treatment monitoring? Semin Dial. 2015;28(2):176–9.

Part IV

Hemodialysis

Hemodialysis Vascular Access in Children

19

Michael Boehm, Deepa H. Chand, and Mary L. Brandt

Background

Considerations about the cause and prognosis of kidney failure and the modality of kidney replacement therapy (KRT) should be made before a vascular access decision is taken.

In general, kidney dysfunction necessitating KRT can be either acute or chronic. With acute kidney injury (AKI), establishment of immediate adequate vascular access to accommodate a high-flow circuit is essential. Long-term consequences must also be considered in case kidney function does not recover. Typically, a central venous catheter (CVC) placed in the internal jugular vein is used on an emergency basis and for a relatively short duration. In CKD, the patient has a few treatment options once end-stage kidney disease (ESKD) is reached: (pre-emptive) kidney transplantation, peritoneal dialysis, or hemodialysis. Given the fact that many children triangulate between these modalities over the course of a lifetime, vein preservation is crucial and should be given consideration at the time of diagnosis [1, 2].

Whether they have AKI requiring KRT or CKD, children should not be considered "small adults". Thus, taking into account medical, psychosocial, socioeconomic, and individual factors, the KRT modality and probability of transplant needs to be clarified before a decision on vascular access can be made. Moreover, a critical issue for these patients is to provide adequate vascular access for current KRT requirements *without compromising future potential access sites*. However, despite data showing this is not ideal, recent studies show that CVC remains the first vascular access in a large proportion of children with ESKD, even though they do not undergo a consecutive transplantation within a few months [3–6]. This underlines the essential importance of well-considered planning, as virtually all children with ESKD find themselves in the *eternal cycle of kidney replacement therapy*. Unlike adults, children may have decades of hemodialysis. This means that an access which is technically easy may not be the best choice since it may sacrifice other, more distal sites for future access. This difference in surgical philosophy is why it is so important to develop a team with expertise in all aspects of care of children with kidney failure.

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Vein Preservation in Children with CKD

In a child with known CKD, vein preservation should start as soon as the diagnosis is made, even at CKD stage 1. In many instances, referral to a pediatric nephrologist is not made until CKD has progressed to stages 3 or 4. For that reason, education regarding vein preservation is important for patients, their families, and the multidisciplinary healthcare team (including phlebotomy staff, nurses, pediatric nephrologists, primary care physicians, emergency room personnel, surgeons, anesthesiologists, or other providers). Early referral and physician education can improve access options and therefore avoid morbidity associated with CVC use and venous access in the patient's arms, both of which can limit options for a later dialysis access (Fig. 19.1) [7–9]. A single venipuncture or placement of an intravenous catheter into the cephalic vein at the age of 2 years can render the vein useless at age 10, making permanent access creation at this site impossible. Ideally, venous catheters, if necessary, should be placed in the dorsum of the hand in order to protect the cephalic vein, particularly at the wrist and in the forearm. If a central venous catheter is indicated for total parenteral nutrition or medication administration, the subclavian vein should be avoided. The incidence of subclavian stenosis following insertion of a single-lumen, small-caliber percutaneous line is well known and can permanently affect outflow for future access. Subclavian stenosis in adults has been shown to occur in 5/15 patients at 1 week, in 6/13 patients after 2–6 weeks, and in almost 50% of patients studied following catheter removal (Fig. 19.2) [10–13].

Hemodialysis Vascular Access Choices and Outcomes

In patients with advanced and progressing CKD in whom the decision for hemodialysis has been made, vascular access planning should be initiated

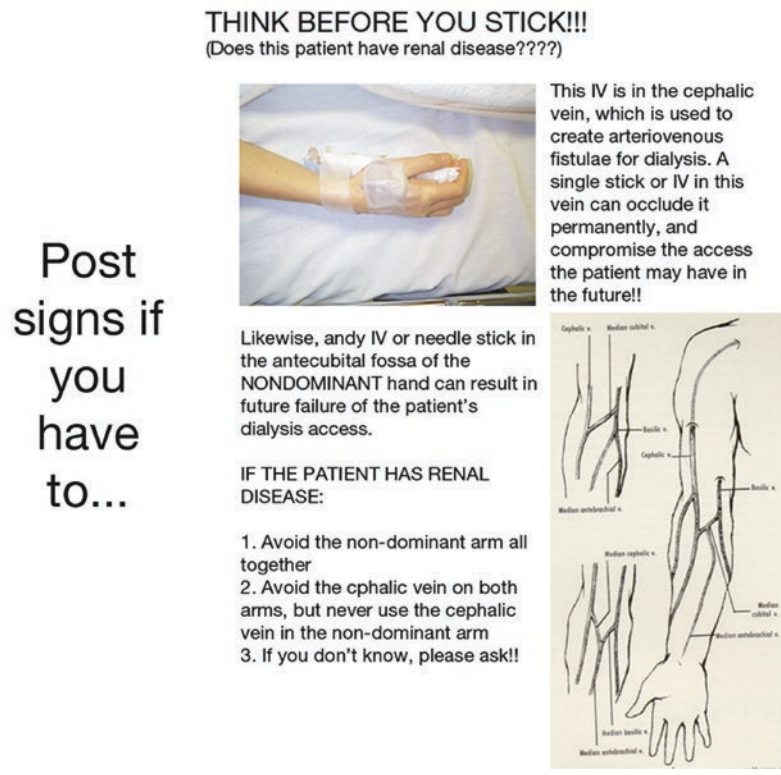

Fig. 19.1 Example of posted vein preservation education in healthcare facility

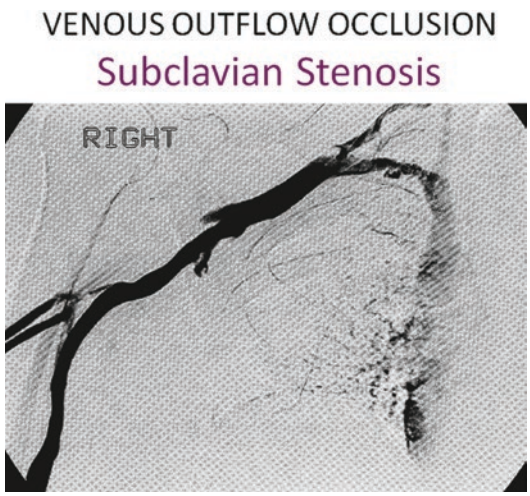

Fig. 19.2 Subclavian vein stenosis following central venous catheter placement in the subclavian vein precludes forever the use of that extremity for HD access

Table 19.1 Advantages of hemodialysis vascular access in children: AVF versus CVC

AVF	CVC
Better access survival	Access for very young children
Higher patency	Acute vascular access for urgent dialysis
Less interventions necessary	Less risk of high-output cardiac failure
Lower rates of related infections	No vascular steal phenomena
Lower morbidity and mortality rates	Painless (no needles)
Higher quality of life (e.g., activities like bathing and swimming)	For children with an expected kidney transplantation in a short term
Improved dialysis adequacy	Easily to remove
Lower costs and hospitalization rate	

6–12 months prior to the anticipated start of dialysis [8, 9]. A chronic hemodialysis access can be obtained in children by creation of a primary arteriovenous fistula (AVF), placement of an arteriovenous synthetic graft (AVG), or use of a cuffed central venous catheter (CVC) [14–16]. Ample evidence supports the concept of "fistula first"; whenever feasible, a primary fistula should be the access of choice [17, 18]. However, the decision which access is best for an individual patient should be based on patient age and size, diagnosis, the likelihood of transplantation, the procedural risks, and the probability of long-term patency. The advantages of AVF and CVC, respectively, are summarized in Table 19.1 [6, 8, 17, 18].

The National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-K/DOQI) guidelines recommend the creation of a permanent access in all children weighing more than 20 kg in whom transplantation is not imminent [19].

The functional survival of a vascular access technique is usually assessed by the primary and secondary patency rates. Primary patency is defined as the time from placement to thrombosis or the first required intervention. The secondary or cumulative patency is the time interval until the access is abandoned [20, 21]. AVFs provide the best vascular access option in long-term hemodialysis because of excellent primary patency and low complication rates. Several studies have demonstrated that quality of life for children is equivalent, if not better, in children with AVF as compared to children with CVC-based hemodialysis [17, 18]. The European Society for Paediatric Nephrology (ESPN) Dialysis Working Group recently suggested that for children with ESKD in whom "a kidney transplant is deemed unlikely within the following 6 months a functioning AVF is appropriate" [9].

Despite the data supporting the use of AVF as the first access, in a population-based study of European children commencing chronic hemodialysis between 2000 and 2013, 55.1% of children started dialysis with a CVC. Approximately 25% of these children subsequently underwent creation of an AVF. Pertinent to this discussion, most of these AVFs were created in the first 3 months after placement of the CVC (Fig. 19.3) [5]. In the North American NAPRTCS consortium, 78.7% of pediatric HD patients used CVC as primary access compared to AVF (11.8%) and AVG (6.7%) [4]. The 2019 report of the population-based USRDS database disclosed primary CVC use in even 87.6% of pediatric patients [3]. These data were further confirmed on a global scale by a report of the International Pediatric Hemodialysis Network (IPHN) registry, with

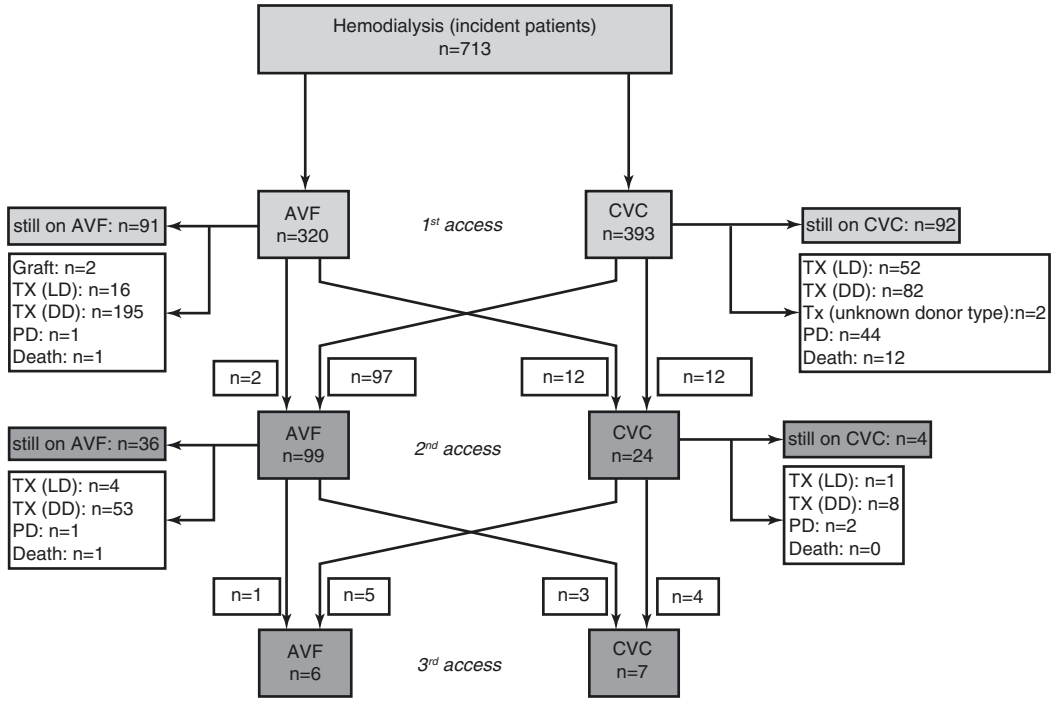

Fig. 19.3 Hemodialysis vascular access in 713 incident pediatric hemodialysis patients reported to the ESPN/ERA-EDTA registry. The majority of patients started hemodialysis with a CVC, with 97 of these 393 children switching to AVF during follow-up. (Modified from Ref. [5])

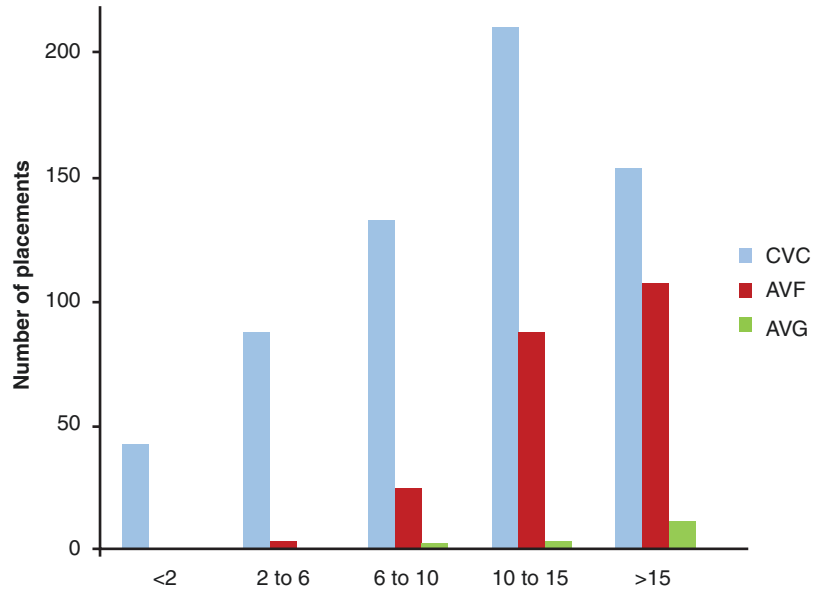

Fig. 19.4 Hemodialysis vascular access placements in 552 patients reported to the International Pediatric Hemodialysis Network (IPHN) registry, stratified by age. In total 870 placements were reported (cuffed CVC, $n = 628$; AVF, $n = 225$; AVG, $n = 17$). (Modified from Ref. [6])

only 26% of children starting hemodialysis with an AVF (Fig. 19.4). The latter study documented better treatment outcomes with AVF compared to CVC including superior dialysis efficacy, less access infections, and lower need for access replacement [6]. Hence, there is a remarkable

discrepancy between clinical evidence indicating superior outcomes with AVF and the persistent preference for the use of CVC as the first access choice.

The most common explanation for this phenomenon is the notion that families are often hesitant about AVF. However, a survey by Chand et al. showed that the three most important impediments to seeking an AVF in a child with ESKD were "nurse resistance to sticking," "no nephrologist referral," and "surgeon resistance" [22]. Some of these survey results are supported by epidemiological information. For instance, in the USRDS database, the use of an AVF was significantly higher in patients referred to a (pediatric) nephrologist >12 months before starting dialysis [3]. Furthermore, the ESPN/ERA-EDTA registry reported more than 10% of children younger than 6 years of age starting HD with an AVF. The implementation of a dedicated *vascular access clinic* significantly increased the usage of AVF, even in small children with ESKD [5, 23].

Arteriovenous Fistula

General Remarks, Patient Evaluation, and Preparation

Keeping in mind that AVFs often take longer to mature in children than adults – sometimes up to several months after creation – timely placement should be considered. Based on the center, the vascular access may be placed by a vascular surgeon, a pediatric surgeon, or a transplant surgeon, as long as the surgeon is trained in and willing to accept the challenges of pediatric vascular access. To quote Davidson et al., "… the issue is not who places the access, but who does it right, every time, to everyone, and everywhere…" [8]. Shroff et al. reported good outcomes after implementation of a vascular access clinic, which includes as "one-stop approach" all necessary diagnostic and interventional steps. Such patient-focused management leads to a decreased use of CVC as hemodialysis access and to a higher access patency of AVF [23].

The preoperative evaluation is crucial to maximize primary access patency. It includes a detailed medical history, an exact physical examination of veins and arteries, and appropriate diagnostic imaging. Specific attention is necessary to evaluate the entire central line history and prior hospitalizations, including intensive care unit stays. Physical examination should include observation for extremity deformation and/or venous distention indicative of obstruction and evidence of prior central line placement or previous arterial punctures. Using Allen's test, the blood supply via the ulnar artery and thus the suitability of the radial artery for an AVF can be evaluated [24].

In general, major risk factors for failure of an AVF are insufficient vein diameter and distal obstruction to flow, usually due to stenosis. Doppler vein mapping should be performed to establish vein diameter and patency (Fig. 19.5). Vein mapping is considered standard of care in planning the vascular access, although, in rare situations, contrast venography may be necessary (Fig. 19.6). Regarding optimal vessel sizes, venous diameters of 1.5–2.5 mm and a minimum arterial diameter of 2 mm are suggested. However, these recommendations are largely based on reviews or studies in adults. There are no good data in children, but is clear that smaller and/or younger children may have adequate diameters which are smaller than these numbers. Magnetic resonance venography examination or, less commonly, contrast venography is recommended for any child with collaterals present on physical examination or if there is suspicion of thrombosis due to prior CVCs, since Doppler ultrasound cannot identify subclavian stenosis [9].

Placement and Perioperative Handling

The general surgical principle in placing fistulae is to use the most distal vessels possible in the nondominant extremity, preserving the more proximal vessels for future access. For that reason, primary fistulae are most commonly created between the radial artery and cephalic vein

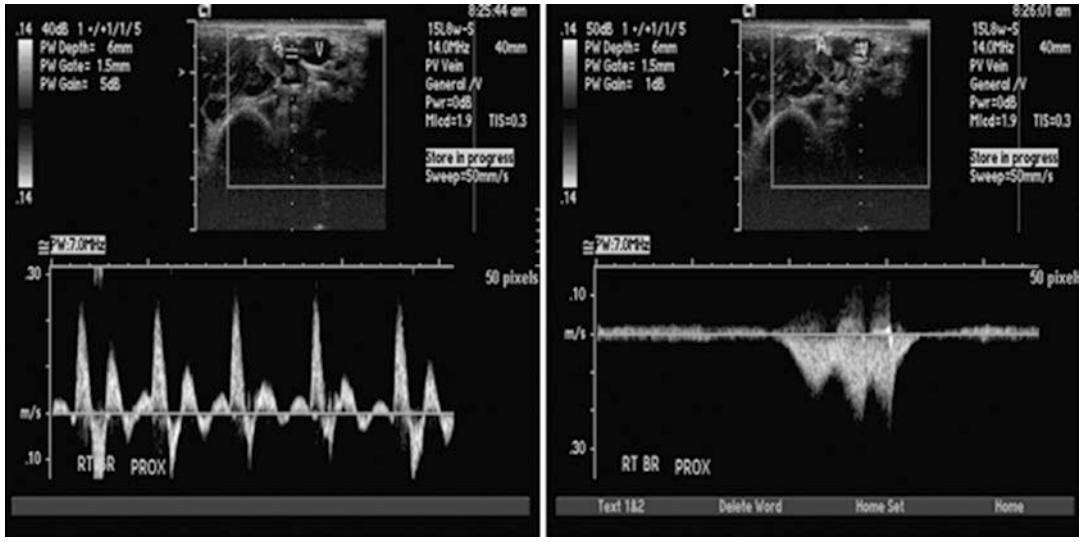

Fig. 19.5 Preoperative Doppler vein mapping. (Courtesy of Maria Alonso, MD, Cincinnati Children's Hospital Medical Center)

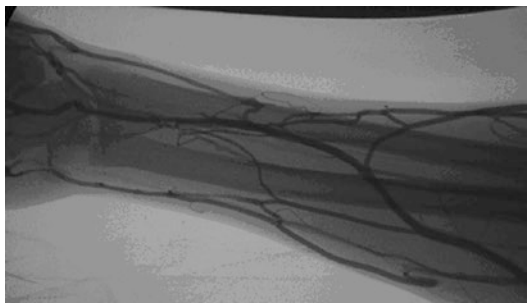

Fig. 19.6 Preoperative venography. (Courtesy of Maria Alonso, MD, Cincinnati Children's Hospital Medical Center)

Table 19.2 Arteriovenous sites

Artery	Vein	Fistula
Radial	Cephalic	Wrist
Brachial	Cephalic	Antecubital
Brachial	Basilic	Forearm
Brachial	Basilic	Upper arm/transposed
Femoral	Saphenous	Thigh

at the wrist (Brescia-Cimino), but can also be formed between the brachial artery and cephalic vein in the antecubital fossa, between the brachial artery and brachial vein (with transposition of the vein to the subcutaneous tissue), and, rarely, between arteries and veins in the lower extremity. Table 19.2 depicts AVF options. The Brescia-Cimino (radiocephalic) AVF has been the preferred vascular access for decades in adults due to its low complication rates and longevity [25–32].

The pediatric population poses a challenge in creating distal fistulae due to small vessel caliber. Without special expertise and magnification, a higher primary failure rate is to be expected. The use of microscopic vascular techniques has allowed for successful creation of AVF in children below <10 kg and, in some cases, even down to 5 kg body weight [32].

Monitoring and Complications

Prospective studies in children showed primary patency rates between 78% and 94%, respectively [26–28]. Primary patency may be jeopardized by puncturing an AVF too early [33, 35]. Because of their small vessel size and lower systemic blood pressure, primary AVFs in children take significantly longer to mature than in adults, up to 4 months (and longer) in some patients compared to the usual 6 weeks recommended for maturation of AVF in adolescents and adults. Although published guidelines regarding optimization of maturation do not exist, a few general

principles hold true. Venipunctures and blood pressure measurements should be avoided at the ipsilateral arm of a patient with a fistula to avoid compression. Although there are no data, exercising the AVF arm is generally believed to improve maturation, and it may increase the diameter of the AVF by up to 10% [35].

The first puncture should always be performed under optimal conditions by an experienced nurse or physician well known to the child. Furthermore, education regarding AVF cannulation, the support of a psychologist or a child life specialist and peer-to-peer observation/interaction, can be valuable in cannulation preparedness once the access is in place. Topical analgesia and psychological support are essential. Adequate cleaning of the skin is mandatory. There are three principal techniques for cannulation: "rope ladder," "buttonhole," and "area puncture." Rope ladder technique uses the entire length of an AVF, avoiding previous puncture sites. This can be limited by a short venous interval available for puncture. In such cases, the buttonhole technique (same site, same insertion angle, same depth, same nurse and physician) may be preferable, but a higher risk of infections has been reported with this technique in adults. Due to a significantly higher risk of aneurysmal stenosis of AVF, the area puncture technique is not suggested anymore [36, 37].

Regular Doppler ultrasound examinations assessing the anatomy and blood flow rates of the AVF have been recommended. Sonographic monitoring should be performed at 3- to 6-monthly intervals, and any signs of AVF dysfunction or stenosis should prompt referral to the surgeon [9]. Guidelines for adults recommend a flow more than >600 mL/min and a minimum vein diameter of 6 mm [19]. Although interval angiography can identify an area of stenosis prior to graft thrombosis, this technique is more invasive and should be preferentially used once a problem has been identified by ultrasound rather than for surveillance [9].

No evidence-based recommendations regarding prevention of thrombosis exist. Peri- and intraoperative heparinization may help maximizing patency rates in the early postoperative period but also increases the risk of bleeding. Maintenance of good hydration by low ultrafiltration rates during HD sessions and avoidance of hypotensive episodes may lower the risk of early AVF thrombosis, as well as the use of anti-platelet agents (e.g., aspirin) for a few months [9, 38].

If venous stenosis or thrombosis are present, angiography allows the vascular surgeon or interventional radiologist to perform balloon angioplasty, which can successfully extend the lifetime of the AVF and avoid surgical revisions. In the setting of acute thrombosis due to stenosis, a thrombectomy must be performed. If blood flow can be restored, the patient can subsequently undergo angiography with balloon dilatation. If there are persistent problems or if blood flow cannot be restored, surgical revision should be undertaken.

Most of the very rare infectious complications of AVF manifest as local infection (edema and erythema) and need only antibiotic therapy. Surveillance of 6000 outpatient hemodialysis facilities by the US National Healthcare Safety Network yielded 0.26 bloodstream infections per 100 patient-months in AVF patients, a much lower incidence than observed with AVG (0.39) and CVC (2.19), respectively [39]. In children, no AVF infections were observed in the IPHN registry during a cumulative observation period of 1024 patient years [6].

Arteriovenous Graft

General Remarks, Evaluation, and Preparation

An arteriovenous graft (AVG) utilizes a synthetic graft to create an arteriovenous anastomosis. The AVG is an alternative when primary AVFs have failed or are not technically possible. Latest US prevalence data from the USRDS registry indicate usage of AVGs in 6.3% of pediatric hemodialysis patients as compared to 41.3% with an AVF, with a decreasing trend over the past decade. Hence, whereas the use of AVGs is more common in adults, in children they are used rarely and should be considered only as a last

resort when there are no alternatives [3, 8, 9]. The preoperative workup (i.e., medical history, radiologic diagnostics) is the same as described for AVF above.

Placement and Perioperative Handling

The surgical technique for creating AVG in children has been well described [16, 40]. The most common site for placement of an AVG is the forearm, and straight grafts (radial artery to brachial vein) are more commonly placed in younger children, whereas loop grafts (brachial artery to brachial vein) are preferred in adolescents. Polytetrafluoroethylene (PTFE) is the material of choice for AVGs in children and adults due to its superior biocompatibility.

Monitoring and Complications

When compared to AVF, AVG can be used sooner, typically within 2–4 weeks following placement, or even immediately after creation and may have higher primary patency rates.

While AVG may achieve higher primary patency rates compared with AVF, secondary patency rates of AVF are significantly better and complication rates lower than those observed with PTFE grafts. Five-year access survival rates range around 40% for AVG. Graft stenosis, usually near the venous anastomosis, is common and eventually inevitable. Children with high-flow AV accesses, particularly PTFE femoral grafts, are at risk for "steal" phenomena and unequal limb growth [41–45]. Overall, their higher rates of secondary failure and other complications make AVG a less desirable access. After failure of an AVG, the child's vascular anatomy should be re-assessed to determine if an AVF might be feasible. In many circumstances, a more proximal AVF can be created due to the vascular enlargement secondary to the high-flow dynamics induced by the previous AVG.

Central Venous Catheters

General Remarks, Evaluation, and Preparation

As stated before, although it is not ideal, an external hemodialysis catheter is often the first access placed in children with ESKD and, for some patients, may be the only access ever used. The most important factor when using a CVC for HD is the insertion site. Therefore, the individual medical history, particularly former central venous catheters, and the necessity of an appropriate diagnostic imaging should be evaluated prior to catheter placement. Specifically, the subclavian vein should be avoided; subclavian vein stenosis is common after placement of central venous catheters. Since this will create an obstruction for outflow from a forearm or arm AVF, this can profoundly affect subsequent permanent access placement [8–13].

Placement and Perioperative Handling

Acute hemodialysis access is obtained by placing a non-cuffed, dual-lumen catheter into the superior or inferior vena cava, using the Seldinger technique. The smallest effective catheter should be used to avoid vein injury and thrombosis. A general guideline for CVC sizes matching patient size is given in Table 19.3 [19, 46–48]. Due to anatomic differences, smaller or larger catheter may be required in individual cases.

The right jugular vein is the optimal vein to insert a CVC into the superior vena cava. The femoral route may be preferred in acute, intensive care settings when dialysis will be needed only for a short period, in order to preserve all future routes of access to the superior vena cava. On the other hand, the risk of inferior vena cava thrombosis after CVC via the femoral route should be considered particularly in patients with CKD as a thrombosed vena cava will preclude conventional transplantation [49, 50].

Table 19.3 Hemodialysis vascular access: (A) Recommendations for patient and catheter size and examples for products, stratified by size (≤14.5 Fr), and (B) short-term catheter and (C) long-term catheters, respectively

A. Hemodialysis vascular access: Summary of recommendations for patient and catheter size, based on *KDOQI Guidelines* [19] and other published literature [46, 47, 48]	
Patient size	*Catheter size and configuration*
Neonate	≤7 Fr, double lumen
3–10 kg	7 Fr, double lumen
10–20 kg	8–9 Fr, double lumen
20–30 kg	9–10 Fr, double lumen
30–40 kg	10–11 Fr, double lumen
>40 kg	11.5–12.5 Fr, double lumen
B. Short-term catheters: Size (French), product names, configuration, and length (cm)	
5 Fr	Continuous C.A.V.H. (*Medcomp*®); straight (7.6 cm)
6 Fr	Pediatric short-term hemodialysis catheter, double lumen (*AMECATH*®); PUR; subclavian/jugular (8 cm); GamCath® double-lumen catheters (*Baxter*®); PUR; double lumen; straight (7.5 cm)
6.5 Fr	Pediatric dialysis catheter (*Joline*®); PUR; straight/curved (7.5, 10, 12.5 cm)
7 Fr	Femoral (*Medcomp*®); single or double lumen; rigid; straight (13.5 cm) Pediatric short-term hemodialysis catheter (*AMECATH*®); PUR; single lumen: subclavian/jugular/pre-curved (10, 12 cm); double lumen: subclavian/jugular (10 cm) Soft-Line (*Medcomp*®); PUR; coaxial internal lumen; straight (7, 10 cm)
8 Fr	Pediatric dialysis catheter (*Joline*®); PUR; straight/curved (10, 12.5, 15 cm) Continuous C.A.V.H. (*Medcomp*®); straight (11, 15 cm) Hemo-Cath (*Medcomp*®); SI; double lumen; tapered tip; straight (12 cm) MAHURKAR™* catheter (*MEDTRONIC*®); dual lumen; straight (9 cm); straight/curved (12, 15 cm) Pediatric short-term hemodialysis catheter (*AMECATH*®); PUR; single lumen: subclavian/jugular/pre-curved (10, 12, 15, 20 cm); double lumen: subclavian/jugular (10, 13 cm) Subclavian (*Medcomp*®); smooth material; straight (15, 20 cm) with removable "Y" hub
8.5 Fr	Femoral (*Medcomp*®); single or double lumen; rigid; straight (14, 25 cm); straight with "Y" hub (15 cm)
9 Fr	Duo-Flow (*Medcomp*®); PUR; coaxial internal lumen; tapered tip; straight/pre-curved (12, 15, 20 cm) Soft-Line (*Medcomp*®); PUR; coaxial internal lumen; straight (12, 15, 20 cm)
10 Fr	MAHURKAR™* catheter (*MEDTRONIC*®); dual lumen; straight/curved (12, 15 cm); curved (19.5 cm)
11 Fr	Brevia™ short-term dialysis catheter (*Bard Access Systems*®); round dual lumen; 8 Fr tapered venous tip; curved extension leg (12.5, 15, 20, 24 cm); straight (15, 20, 24 cm) High-flow double lumen (*Joline*®); polyurethane; step tip; straight/curved (15, 17.5, 20, 25 cm)
11.5 Fr	Duo-Flow (*Medcomp*®); PUR; coaxial internal lumen; tapered tip; straight/pre-curved/Raulerson IJ (12, 15, 20 cm); straight (24 cm) Hemo-Cath (*Medcomp*®); SI; double lumen; tapered tip; straight (15, 20, 24, 27 cm) MAHURKAR™* catheter (*MEDTRONIC*®); PUR; dual lumen; straight/curved (13.5, 16, 19.5 cm); straight (24 cm) Soft-Line (*Medcomp*®); PUR; coaxial lumen; straight/pre-curved (12, 15, 20 cm); straight (24 cm) Tri-Flow (*Medcomp*®); PUR; triple lumen; tapered tip; straight/pre-curved (12, 15, 20 cm); straight (24 cm)
12 Fr	Altius RT Acute (Kimal®); PUR; dual lumen; straight (15, 20, 25 cm) DUALYSE EXPERT (*Vygon*®); PUR; double lumen; containing silver ions; straight (Z-MAN 15, 20 cm; Safe +24 cm) MAHURKAR™* catheter (*MEDTRONIC*®); PUR; dual lumen; straight (13, 16, 20, 24, 30 cm); curved (13, 16, 20, 24 cm); pre-curved (13, 16, 20 cm) Niagara™ short-term dialysis catheter (*Bard Access Systems*®); PUR; oval design, straight/curved (15, 20, 24 cm); curved (12.5 cm) Power-Trialysis™ Slim-Cath™ short-term triple-lumen dialysis catheter (*Bard Access Systems*®); PUR; kidney-shaped lumen; three lumens; curved (12.5, 15, 20, 24 cm); straight (15, 20, 24, 30 cm) TRILYSE (*Vygon*®); PUR; triple lumen; containing silver ions; straight (Z-MAN/Safe: 15, 20, 24 cm)
12.5 Fr	MAHURKAR™* catheter (*MEDTRONIC*®); PUR; triple lumen; straight/curved (13, 16, 20, 24 cm); straight (30 cm)

(continued)

Table 19.3 (continued)

13 Fr	Duoglide™ short-term dialysis catheter (*Bard Access Systems*®); PUR; double lumen; curved (12.5, 15, 20, 24 cm); straight (15, 20, 24, 30 cm) Duo-Split (*Medcomp*®); PUR; split tip; straight/pre-curved/Raulerson IJ (12, 15, 20, 24 cm); straight (30 cm) High-flow double lumen (*Joline*®); PUR; step tip; straight/curved (15, 17.5, 20, 25 cm); straight (30 cm) Power-Trialysis™ short-term dialysis catheter (*Bard Access Systems*®); PUR; curved/alphacurve® (12.5, 15, 20, 24 cm); straight (15, 20, 24, 30 cm)
13.5 Fr	Hemo-Cath (*Medcomp*®); SI; double lumen; straight (15, 20, 24, 28, 35 cm) High-flow triple lumen (*Joline*®); PUR; step tip; straight/curved (15, 17.5, 20, 25 cm) MAHURKAR™* catheter (*MEDTRONIC*®); PUR; high-flow dual lumen; straight (13, 16, 20, 24, 30 cm); curved (13, 16, 20, 24 cm); pre-curved (13, 16, 20 cm) Niagara™ short-term dialysis catheter (*Bard Access Systems*®); PUR; oval design; curved (12.5 cm)/ straight (15, 20, 24 cm) Trio-CT (*Medcomp*®); PUR; three oval lumens; tapered tip; straight (12, 15, 20, 24, 30 cm)
14 Fr	Altius RT Acute (Kimal®); PUR; dual lumen; straight (15, 20, 28 cm) 400XL (*Medcomp*®); PUR; coaxial lumen; tapered tip; straight/pre-curved (12, 15, 20, 24 cm); curved (15, 20, 24 cm) SLX (*Medcomp*®); SI; double D lumen; tapered tip; straight (15, 20, 24, 30 cm)
C. Long-term catheters: Size (French), product names, configuration, and length (cm)	
6.5 Fr	Bio-Flex Tesio (*medcomp*®); PUR; single lumen; straight (29 cm)
8 Fr	GamCath® GDK-607,5P/Paediatric (*Baxter*®); PUR; single lumen; straight (15, 17.5, 20, 25 cm); curved (12.5, 15, 20, 24 cm) HEMO-CATH LT (*medcomp*®); SI; step tip; straight (18, 24 cm) Pediatric long-term hemodialysis catheter (*AMECATH*); PUR; tip-cuff (total length): 9 (12), 12 (15), 15 (18) cm
10 Fr	Bio-Flex Tesio (*medcomp*®); PUR; two single lumen; straight (40, 52, 70 cm) LIFECATH TWIN (*Vygon*®); PUR; two single lines; straight-art./ven. (18/21, 22/25, 27/30 cm) Pediatric long-term hemodialysis catheter (*AMECATH*); PUR; tip-cuff (total length): 9 (13), 13 (17), 15 (19), 19 (23) cm PEDIATRIC SPLIT CATH III (*medcomp*®); PUR; split tip; straight (15, 18, 24 cm)
11 Fr	GamCath® double-lumen catheters (*Baxter*®); *PUR;* double lumen; straight (12.5, 15, 20 cm); curved (15, 17.5, 20, 25 cm)
12 Fr	GamCath® triple-lumen catheters (*Baxter*®); PUR; triple lumen; straight (20 cm); curved (15, 17.5, 20 cm) Kflow Epic long-term hemodialysis catheters (*KIMAL*®); PUR; tip-cuff (total length): 16 (21), 19 (24) cm Pediatric long-term hemodialysis catheter (*AMECATH*); PUR; tip-cuff (total length): 24 (28), 28 (32) cm
12.5 Fr	HEMO-CATH LT (*medcomp*®); *SI*; step tip; straight/pre-curved (15, 28, 32 cm) SOFT-CELL® long-term hemodialysis catheter (*BD*®); PUR; straight, step tip; tip-cuff (total length): 12 (17), 19 (26) cm
13.5 Fr	HICKMAN® long-term hemodialysis catheter (*Bard Access Systems*®); SI; tip-hub: 19, 27, 31, 35 cm; total length: 28, 36, 40, 45 cm
14 Fr	Kflow Epic long-term hemodialysis catheters (*KIMAL*®); Carbothane, double D lumen; straight/ pre-curved; tip-cuff (total length): 19 (24), 23 (28), 27 (32), 31 (36), 35 (40), 50 (55) cm SPLIT CATH III (*medcomp*®); PUR; split tip; double D lumen; straight/pre-curved (24, 28, 32, 36 cm); straight (40, 55 cm) SPLIT CATH RG (*medcomp*®); PUR; split tip; double D lumen; straight (24, 28, 32, 36, 40 cm) SPLIT STREAM (*medcomp*®); PUR; split tip; double D lumen; straight (24, 28, 32, 36, 40 cm)
14.5 Fr	Hemo-Flow (*medcomp*®); PUR; straight/pre-curved (24, 28, 32, 36 cm); straight (40, 55 cm) MAHURKAR Chronic Carbothane™* (*MEDTRONIC*®); length: 36, 40, 45, 50 cm Palindrome™ Precision chronic dialysis catheter (base, SI, HSI or RT-) (*MEDTRONIC*®); Carbothane; length: 36, 40, 45, 50, (61, 72) cm; base; heparin-coated; +/− silver ion antimicrobial; reverse-tunneled catheter Permcath™ dual-lumen catheter (*MEDTRONIC*®); *SI*; oval shaped; straight (28 cm)

Abbreviations: *PUR* polyurethane, *SI* silicone, *Fr* French

Chronic hemodialysis catheters in children are most commonly cuffed dual-lumen catheters although two single-lumen catheters are occasionally used in infants or very small children (Table 19.3). Materials like polyurethane, silicone, or Carbothane are used in manufacturing process. They differ greatly in rigidity and tolerance to disinfectants (e.g., iodine or alcohols) [51–53].

Ultrasound and fluoroscopic guidance should be used for all catheter placements. The ultrasound is used to guide the initial puncture, and fluoroscopy is used to ensure that the distal catheter is placed in the proximal right atrium. In small children, this may not be possible; however, CVCs often function well with the tip in the superior vena cava. More distal placement should be avoided to avoid arrhythmias and proximity to the valve. The cuff should be positioned 1.5–2 cm proximal to the exit site to allow for optimal epithelial ingrowth. Consequently, the choice of the exit site is critical to the final CVC position. In other words, the exit site should be well chosen to optimize the position of the cuff. This may mean placing the exit site in positions which are more inferior or superior on the chest wall than is usual for most catheters.

Monitoring and Complications

Vessel dysfunction (thrombosis and/or stenosis) is observed in about 25% of children receiving a new CVC, particularly in patients with a previous CVC history [9]. In 1991 Schillinger et al. first described high venous stenosis rates following CVC placement for an average period of 1 month, with a striking difference between the subclavian (42%) and the internal jugular vein (10%) [54]. In children on chronic hemodialysis, the IPHN registry recently demonstrated lower dysfunction rates of CVCs placed in the internal jugular as compared to the subclavian or femoral vein [6, 9]. Despite this clinical evidence, 51% of dialysis catheters reported in the NAPRTCS registry were placed in the subclavian vein, documenting a strong need for further education [4]. Under no circumstances should the subclavian vein be the initial vein used for dialysis access. The smaller the child, the greater the likelihood that a puncture of the subclavian vein will lead to stenosis, due to the smaller diameter of the subclavian vein. Even smaller catheters used for parenteral nutrition or medications can lead to stenosis and should therefore also be avoided. This needs to be emphasized, because future forearm fistulae in the ipsilateral extremity can fail from outflow obstruction associated with a "minor" stenosis in the subclavian vein.

Complications of CVC can occur at the time of placement as well as during usage. Risks associated with catheter insertion include vessel perforation and hemorrhage, pneumothorax, hemothorax, infection, formation of emboli, and arrhythmias caused by the catheter tip. Long-term complications of hemodialysis catheters are common and include kinking or displacement, infection, fibrin sheath formation, and thrombosis [17, 55].

The most common complication observed with indwelling CVCs is catheter flow obstruction due to thrombus formation in the catheter lumen and/or around the catheter tip.

The ESPN Dialysis Working Group recently published clinical practice recommendations for the prevention and treatment of CVC-associated thrombosis in children, based on a thorough evidence review [9]. Pharmacological fibrinolysis with recombinant tissue plasminogen activator (rt-PA) was recommended as an effective *therapy* for CVC thrombosis, leading to restoration of catheter patency in 50–100% of cases [56]. Figure 19.7 shows a suggested algorithm of investigations and treatment for a CVC-related thrombosis. A deep vein thrombosis requires anticoagulation for up to 3 months, whereby the accumulation of heparin must be taken into account [57]. For *prevention* of catheter thrombosis in patients on chronic hemodialysis, the intraluminal instillation of rt-PA once weekly combined with heparin locks at the other sessions was suggested since this protocol was demonstrated in adults to effectively reduce catheter malfunction rates and the risk of bacteremia. Other preventive approaches appear to be less effective and safe. While locks with high-dose

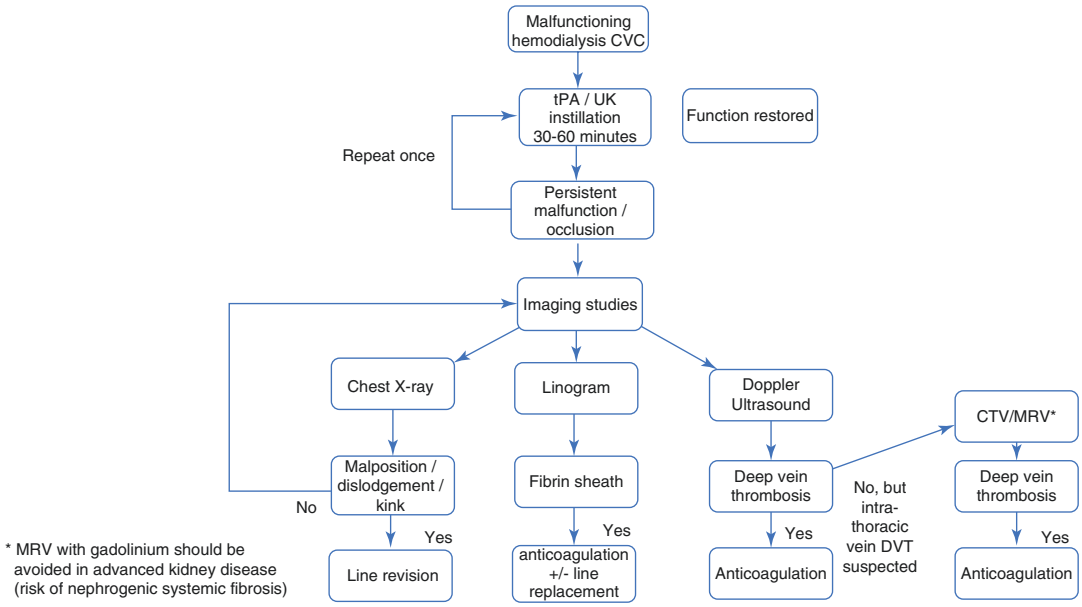

Fig. 19.7 Proposed algorithm for investigation and treatment in malfunctioning CVC. (Modified from Ref. [57])

unfractionated heparin (≥5000 IU/mL) lower clot formation at the cost of but an increased risk of bleeding complications, low-dose heparin solutions (1000 U/mL) decrease the incidence of CVC infections and bleeding but are ineffective in reducing the incidence of thrombotic complications. Likewise, citrate lock solutions and added antimicrobial agents do not appear to be effective in lowering the risk of clot formation [58].

Despite these therapeutic options, CVC line removal/exchange is often required [51, 55]. CVC replacement may also be necessary for mechanical catheter problems (breakage, displacement, and inadequacy due to growth of the child). Replacement of a non-functional CVC can often be performed using the catheter already in place. A small incision can be made over the catheter in the neck. The catheter is divided and used to place the wire, taking care not to displace the distal catheter into the vein during manipulation.

Infectious complications of CVCs are a leading cause of morbidity in pediatric HD patients [6, 9]. CVC-related infections were recently reported at an incidence of 1.3 per 1000 CVC days. Catheter replacement was required in 47% of these cases [6]. Infections can occur inside the CVC itself, at the exit site, or both. If a dialysis patient presents with fever and/or exit-site erythema or secretion, a blood culture must be obtained. Initially, broad-spectrum antibiotics (guided by antibiotic stewardship) should be given for empiric coverage. Exit-site infections should be confirmed by culture of the exudate, and antibiotics should be given empirically pending culture results [39, 59, 60]. Indications for immediate removal of the CVC include serious systemic symptoms such as septic shock or thrombocytopenia, persistently positive blood cultures, or the presence of specific microorganisms that do not respond to a conservative approach (such as *Candida* or other fungi). If possible, the central venous system should be kept free of any catheter for at least 2–3 days before a new CVC is placed.

Summary

Access for hemodialysis in children is a surgical challenge because of the size of the vessels and the unique physiology of the patients. In all cases, access must be planned as early as possible in the course of the renal disease, with the long-term

need for dialysis in mind. Primary AVF, with a lower rate of secondary failure and complications, is preferred for long-term hemodialysis access in children. The decision which patients are "too small" for this surgical approach varies from institution to institution, based on the experience of the surgeon and the availability of microsurgical techniques. The implementation of a multidisciplinary vascular access clinic providing patient-focused management ("one-stop approach") may decrease the use of CVCs, which should be reserved as a "bridge" to a more permanent access or used only in children so small that the risk of primary failure of an AVF is unacceptably high. Whether the surgeon creating the access is a vascular surgeon, pediatric surgeon, or transplant surgeon, it is imperative that the surgeon who is providing the access is an active participant in the decision-making process. Ultimately, the decision is a balance between the risk of primary failure (and subsequent loss of that site for a future fistula) and the complications of central venous access, which may also prevent creation of an effective future access.

References

1. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. Pediatr Nephrol. 2007;22:1999–2009.
2. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F. World kidney day steering committee. World Kidney Day 2016: Averting the legacy of kidney disease-focus on childhood. Pediatr Nephrol. 2016;31(3):343–8.
3. United States Renal Data System. 2019 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2019.
4. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). 2011 Annual Dialysis Report. https://naprtcs.org/system/files/2011_Annual_Dialysis_Report.pdf
5. Boehm M, Bonthuis M, Noordzij M, Harambat J, Groothoff JW, Melgar ÁA, et al. Hemodialysis vascular access and subsequent transplantation: a report from the ESPN/ERA-EDTA Registry. Pediatr Nephrol. 2019;34(4):713–21.
6. Borzych-Duzalka D, Shroff R, Ariceta G, Yap YC, Paglialonga F, Xu H, et al. Vascular access choice, complications, and outcomes in children on maintenance hemodialysis: findings from the international pediatric hemodialysis network (IPHN) registry. Am J Kidney Dis. 2019;74(2):193–202.
7. Harambat J, Ekulu PM. Inequalities in access to pediatric ESRD care: a global health challenge. Pediatr Nephrol. 2016;31(3):353–8.
8. Davidson I, Gallieni M, Saxena R, Dolmatch B. A patient centered decision-making dialysis access algorithm. J Vasc Access. 2007;8(2):59–68.
9. Shroff R, Calder F, Bakkaloğlu S, Nagler EV, Stuart S, Stronach L, et al. European Society for Paediatric Nephrology Dialysis Working Group. Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group. Nephrol Dial Transplant. 2019;34(10):1746–65.
10. Zingraff J, et al. Stenosis of the subclavian vein after percutaneous catheterization. In: Koostra G, Jorning P, editors. Proceedings of the international congress on access surgery. Ridgewood, NJ: Bogden & Sons, Inc.; 1983.
11. Stalter K, Stevens G, Sterling W. Late stenosis of the subclavian vein after hemodialysis catheter injury. Surgery. 1986;100:924–7.
12. Fant G, Dennis V, Quarles L. Late vascular complications of the subclavian dialysis catheter. Am J Kidney Dis. 1986;7:225–8.
13. Konner K. Subclavian haemodialysis access: is it still justified in 1995? Nephrol Dial Transplant. 1995;10(11):1988–91.
14. Franzone AJ, Tucker BL, Brennan LP, Fine RN, Stiles QR. Hemodialysis in children. Experience with arteriovenous shunts. Arch Surg. 1971;102(6):592–3.
15. Idriss FS, Nikaidoh H, King LR, Swenson O. Arteriovenous shunts for hemodialysis in infants and children. J Pediatr Surg. 1971;6(5):639–44.
16. Buselmeier TJ, Kjellstrand CM, Rattazzi LC, Simmons RL, Najarian JS. A new subcutaneous prosthetic a-V shunt: advantageous over the standard Quinton-Scribner shunt and a-V fistula. Proc Clin Dial Transplant Forum. 1972;2:67–75.
17. Valentini RP, Chand DH. Catheter craze continues for pediatric hemodialysis vascular access: the need to move from catheter first to catheter last. Am J Kidney Dis. 2019;74(2):155–7.
18. Chand DH, Valentini RP. International pediatric fistula first initiative: a call to action. Am J Kidney Dis. 2008;51(6):1016–24.
19. National Kidney Foundation. KDOQI Clinical practice guidelines and clinical practice recommendations for 2006 updates: haemodialysis adequacy, peritoneal dialysis and vascular access. Am J Kidney Dis. 2006;48:S1–S322.
20. Sidawy AN, Gray R, Besarab A, et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. J Vasc Surg. 2002;35(3):603–10.
21. Lee T, Mokrzycki M, Moist L, et al. Standardized definitions for hemodialysis vascular access. Semin Dial. 2011;24(5):515–24.
22. Chand DH, Geary D, Patel H, Greenbaum LA, Nailescu C, Brier ME, Valentini RP. Barriers, biases,

and beliefs about arteriovenous fistula placement in children: a survey of the international pediatric fistula first initiative (IPFFI) within the Midwest pediatric nephrology consortium (MWPNC). Hemodial Int. 2015;19(1):100–7.
23. Shroff R, Sterenborg RB, Kuchta A, Arnold A, Thomas N, Stronach L, et al. A dedicated vascular access clinic for children on haemodialysis: two years' experience. Pediatr Nephrol. 2016;31:2337–44.
24. Cagli K, Uzun A, Emir M, Bakuy V, Ulas M, Sener E. Correlation of modified allen test with Doppler ultrasonography. Asian Cardiovasc Thorac Ann. 2006;14:105–8.
25. Brittinger WD, Walker G, Twittenhoff WD, Konrad N. Vascular access for hemodialysis in children. Pediatr Nephrol. 1997;11:87–95. 17.
26. Bagolan P, Spagnoli A, Ciprandi G, et al. A 10 year experience of brescia-cimino arteriovenous fistula in children: technical evolution and refinements. J Vasc Surg. 1998;27(4):640–4.
27. Bourquelot P, Cussenot O, Corbi P, Pillion G, Gagnadoux MF, Bensman A, Loirat C, Broyer M. Microsurgical creation and follow-up of arteriovenous fistulae for chronic haemodialysis in children. Pediatr Nephrol. 1990;4:156–9.
28. Matoussevitch V, Taylan C, Konner K, Gawenda M, Kuhr K, Hoppe B, et al. AV fistula creation in paediatric patients: outcome is independent of demographics and fistula type reducing usage of venous catheters. J Vasc Access. 2015;16:382–7.
29. Bender M, Bruyninckx C, Gerlag P. The brachiocephalic elbow fistula: a useful alternative angioaccess for permanent hemodialysis. J Vasc Surg. 1994;20:808–13.
30. Rooijens PP, Tordoir JH, Stijnen T, Burgmans JP, Smet de AA, Yo TI. Radiocephalic wrist arteriovenous fistula for hemodialysis: meta-analysis indicates a high primary failure rate. Eur J Vasc Endovasc Surg. 2004;28:583–9.
31. Chand DH, Bednarz D, Eagleton M, Krajewski L. A vascular access team can increase AV fistula creation in pediatric ESRD patients: a single center experience. Semin Dial. 2009;22(6):679–83.
32. Karava V, Jehanno P, Kwon T, Deschênes G, Macher MA, Bourquelot P. Autologous arteriovenous fistulas for hemodialysis using microsurgery techniques in children weighing less than 20 kg. Pediatr Nephrol. 2018;33(5):855–62.
33. Almási-Sperling V, Galiano M, Lang W, Rother U, Rascher W, Regus S. Timing of first arteriovenous fistula cannulation in children on hemodialysis. Pediatr Nephrol. 2016;31:1647–57.
34. Onder AM, Flynn JT, Billings AA, Deng F, DeFreitas M, Katsoufis C, et al. Predictors of time to first cannulation for arteriovenous fistula in pediatric hemodialysis patients: Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol. 2020;35(2):287–95.
35. Oder TF, Teodorescu V, Uribarri J. Effect of exercise on the diameter of arteriovenous fistulae in hemodialysis patients. ASAIO J. 2003;49:554–5.
36. Van Loon MM, Goovaerts T, Kessels AG, van der Sande FM, Tordoir JH. Buttonhole needling of haemodialysis arteriovenous fistulae results in less complications and interventions compared to the rope-ladder technique. Nephrol Dial Transplant. 2010;25(1):225–30.
37. Wong B, Muneer M, Wiebe N, Storie D, Shurraw S, Pannu N. Buttonhole versus rope-ladder cannulation of arteriovenous fistulas for hemodialysis: a systematic review. Am J Kidney Dis. 2014;64(6):918–36.
38. Tanner NC, Da Silva AF. Medical adjuvant treatment to improve the patency of arteriovenous fistulae and grafts: a systematic review and metaanalysis. Eur J Vasc Endovasc Surg. 2016;52:243–52.
39. Nguyen DB, Shugart A, Lines C, Shah AB, Edwards J, Pollock D, Sievert D, Patel PR. National Healthcare Safety Network (NHSN) Dialysis event surveillance report for 2014. Clin J Am Soc Nephrol. 2017;12(7):1139–46.
40. Sheth RD, Brandt ML, Brewer ED, Nuchtern JG, Kale AS, Goldstein SL. Permanent hemodialysis vascular access survival in children and adolescents with end-stage renal disease. Kidney Int. 2002;62:1864–9.
41. Gradman WS, Lerner G, Mentser M, Rodriguez H, Kamil ES. Experience with autogenous arteriovenous access for hemodialysis in children and adolescents. Ann Vasc Surg. 2005;19(5):609–12.
42. Guzzetta PC, Salcedo JR, Bell SB, Ruley EJ. Limb growth and cardiac complications of fistulas in children. Int J Pediatr Nephrol. 1987;8:167–70.
43. O'Regan S, Danais S, Yazbeck S. Posttransplantation complications of lower limb polytetrafluoroethylene grafts in children. Nephron. 1989;52:90–2.
44. Conlon P, Nicholson M, Schwab SJ. Hemodialysis vascular access: practice and problems. New York: Oxford University Press; 2000.
45. Wilson S. Vascular access: principles and practice. 3rd ed. St. Louis: Mosby; 1996.
46. Rees L, Mattoo TK, Kim MS. Hemodialysis for children with chronic kidney disease. www.uptodate.com. 2020.
47. Bunchman TE, Brophy PD, Goldstein SL. Technical considerations for renal replacement therapy in children. Semin Nephrol. 2008;28(5):488–92.
48. De Galasso L, Picca S, Guzzo I. Dialysis modalities for the management of pediatric acute kidney injury. Pediatr Nephrol. 2020;35(5):753–65.
49. Szymczak M, Kaliciński P, Rubik J, Broniszczak D, Kowalewski G, Stefanowicz M, Kowalski A, Ciopiński M, Grenda R. Kidney transplantation in children with thrombosed inferior caval vein – atypical vascular anastomoses. Ann Transplant. 2019;24:25–9.
50. Shishido S, Kawamura T, Hamasaki Y, Takahashi Y, Itabashi Y, Muramatsu M, et al. Successful kidney transplantation in children with a compromised inferior vena cava. Transplant Direct. 2016 May 23;2(6):e82.
51. Geary DF, Schaefer F. Chapter 56, Hemodialysis vascular access: complications and outcomes. In: Chand

DH, Ramage IJ, editors. Comprehensive pediatric nephrology. St. Louis: Mosby; 2008.
52. Sheth RD, Kale AS, Brewer ED, Brandt ML, Nuchtern JG, Goldstein SL. Successful use of Tesio catheters in pediatric patients receiving chronic hemodialysis. Am J Kidney Dis. 2001;38:553–9.
53. Richard HM 3rd, Hastings GS, Boyd-Kranis RL, et al. A randomized, prospective evaluation of the Tesio, Ash split, and Opti-flow hemodialysis catheters. J Vasc Interv Radiol. 2001;12(4):431–5.
54. Schillinger F, Schillinger D, Montagnac R, Milcent T. Post catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses. Nephrol Dial Transplant. 1991;6:722–4.
55. Chand DH, Valentini RP, Kamil ES. Hemodialysis vascular access options in pediatrics: considerations for patients and practitioners. Pediatr Nephrol. 2009;24:1121–8.
56. Firwana BM, Hasan R, Ferwana M, Varon J, Stern A, Gidwani U. Tissue plasminogen activator versus heparin for locking dialysis catheters: a systematic review. Avicenna J Med. 2011;1:29–34.
57. Mandel-Shorer N, Tzvi-Behr S, Harvey E, Revel-Vilk S. Central venous catheter-related venous thrombosis in children with end-stage renal disease undergoing hemodialysis. Thromb Res. 2018;172:150–7.
58. Golestaneh L, Mokrzycki MH. Prevention of hemodialysis catheter infections: Ointments, dressings, locks, and catheter hub devices. Hemodial Int. 2018;22(S2):S75–82.
59. Tokars JI, Arduino MJ, Alter MJ. Infection control in hemodialysis units. Infect Dis Clin N Am. 2001;15:797–812.
60. D'Agata EM. Antimicrobial use and stewardship programs among dialysis centers. Semin Dial. 2013;26(4):457–64.

Technical Aspects of Hemodialysis in Children

20

Franz Schaefer and Jordan M. Symons

Introduction

Hemodialysis systems have advanced considerably from the original prototypes developed by Kolff [1]. With these advances, the delivery of hemodialysis has become safer, more predictable, and more efficient for patients and providers alike. Systems originally developed for adults have been adapted for hemodialysis in children. A hemodialysis system consists of an extracorporeal blood circuit, including a dialyzer, a system to prepare and deliver dialysate to the dialyzer, a system to generate an ultrafiltrate to remove volume from the patient, and a series of safety, control, and monitoring devices. Careful integration of these various systems permits safe and efficient dialysis for the patient. This chapter will provide an overview of the technical aspects of hemodialysis systems with special considerations related to pediatric hemodialysis.

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The Extracorporeal Blood Circuit (Fig. 20.1)

Blood leaves the patient through the vascular access and enters the extracorporeal blood circuit. The blood circuit consists of tubing to the dialyzer (arterial segment), the dialyzer, and tubing from the dialyzer back to the vascular access (venous segment). The blood circuit incorporates numerous monitoring systems to assure patient safety.

Hemodialyzer

The dialyzer is the key component of the hemodialysis system where blood purification occurs. Blood and dialysate pass through the dialyzer in a countercurrent direction, separated by a semipermeable membrane. The material of manufacture and physical properties characterize dialyzer membranes; surface area and fill volume further define differences between dialyzers. For optimal efficacy, manufacturers design dialyzers to minimize diffusion distances by maximizing the ratio of membrane surface to blood volume. The most commonly used dialyzers at this time, and used almost exclusively for pediatric care, are of hollow fiber design. Hollow fiber dialyzers consist of a bundle of capillaries potted at both ends into a plastic tubular housing with sealing material. The high blood compartment resistance of hollow fiber dialyzers enhances the efficiency of

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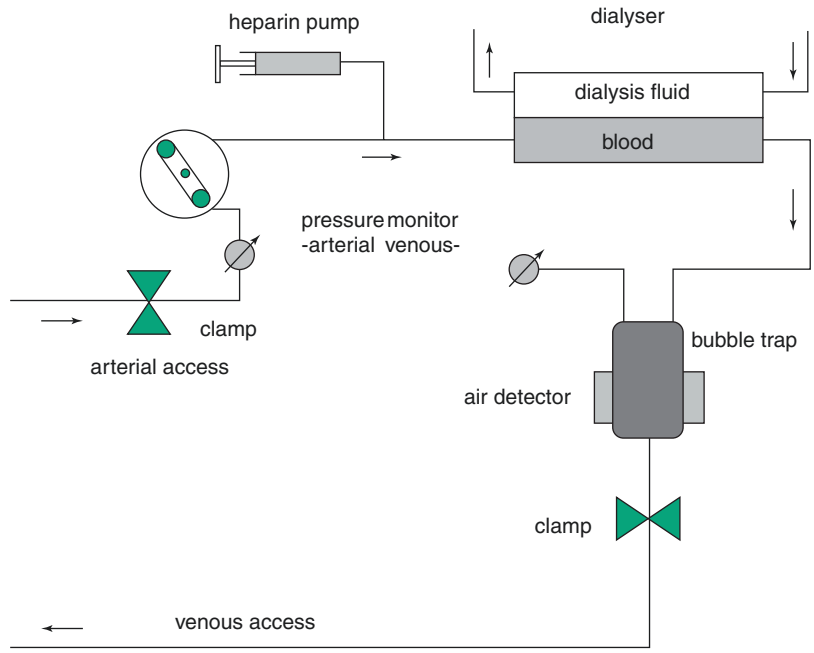

Fig. 20.1 Schematic of hemodialysis extracorporeal blood circuit

therapy, as they permit high blood flow rates at acceptable axial (arterial-to-venous) pressure drops. Various membrane materials may be used to construct hollow fiber dialyzers.

Hemodialyzer Membranes

The materials used for dialyzer membranes have evolved over time [2]. Cellulose-based membranes are made of reconstituted cellulose and are relatively inexpensive. Cellulose membranes have many hydroxyl residues, which can activate complement and lead to patient reactions. In modified or substituted cellulose membranes, some or all of the hydroxyl residues are esterified to reduce interaction with complement. The most common type of modified cellulose membrane is cellulose acetate, in which the majority of hydroxyl groups on the cellulose membrane are replaced with acetate. Modified cellulose membranes have a range of reactivity; cellulose triacetate is less reactive than cellulose acetate. Synthetic membranes are manufactured polymers classified as thermoplasts and made from polysulfone, polyamide, polyacrylonitrile (PAN), polyethersulfone, polyarylethersulfone/polyamide, or poly(methyl methacrylate) (PMMA). These materials show significantly lower complement activation. Variation in reactivity and likelihood of causing a deleterious reaction in the patient has led to the concept of membrane biocompatibility; membranes less likely to cause reactions are considered more biocompatible (see below). However, it remains unclear as to whether a more biocompatible membrane will yield better long-term patient outcomes [2].

Synthetic membranes lead to some technical advantages as well. The large pore size and thick wall structure of synthetic membranes allow the high ultrafiltration rates necessary in hemofiltration and high-flux hemodialysis at relatively low transmembrane pressures. Synthetic membranes have a wall thickness of at least 20 μm (cellulose membranes 6–15 μm) and may be structurally symmetric (e.g., PMMA) or asymmetrical (e.g., polysulfone, polyamide, polyethersulfone, polyarylethersulfone/polyamide). In the asymmetrical type, a very thin "skin" (about 1 μm) contacting the blood compartment lumen acts as the membrane's separating element with regard to solute removal. Many of the polymers used in manufacturing synthetic membranes are hydrophobic and require the addition of a hydrophilic

agent (e.g., polyvinylpyrrolidone (PVP)) to avoid excessive protein adsorption upon blood exposure.

The hollow fibers of a hollow fiber dialyzer serve as capillaries for blood transit and as the semipermeable membranes across which dialysis occurs. Most hollow fibers have a relatively standard inner diameter (180–240 μm) and length (20–24 cm). A small inner diameter is desirable as it provides a short diffusive distance for solute mass transfer, although it will also lead to increased resistance and high axial pressure drop, requiring a higher blood flow rate. The total nominal membrane surface area depends on the inner diameter, fiber length, and overall number of fibers (7000–14,000). Manufacturers create dialyzers for children of smaller surface area by using fewer hollow fibers per dialyzer or reducing the length of the hollow fibers used.

Several properties of hemodialysis membranes influence dialyzer performance, including the number of pores per unit surface area and the size of the pores. Dialyzer membranes can be categorized as high-flux (larger pores of approximately 60 kDa with high pore density) versus low-flux (smaller pores of approximately 10 kDa).

One may further characterize the performance of dialyzers by clearance, sieving coefficient, and ultrafiltration coefficient. Clearance capabilities for specific molecules of varying sizes can be defined based on the diffusive capacity of the dialyzer (related to porosity, pore size, and surface area). The ability of any molecule to pass through the dialyzer membrane defines the sieving coefficient, which is the ratio of the concentration of the molecule in the effluent versus that in the plasma water. For small molecules, the sieving coefficient will be close to 1; larger molecules, whose movement across the membrane may be restricted due to size, will have lower sieving coefficients. Water permeability is described by the ultrafiltration coefficient (K_{UF}) of the dialyzer, defined as the volume of ultrafiltrate produced per hour per mmHg of transmembrane pressure, determined at a blood flow rate of 200 mL/min. The K_{UF} depends not only on membrane characteristics but also on membrane surface area. High-flux dialyzers, mostly made of synthetic membranes, achieve ultrafiltration coefficients up to 60 mL/hr./mmHg. While manufacturers traditionally report K_{UF} as a single value intrinsic to the dialyzer based on in vitro testing, careful analysis suggests that K_{UF} may actually vary *in vivo* depending on session and patient characteristics [3].

Sterilization and Reuse

Dialyzers, and all other materials exposed to the patient's blood, must be sterilized prior to use. Multiple methods for dialyzer sterilization exist. Steam and gamma irradiation have largely replaced the older methods using ethylene oxide for dialyzer sterilization. Ethylene oxide has proven to be a cause for anaphylactoid reactions (see below), and many dialysis programs avoid the use of ethylene oxide-sterilized dialyzers wherever possible.

Dialyzers are used for one patient and one treatment, or the dialyzer can be rinsed and disinfected after use and then reused in the same patient [4]. The reuse procedure is complex and requires significant investment in materials by the dialysis unit but may, ultimately, have economic advantages by extending the useable life of a single dialyzer. There is considerable debate as to whether dialyzer reuse is justified [5]; worldwide, dialyzer reuse is now much less common than in the past although it is still used more widely in lower-resourced areas [6]. Few pediatric dialysis units engage in reuse for their pediatric patients.

Blood Tubing

The blood tubing of the hemodialysis system delivers blood to the dialyzer and then returns it to the patient. Blood tubing for dialysis is mainly made of polyvinylchloride and polycarbonate. As is necessary for the dialyzer, blood tubing sets must be appropriately sterilized. Several manufacturers make tubing systems with reduced diameters and fill volumes (approx. 50–80 mL

versus 150 mL in adult size systems) to permit hemodialysis in small children and infants. As a rule of thumb, the total extracorporeal blood volume (needles, tubes, and dialyzer) should not exceed 10% of total patient blood volume (i.e., 7–8 ml/kg body weight); extracorporeal volumes in excess of this value will increase risk for hypotension and vascular collapse at hemodialysis initiation. If it is not possible to limit extracorporeal volume, the dialysis physician must consider mitigating strategies such as priming the extracorporeal circuit with whole-blood equivalent (e.g., packed red blood cells mixed with albumin).

Blood Pump

A compressible portion of the arterial tubing segment interacts with the blood pump. This peristaltic roller pump generates blood flow through the extracorporeal blood circuit. During operation, at least one of the rollers completely occludes the tube all times, preventing uncontrolled flow from the patient into the extracorporeal circuit as well as backflow of blood when the pump stops. Thus, when blood flow ceases, the rotor in the arterial line segment acts as an arterial clamp. Blood pump rollers and the roller track must interact precisely; inadequate occlusion of the blood tubing could result in backflow, foaming, and hemolysis, while over-occlusion may lead to damage of the tubing resulting in spallation of silicone particles, tube rupture, or hemolysis. High outflow pressures, "downstream" of the pump in the venous segment, can lift the rollers and permit backflow of blood because the rollers no longer completely occlude the pump segment. Highly negative inflow pressures, "upstream" of the pump in the arterial segment, may incompletely fill the blood pump tubing, leading to a reduced stroke volume with each pump rotation. Low inflow and high outflow pressures together cause a characteristic thumping noise or "clunk" when the pump turns. This may be due to backflow from the high-pressure venous limb into the underfilled blood pump segment.

The blood flow rate (Q_B) and the duration of dialysis are important factors in determining treatment efficiency. The hemodialysis machine calculates blood flow rate from the rotation velocity and the assumed stroke volume of the roller pump. The stroke volume depends on the internal diameter of the pump segment, inlet suction pressure, and the elastic recoil of the flexible tube segment following occlusion of the moving rollers. Since these variables may cause errors in the displayed flow rate, regular calibrations of the blood pump are advisable. A corrected blood flow rate can be calculated from the actual arterial line pressure and the number of revolutions of the pump rotor. Some dialysis machines display a so-called effective blood flow rate, which takes the effect of a reduced arterial line pressure into account.

Heparin Pump

The majority of modern hemodialysis machines have an integrated pump for delivery of heparin, the most commonly used anticoagulant for hemodialysis. This is usually a syringe pump, although some manufacturers employ a roller pump. Entry to the blood circuit is most often post-pump, predialyzer, to limit the risk of air entry to the negative-pressure pre-pump limb of the circuit.

The Dialysate Circuit (Fig. 20.2)

The components of the dialysis system designed for delivery of dialysate to the dialyzer are usually more complex than the extracorporeal blood circuit. This is especially true for the majority of modern dialysis machines that generate dialysate online for dialysis therapy. Water for dialysate must be appropriately prepared and then blended with concentrates to make dialysate. The dialysate must be tested for biochemical balance; if acceptable, it must be delivered to the dialyzer, or, if deemed unacceptable, it must be shunted away from the dialyzer to avoid harm to the patient. In a system that generates dialysate

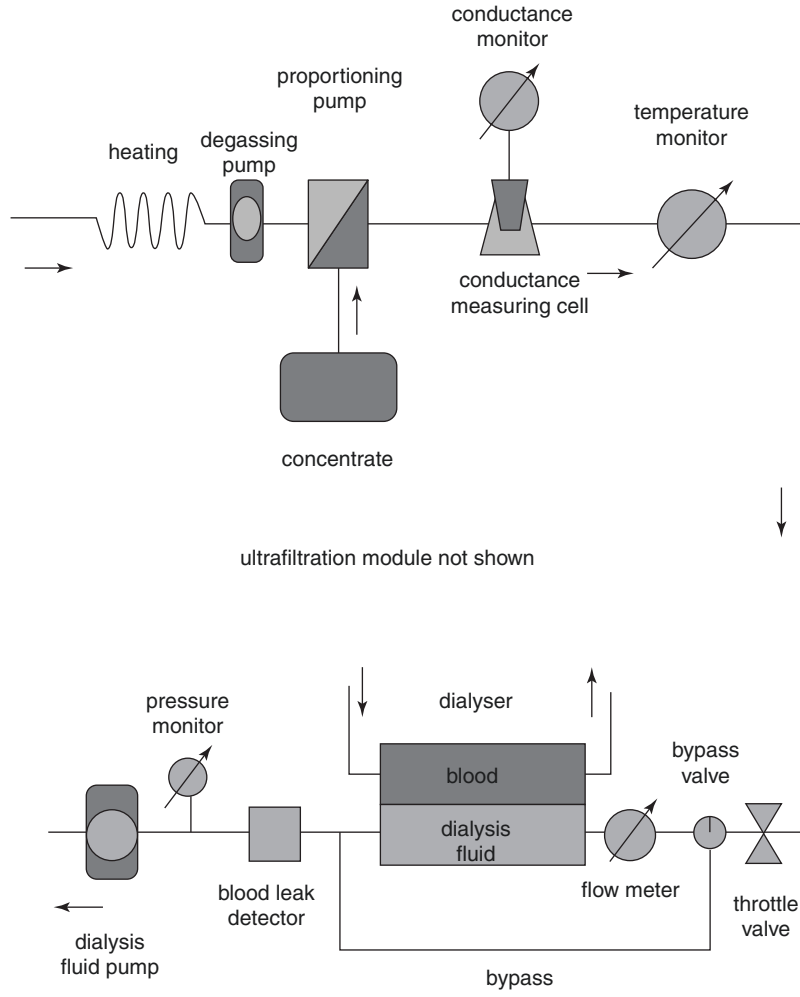

Fig. 20.2 Schematic of hemodialysis dialysate circuit

online during the session, this process occurs continuously throughout the treatment.

Water Purification

Water purification is an essential component to the generation of online dialysate [7]. Patients on hemodialysis are exposed to 300–500 L of dialysis fluid per week. Contamination of dialysate and infusate with chemical or biological impurities may seriously harm the patient. Consequently, regulatory agencies strictly define the quality of dialysis water, and requirements for purity are significantly more stringent than those for drinking water. Municipal water for drinking and general use, treated to limit bacterial growth and enhance palatability, contains many additives that would cause harm if exposed to a dialysis patient's blood across the dialyzer membrane. Therefore, careful purification of water for dialysis is essential.

Most water treatment systems for dialysis consist of a water softener, an activated carbon filter, a sediment filter, and a reverse osmosis system. Water softeners contain a resin that exchanges sodium cations for calcium, magnesium, and other polyvalent cations. Such minerals may improve the taste of drinking water but can cause harm when delivered to a hemodialysis patient. Therefore, water softening is particularly important in municipalities where the water is "hard," i.e., has higher content of calcium and magnesium. Water softening also protects the

reverse osmosis membrane, used in the final step of water treatment, from the buildup of scale and subsequent failure. The exchange resin in the water softener requires regeneration periodically with concentrated sodium chloride solution, which also reduces bacterial growth in the resin bed.

Dialysis units use activated carbon filters to remove chlorine and chloramines from source water. Communities add chlorine and chloramine as part of municipal water disinfection procedures. The presence of chlorine and chloramine in dialysate could lead to erythropoiesis stimulating agent resistance or frank hemolysis [8, 9]. Further, chlorine and chloramine can cause oxidation and degradation of the downstream reverse osmosis membrane. Therefore, water must be free of these substances before using it to prepare dialysate. Carbon filters also remove organic contaminants from the source water; the long-term impact of these contaminants on the health of hemodialysis patients remains uncertain. Carbon filters have a finite lifespan and cannot be regenerated; when no longer functioning, they require replacement. To assure patient safety, dialysis units usually install two carbon filters in series with sequential replacement based on schedule and the results of regular testing of product water for chloramines, multiple times a day.

Carbon beds tend to release carbon particles and therefore may require a sediment filter placed downstream. The filter limits progress of particles to the reverse osmosis membrane, which could lead to membrane damage. Other forms of filters may aid in the water purification process; these include depth filters, which can remove larger particulate matter at first entry of source water, and microbiological filters, designed to eliminate bacterial contaminants or endotoxins from entering the product water delivery system.

The main purification step in preparing dialysis water is reverse osmosis, where the water passes through a semipermeable polyamide or polysulfone membrane at 14–28 bar. This step removes 90–99% of inorganic and organic substances, pyrogens, bacteria, and particular matter. Of note, the reverse osmosis filter does not remove chlorine or chloramine, hence the importance of carbon filtration as part of the overall purification system. Under ideal conditions, approximately 75% of water feeding to the reverse osmosis system exits the filter as product water or permeant. Colder feed water or fouling of the reverse osmosis membrane with particulates reduces the percent of recovered product water from 75% to values of 35–50%; some dialysis units will return a portion of the reject water to the feed water stream to increase recovery of permeant.

As an extra step in purification, some dialysis units pass reverse osmosis permeant through a deionizer. Exchange resins in the deionizer remove ionic contaminants through exchange for hydrogen ions (cationic resins) and hydroxyl ion (anionic resins); the hydrogen and hydroxyl ions combine to form water. Deionizer beds can promote bacterial growth and do not filter out contaminants, bacteria, or other substances trapped by the reverse osmosis membrane. Deionizers require vigilant monitoring and prompt replacement before reaching binding capacity; once exhausted, the exchange resins may release previously sequestered ions into the product water, putting patients at significant risk [10].

After the purification process is complete, the final product water passes out to the hemodialysis stations in a continuously flowing loop. Appropriate booster pumps may be necessary to maintain pressure and forward flow. Continuous flow and avoidance of turbulent areas or "dead ends" will limit the likelihood of bacterial overgrowth within the water loop. Dialysis machines at individual stations use the product water to generate dialysate.

Dialysate

The dialysis machine makes dialysate online for patient treatment from purified water, which it warms and degasses, and then combines with concentrates. The dialysate is an isoosmolar solution containing electrolytes, buffers, and often glucose (Table 20.1). Alternative systems using pre-mixed dialysate also exist.

Table 20.1 Composition of standard dialysate compared to plasma (mmol/L)

Component	Dialysate	Plasma
Na^+	137–144	142
K^+	0–4	4.3
Ca^{++}	1.25–2.0	1.3
Mg^{++}	0.25–1	0.7
Cl^-	98–112	104
HCO_3^-	27–38	24
Glucose	0–11	4.5

Water degassing is necessary to prevent the formation of gas bubbles at the surface of the dialysis membrane. Degassing is achieved by either applying negative pressure or heating in the degassing module of the dialysis machine. The proportioning system then uses the warmed, degassed water to generate dialysate.

The most widely used buffer in dialysis fluids is sodium bicarbonate; it has replaced acetate as the primary buffer due to the negative cardiovascular effects (hypotension, cardiac depression) and poor patient outcomes associated with acetate-based dialysate [11]. Bicarbonate and calcium are prone to precipitate when combined. Therefore, bicarbonate-based dialysate combines two separate concentrates or solid-phase salt mixtures with purified water to create the final dialysate product. The A component of dialysate (color-coded red) is also termed the acid component; conventionally, this is a mixture of sodium, calcium magnesium, potassium, glucose, and chloride combined with an organic acid. The purpose of the small amount of acid is to prevent precipitation of calcium and magnesium as carbonate salts when the system mixes in the bicarbonate base. The organic acid in the A component can be glacial acetic acid, lactic acid, citric acid, or variants of these compounds. The B component (color-coded blue), also termed the base component, contains the bicarbonate (pH around 7.8).

The dialysis machine combines the acid and base concentrates with purified water in the carefully monitored proportioning system to generate dialysate [12]. For the B component, manufacturers offer dry salt mixtures in the form of cartridges or bags, which generate a saturated bicarbonate solution during the dialysis session by passing water through the solid salt container; this is then delivered to the proportioning system as with liquid bicarbonate concentrates. Dry salt mixtures for the B component reduce the chances of bacterial contamination, as liquid bicarbonate concentrate is an excellent bacterial growth medium [13]. Developing dry salt mixtures for the A component of dialysate was more challenging because acetic acid is a liquid at room temperature; manufacturers have now developed fully dry salt mixtures for the A component of dialysate using either sodium diacetate or citrate as the organic acid. Dry salt components require much less storage space and have lower shipping costs than equivalent liquid concentrates. Citrate-based dialysate also may have the advantage of providing local anticoagulation within the dialyzer and improving dialysis efficiency [14, 15]. The dialysis unit mixes these dry salt preparations with purified water to make A component concentrate which the proportioning system then combines with B component and additional purified water to generate dialysate. Due to variations in chemical structure and reactivity, the diverse salts used as the organic acid in A component may generate different levels of total base in the final dialysate. It is important to recognize this variation in potential base delivery as this may have an acute impact on the patient's acid-base status during the hemodialysis session, potentially leading to clinical changes from rapid potassium transport across cell membranes [16]. Careful consideration of overall acid-base status, taking into consideration the impact of dialysate, is an important component of overall dialysis care.

A three-stream proportioning system permits some flexibility in the final dialysate's biochemical content. Operators may adjust the potassium level of the dialysate by using different starting concentrates for the A component, depending on the goals of the session (see below). The dialysis machine permits adjustment of the bicarbonate concentration by programming the proportioning system to change the blend of A component, B component, and purified water; one must recognize that adjusting the proportion of concentrates

and water may also have an impact on the final biochemical balance of all the other electrolytes in the dialysate. Clinician choice of dialysate composition has largely been determined by observational data, rather than by study through clinical trials [17].

In the batch dialysate system, a given dialysate volume of up to 100 L is prepared before the session and held in a sealed tank. The dialysate circulates through the dialyzer and then returns to the reservoir. Batch systems have advantages with respect to the control of volume balance and ultrafiltration. Because of the reduced efficiency of the treatment with the progress of treatment time secondary to mixing of spent dialysate with fresh dialysate in the reservoir tank, and risk of bacterial contamination, single-pass systems have replaced batch systems in most dialysis programs. One updated version of the batch system (Genius, Fresenius Medical Care, Bad Homburg, Germany) addresses issues of efficiency and may have advantages of operating with simplified technology [18].

Historically, early hemodialysis sessions employed hypotonic dialysate sodium in the range of 120 mmol/L. Over several decades, with the advancement of dialysis equipment, dialysate sodium rose to higher levels, most commonly 140 mmol/L [19]. Higher sodium concentrations in dialysate lead to increased thirst and fluid intake between dialysis sessions, complicating volume management, while lower sodium concentrations may increase the incidence of hypotensive episodes and muscle cramps during the dialysis session [20].

Modern dialysis machines permit the operator to program variations in the sodium concentration of dialysate throughout the hemodialysis sessions. This technique, known as "sodium modeling," supposedly reduces intradialytic symptoms of hypotension and cramping; this has been reported in pediatric patients [21]. Manufacturers offer numerous pre-programed "sodium profiles" on their hemodialysis machines from which the operator may choose. There is considerable argument among dialysis providers as to whether sodium modeling is useful or whether it runs the risk of limiting appropriate sodium balance, putting the patient at risk for sodium excess and related issues of volume overload.

The dialysate potassium concentration is most commonly 2 mmol/L, chosen to induce a negative potassium balance in a patient with renal failure. The dialysate can be adjusted to lower values in an effort to remove more potassium in patients with severe hyperkalemia. Studies in adult patients suggest a greater risk when using lower dialysate potassium, likely due to the impact of sudden serum potassium changes on cardiac rhythm [22–24]. For patients with lower serum potassium or those undergoing daily hemodialysis in the acute setting, dialysate potassium is often raised to 3 mmol/L to limit further losses.

The standard dialysate calcium concentration should be 1.25–1.5 mmol/L unless there is substantial hypo- or hypercalcemia. Treatment of mineral bone disorder in patients on long-term hemodialysis with calcitriol and/or calcium containing phosphate binders can induce hypercalcemia [25]. In these patients, dialysate calcium can be reduced to 0.75–1.25 mmol/L [26–28]. In hypocalcemic patients, the dialysate calcium concentration may be increased to 1.75 mmol/L.

Dialysate magnesium concentrations range between 0.5 and 1 mmol/L to maintain normal serum magnesium concentrations [29, 30].

Glucose should be near the physiological concentration. Higher concentrations tend to cause insulin release and drive potassium into the cells, making it inaccessible for extraction.

The dialysis machine is able to provide variable dialysate bicarbonate concentrations because of individual variations of buffer requirements [31]. Recognizing the deleterious impact of metabolic acidosis in patients with chronic kidney disease, guidelines from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) suggested adjusting dialysis therapy to maintain serum bicarbonate levels at 22 mmol/L or greater [32]. One may target slightly higher concentrations in patients with persistent metabolic acidosis, but caution is indicated at concentrations exceeding 35 mmol/L, as this can lead to decreased serum ionized calcium levels, which may lead to impaired vascular tone

and cardiac contractility [33]. A rapid pH increase may be associated with the development of hypokalemia, probably with associated cardiac arrhythmia [34].

Prior to delivery to the dialyzer, the dialysate is heated. The temperature of dialysate entering the dialyzer is usually kept between 36 °C and 38 °C and can be adjusted individually. The cardiovascular effects of dialysate temperature have been extensively studied in adults. Lower dialysate temperatures decrease the incidence of dialysis-induced hypoxia and hypotension [35]. Lower dialysate temperatures are also associated with a lower incidence of hypotensive episodes [36, 37].

The production of an ultrapure dialysate, which is sterile and endotoxin-free, may limit inflammation associated with routine dialysate. Ultrapure dialysate also allows one to perform "online" hemodiafiltration (see below), in which the generated sterile dialysate is also used as a substitution fluid. Dialysis machines of the latest generation can filter the dialysate through a high-flux membrane, thereby further increasing microbiological purity and generating fluid for infusion in the setting of hemodiafiltration (see below).

Dialysate Flow Rates

To avoid saturation of dialysate during standard hemodialysis sessions, a common recommendation is to assure that dialysate flow rate is 1.5–2 times the blood flow rate. Many dialysis machines have a minimum dialysate flow rate of 500 ml/min with the ability to increase flow step-wise to 800 ml/min. These parameters would align with the recommendations in the setting of adult patients who may have vascular access that can generate blood flow rates between 300 and 400 ml/min. Lower dialysate flow rates would limit waste but may also reduce efficiency if saturation of dialysate were to occur. Some dialysis machines permit lower dialysate flow rates for extended hemodialysis as an alternative to continuous renal replacement therapy. In this setting, the longer session length compensates for the lower efficiency that may occur with dialysate saturation.

Ultrafiltration Control

Changes in transmembrane pressure (TMP) yield variation in the ultrafiltration volume as blood passes through the dialyzer. The rate of ultrafiltration depends on the TMP and the ultrafiltration coefficient (K_{UF}) of the dialyzer. Modern dialysis machines employ volumetric ultrafiltration control, in which automated systems adjust TMP to generate the desired ultrafiltration volume. Ultrafiltration control systems for hemodialysis vary in their methods, using systems based on flow sensors, closed loops, or volumetric balancing. The flow sensor system measures and compares dialysis inflow and outflow rates; the difference between these rates is the ultrafiltration rate. The dialysis machine automatically adjusts the TMP to achieve the desired rate, based on the programmed ultrafiltration target. In the closed-loop system, the dialysis fluid circulates in a closed circuit from which an ultrafiltration pump removes the desired fluid volume. The system replaces circulating dialysate with fresh dialysate as needed. The volumetric balancing system is based on matched pumps and balancing chambers separated by diaphragms that keep the dialysate inflow exactly equal to the dialysate outflow, creating a semiclosed loop. The system generates the ultrafiltrate by an additional pump removing fluid from this loop. An alternative to the volumetric methods of ultrafiltration control is gravimetric control, in which the device measures ultrafiltration rate by comparing the weights of bags filled with fresh dialysate and spent effluent.

Safety and Monitoring Systems

Pressure Monitors

Pressure monitors, built into the extracorporeal blood circuit, monitor the pressure of flowing blood both for safety and to assure smooth operation of the dialysis session. Sudden changes exceeding the allowable pressure limits will trigger an alarm, stop the blood pump, and close the venous clamp. Pressure monitoring in the blood

circuit allows detection of disconnections (sudden low pressure) and obstructions caused by tube kinking or blood clotting (sudden high pressure). Pressures in the extracorporeal circuit are measured in the arterial line preceding the blood pump, in the venous line before blood is returned to the patient, and, in some systems, in the line connecting the pump to the dialyzer. The pressure between the vascular access and the blood pump is negative due to the resistances of the access device and tubing, causing the risk of air entry at the connection site. The pressure downstream from the blood pump is always positive. The arterial, venous, and dialysis fluid pressures are used to calculate the transmembrane pressure (TMP), which is the main determinant of fluid removal by ultrafiltration. The maximum tolerance of pressure alarm limits should be set by the machine, and operator adjustments should be possible only within these limits. The lower limit of the venous pressure should be above atmospheric pressure and close to the displayed value to enable early detection of disconnections of the venous blood line. The minimal arterial pressure accepted by current dialysis machines is about −300 mmHg, but should be kept between −150 and −200 mmHg to limit endothelial trauma. The venous return pressure should not exceed +200 mmHg. However, the entire pressure gradient driving blood from the access into the arterial line depends on the negative arterial line pressure as well as on the pressure within the access. Since the intra-access pressure may vary from a few mmHg in central venous accesses to about 25 mmHg in arteriovenous fistulas and about 50 mmHg in arteriovenous grafts [38, 39], the same arterial line pressure produces different pressure gradients depending on the access. On the other hand, using a 16-gauge needle at the same arterial pressure, blood flow would increase from 250 to 320 mL/min when switching from a central venous access to an arteriovenous graft [40].

Air Trap

An air trap is located in the arterial and the venous segments. The air detector, located at the venous blood line, is necessary to prevent air embolism. There are several methods used for air detection systems in hemodialysis; probably the most reliable is the ultrasonic method measuring changes of ultrasound transmittance caused by air bubbles or foam. If foam or air is detected, the blood pump stops, and the blood tubing clamp immediately downstream of the air trap closes, preventing delivery of air to the patient.

Blood Leak Monitors

Blood leakage into the dialysate after rupture of the filter membrane is detected by a blood leak detector located downstream of the dialyzer which measures the change in optical transmission by hemoglobin.

Conductivity Monitor

In dialysis machines that employ single-pass dialysate delivery, as noted above, the proportioning system exactly measures the required amounts of A and B component concentrates, mixes with purified water, and generates the dialysate continuously during the hemodialysis session. After thorough mixing, measurement of the electrical conductivity of the final dialysate plays an important role in detecting any aberrations from the desired concentrate composition. If the conductivity is outside the desired range due to technical problems or running out of concentrate, an alarm sounds, and the system activates a bypass valve to prevent delivery of this inappropriate dialysate to the dialyzer.

To measure conductivity, metal electrodes in the flow of the dialysate apply a constant voltage, which generates an electrical current. The presence of ions in the dialysate reduces resistance to current flow in a predictable manner; thus, dialysate conductivity serves as a method to monitor the dialysate for proper mixing. Conductivity varies with temperature; for this reason, the device corrects readings to a standard temperature. Given the risks to the patient of inappropriately mixed dialysate, the conductivity monitoring

system requires frequent checking and preventive maintenance.

Electrical conductivity has become a surrogate for the concentration of Na^+, especially for the measurement of online clearance or sodium modeling. However, the use of solute conductivity as a surrogate of Na^+ concentration is valid only within well-defined systems and prone to confounding effects; for example, the decrease of K^+ concentration during dialysis will cause a parallel drop in effluent dialysate conductivity.

Non-invasive Blood Volume Monitoring

In hemodialysis, fluid is removed by ultrafiltration from the intravascular space. However, most of the fluid accumulated in the interdialytic period distributes in the extravascular space. The fluid shift during the hemodialysis session between extra- and intravascular compartments (i.e., vascular refilling) is limited by physiologic factors such as the hydraulic conductivity of the microvascular wall [41]. If the vascular refilling rate does not match the ultrafiltration rate, blood volume will drop, and a cascade of compensatory mechanisms will arise. When a critically low blood volume is reached, symptomatic hypotension will occur [42]. While it is somewhat challenging technically to measure accurately a patient's absolute blood volume, technology exists to measure changes in the relative volume of blood that passes through the hemodialysis blood circuit. Techniques include instantaneous hematocrit by optical density or density by sound velocity. Proprietary algorithms in devices attached to the dialysis system can translate changes in blood density during ultrafiltration to a measurement of variation in blood volume from the start of the hemodialysis session. The operator can monitor the change in relative blood volume as a marker of intravascular volume; observational studies have correlated higher rates of change in relative blood volume measured by these techniques with incidence of intradialytic symptoms and hypotension [43, 44]. By contrast, little or no change in the slope of the relative blood volume monitor suggests constant refilling of the vascular compartment from the interstitial space, possibly indicating fluid excess within the patient (Fig. 20.3) [45].

The existence of this technology, which some manufacturers integrate directly in their hemodialysis machines, raises questions as to whether online monitoring of relative blood volume may permit an automated feedback system to control ultrafiltration rate and reduce the risk of symptomatic hypotension related to overly aggressive fluid removal. A study in adults did not demon-

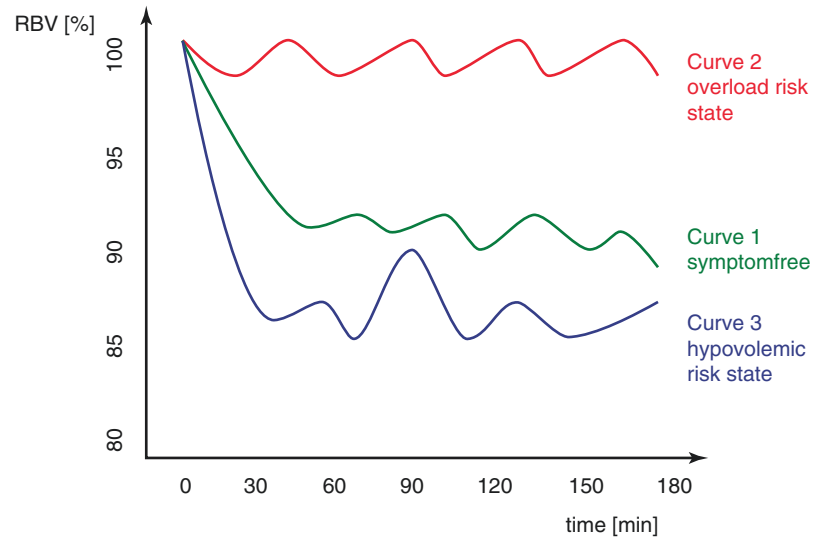

Fig. 20.3 Schematic curve shapes of relative blood volume (RBV) measured by blood volume monitoring (BVM). Three major curve shapes can be distinguished

strate a clear improvement in intradialytic symptoms when an automated relative blood volume monitoring protocol was compared to standard patient monitoring with manual adjustment by dialysis staff [46].

Dialysance and Online Monitoring of Clearance

Ionic dialysance and patient's plasma conductivity can be calculated easily from online inlet and outlet dialysate conductivity measurements at two different steps of dialysate conductivity [47, 48]. This technique forms the basis for online monitoring of clearance, serving as a proxy for urea clearance. Several manufacturers include online conductivity measurements in latest-generation dialysis machines. Online urea kinetics removes the need for blood sampling and complex mathematical calculations in determining dialysis efficacy and provides immediate clearance information while dialysis is ongoing. However, experience with online Kt/V is still limited, and validation studies are still lacking in both adults and children [49].

Ionic dialysis may have other potential uses. The implementation of the conductivity kinetic model also permits monitoring to achieve a neutral sodium balance at each HD session [50], an improvement over previous approaches to sodium kinetic modeling which required blood sampling. The conductivity kinetic modeling technique may improve intradialytic cardiovascular stability in adult hypotension-prone patients [51]. Ionic dialysance can also be used to monitor the blood flow through the vascular access [52].

Maintenance

Disinfection and Sterilization

Bacterial contamination inevitably occurs at various sites of the dialysis system. The degree of contamination with pathogenic organisms, bacterial proliferation, and subsequent endotoxin release must be limited by technical measures and regular disinfection. Bacterial adhesion and subsequent growth predominantly occur at rough surfaces or in stagnant water. Ring loop systems are designed to prevent microbial proliferation in stagnant water. Purified water is produced in excess by the water treatment module and pumped to the individual hemodialysis treatment stations. The excess water is recirculated to the water treatment device, where refiltration in the reverse osmosis module permits reduction of the microbial load. Although reverse osmosis is effective in removing bacteria, viruses, and pyrogens, small defects in the membrane may allow bacteria and pyrogens to penetrate and contaminate the water produced. Reverse osmosis modules and ring loop systems must therefore be disinfected regularly with chemicals such as formaldehyde, peracetic acid, or other disinfectants or by high heat. Stainless steel tubing should be preferred for the ring loop over plastic since plastic surfaces are progressively roughened by aging and disinfectants.

Bacterial growth in the resin bed of the water softener is restricted by regular regeneration with concentrated sodium chloride solution. In case of excessive bacterial colonization, disinfection with formaldehyde solution, peracetic acid, or others can be performed. Water treatment devices are operated intermittently by automatic control systems during nights and at weekends to flush away adherent bacteria. The limit for microbial contamination has been set to a maximum of 200 colony-forming units (CFU) for purified water used to prepare the dialysis fluid and to 2000 CFU for effluent dialysate after the dialysis procedure. Substantial bacterial proliferation occurs in the dialysis machine itself. Bacterial adhesion and subsequent proliferation is facilitated by numerous angles, valves, pumps, regions of low fluid flow rates, and temperatures around 37 °C. Contamination of the dialysis fluid can only be limited by regular cleaning and disinfection of the dialysis machine. The cleaning process includes the removal of protein layers or biofilms generated by slime-forming bacteria and decalcification. Disinfection can be performed by thermic, chemical, or combined procedures. Thermochemical disinfection with hot citric acid permits simultaneous decalcification.

Descaling

Due to the inevitable deposition of calcium and magnesium salts in the dialysis machine over time, the dialysate system must be decalcified daily, e.g., by rinsing with 20% citric or hydroxyacetic acid.

Complications and Troubleshooting

Dialyzer Reactions and Biocompatibility

Dialyzer membranes and blood tubing materials interact with plasma proteins and blood cells. Due to its high surface area, the largest amount of these interactions occurs at the filter membrane. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. This response involves, among others, complement activation, monocyte and granulocyte activation, and endotoxin transfer.

Minimizing the biological response during dialysis is important since there may be an impact on long-term patient morbidity and survival. Dialyzers with synthetic membranes induce a much lower activation of complement factors than cellulose-based membranes [53]. Dialyzer membranes activate the alternative complement pathway. Plasma concentrations of activated complement factors C3a and C5a increase during the first 15 min of hemodialysis. This may lead to many of the clinical reactions observed during hemodialysis including anaphylactoid reactions, neutrophil trapping in the lung, and dialysis-related hypoxemia [54, 55].

Activation of circulating mononuclear cells by complement and bacterial endotoxins can induce the production of cytokines [56]. Cytokine induction during hemodialysis may cause fever and chills, which are observed during hemodialysis with bacterially contaminated dialysate. Synthetic high-flux membranes have greater adsorptive capacity for small molecular pyrogens than cellulosic membranes and may therefore lead to a lower incidence of chronic inflammatory responses. There is speculation that suppressing inflammation may be useful in treating an inflammatory-malnutrition syndrome in dialysis patients [57]. Protein adsorption at membrane surfaces generates a biofilm that results in a progressive loss of the diffusive and convective capacity. On the other hand, membrane-induced reactions such as complement activation are reduced by biofilm formation.

The overall effects of the membrane type on treatment outcomes are controversial and may have been overestimated in the past. This may be due to the complex biological effect profiles of individual membranes: A membrane which leads to exorbitant activation of one molecular cascade may exert a much lower activation of other biomolecules compared to another membrane.

The contact system of plasma can be activated by negatively charged surfaces of dialysis membranes. Activation leads to cleavage of kininogen by kallikrein and the release of bradykinin into the circulation, where it is normally inactivated immediately by kininase I and angiotensin-converting enzyme. The negatively charged AN69 polyacrylonitrile membrane generates small amounts of bradykinin in vitro [58]. This has led to severe clinical reactions in patients dialyzed with AN69 membranes who are treated with ACE inhibitors [59] and angiotensin II receptor antagonists [60].

Patient reactions to hemodialyzers are classified as type A reactions, which occur soon after initiation of the hemodialysis session, and type B reactions, which are delayed. Type A reactions are thought to be related to substances involved in dialyzer manufacture that may seep from the dialyzer into the flowing blood and then enter the patient. A well-described example is ethylene oxide, which is used in one method for dialyzer sterilization. Some patients may have anaphylactoid reactions related to use of ACE inhibitors in conjunction with dialyzer membranes made from polyacrylonitrile (PAN); this reaction has also been reported in CRRT with use of the AN-69 membrane, one form of PAN membrane. Numerous case reports describe other circumstances associated with type A reactions. Type A reactions may also be seen with bacterial con-

tamination of dialysis materials. Type A reactions are, by definition, sudden in onset and may be severe; patients may experience severe dyspnea, chest pain, hypotension, and cardiovascular collapse. Dialysis staff must maintain a high index of suspicion and vigilance; if a patient is suspected of having a type A reaction, either mild or severe, the hemodialysis treatment should be stopped, and blood should not be returned to the patient to avoid introducing more irritant. Supportive care should be employed, followed by a careful review of the circumstances to identify the cause.

Type B reactions tend to be more common than type A reactions. They are usually much less severe, often manifesting as chest discomfort, back pain, dyspnea, nausea, emesis, or hypotension. Anaphylaxis is very uncommon. Type B reactions are thought to be complement mediated and possibly related to membrane biocompatibility.

Hemodialysis Technique Variations

Hemodiafiltration

The combination of high diffusive clearance rates in conventional hemodialysis with convective clearance yields a hybrid system known as hemodiafiltration. Indications for hemodiafiltration include frequent hypotensive episodes and excessive serum phosphate levels. Online production of substitution fluid by sterile ultrafiltration of dialysis solution has made hemodiafiltration safe and helped to reduce treatment costs. Hemodiafiltration with a high-flux membrane is as efficient as HD for low molecular weight compounds but is more efficient than pure convective clearance (hemofiltration) for low molecular weight compounds [61]. Online hemodiafiltration, in which filtered dialysate free of toxins and pyrogens is used as replacement fluid, allows a high convection fluid rate (especially in predilution mode) and facilitates a dialysis dose increase without an increase in cost [62]. The use of hemodiafiltration has grown considerably such that it is the standard method in many adult and pediatric dialysis units around the world.

Single-Needle Dialysis

In standard hemodialysis, blood enters the arterial limb of the blood circuit through one lumen of the vascular access and returns to the patient from the venous limb through a different lumen. This could be through two needles placed in a permanent subcutaneous hemodialysis access or through two separate lumens of a central venous catheter (either a double-lumen catheter or two single-lumen catheters). In the case of a single vascular access lumen such as one single-lumen catheter or the inability to place two needles in the permanent vascular access, so-called "single-needle" dialysis is an option. This requires a special system in the blood path that alternates the direction of blood flow through a single vascular access joined to a Y junction that connects the arterial and venous ends of the blood circuit. One such system uses two clamps at both arterial and venous limbs. When the arterial clamp is open, the pump draws blood into the circuit against the closed venous clamp, raising the pressure in the blood compartment. When the pressure in the venous line reaches an upper limit, the arterial clamp closes, the blood pump stops, and the venous clamp opens, allowing the blood to flow back to the patient. When the pressure reaches a lower limit, the venous clamp closes and the arterial clamp opens, after which the blood pump starts again to repeat the cycle. Alternatively, the efficacy of single-needle circuits improves by using two separate pumps, one for arterial blood withdrawal and another for venous return. During single-needle dialysis, an arterial bubble trap placed between the blood pump and the dialyzer serves as an expansion chamber, enhancing the compliance of the blood circuit. Recirculation of blood in the Y connection can reach 20% of total blood flow, reducing overall efficiency when compared to standard "double-needle" hemodialysis.

Summary

Significant advancements have made hemodialysis safer and more effective for pediatric patients than ever before. Sophisticated technology and multiple safety systems combine to provide this complex therapy. Even the most sophisticated technology, however, requires careful thought and observation by experienced human beings participating at the bedside. Dialysis nurses, technicians, and physicians work in partnership to assure the best possible outcomes to children who require hemodialysis.

References

1. Kolff WJ, Berk HT, ter Welle M, van der LA, van Dijk EC, van Noordwijk J. The artificial kidney: a dialyser with a great area. 1944. J Am Soc Nephrol. 1997;8(12):1959–65.
2. Boure T, Vanholder R. Which dialyser membrane to choose? Nephrol Dial Transplant. 2004;19(2):293–6.
3. Ficheux A, Kerr PG, Brunet P, Argiles A. The ultrafiltration coefficient of a dialyser (KUF) is not a fixed value, and it follows a parabolic function: the new concept of KUF max. Nephrol Dial Transplant. 2011;26(2):636–40.
4. Lacson E Jr, Lazarus JM. Dialyzer best practice: single use or reuse? Semin Dial. 2006;19(2):120–8.
5. Galvao TF, Silva MT, Araujo ME, Bulbol WS, Cardoso AL. Dialyzer reuse and mortality risk in patients with end-stage renal disease: a systematic review. Am J Nephrol. 2012;35(3):249–58.
6. Upadhyay A, Jaber BL. Reuse and biocompatibility of hemodialysis membranes: clinically relevant? Semin Dial. 2017;30(2):121–4.
7. Martin K, Laydet E, Canaud B. Design and technical adjustment of a water treatment system: 15 years of experience. Adv Ren Replace Ther. 2003;10(2):122–32.
8. Perez-Garcia R, Rodriguez-Benitez P. Chloramine, a sneaky contaminant of dialysate. Nephrol Dial Transplant. 1999;14(11):2579–82.
9. Junglee NA, Rahman SU, Wild M, Wilms A, Hirst S, Jibani M, et al. When pure is not so pure: chloramine-related hemolytic anemia in home hemodialysis patients. Hemodial Int. 2010;14(3):327–32.
10. Arnow PM, Bland LA, Garcia-Houchins S, Fridkin S, Fellner SK. An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. Ann Intern Med. 1994;121(5):339–44.
11. Hakim RM, Pontzer MA, Tilton D, Lazarus JM, Gottlieb MN. Effects of acetate and bicarbonate dialysate in stable chronic dialysis patients. Kidney Int. 1985;28(3):535–40.
12. Sargent JA, Gotch FA, Lam M, Prowitt M, Keen M. Technical aspects of on-line proportioning of bicarbonate dialysate. Proc Clin Dial Transplant Forum. 1977;7:109–16.
13. Stragier A, Wenderickx D. Bacterial growth prevention in liquid bicarbonate concentrate. Edtna Erca J. 1998;24(3):40–2. 4
14. Ahmad S, Callan R, Cole JJ, Blagg CR. Dialysate made from dry chemicals using citric acid increases dialysis dose. Am J Kidney Dis. 2000;35(3):493–9.
15. Kossmann RJ, Gonzales A, Callan R, Ahmad S. Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. Clin J Am Soc Nephrol. 2009;4(9):1459–64.
16. Heguilen RM, Sciurano C, Bellusci AD, Fried P, Mittelman G, Rosa Diez G, et al. The faster potassium-lowering effect of high dialysate bicarbonate concentrations in chronic haemodialysis patients. Nephrol Dial Transplant. 2005;20(3):591–7.
17. McGill RL, Weiner DE. Dialysate composition for hemodialysis: changes and changing risk. Semin Dial. 2017;30(2):112–20.
18. Fassbinder W. Experience with the GENIUS hemodialysis system. Kidney Blood Press Res. 2003;26(2):96–9.
19. Flythe JE, Mc Causland FR. Dialysate sodium: rationale for evolution over time. Semin Dial. 2017;30(2):99–111.
20. Munoz Mendoza J, Arramreddy R, Schiller B. Dialysate sodium: choosing the optimal hemodialysis bath. Am J Kidney Dis. 2015;66(4):710–20.
21. Sadowski RH, Allred EN, Jabs K. Sodium modeling ameliorates intradialytic and interdialytic symptoms in young hemodialysis patients. J Am Soc Nephrol. 1993;4(5):1192–8.
22. Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lazarus JM, et al. Cardiac arrest and sudden death in dialysis units. Kidney Int. 2001;60(1):350–7.
23. Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int. 2011;79(2):218–27.
24. Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, et al. Modifiable practices associated with sudden death among hemodialysis patients in the dialysis outcomes and practice patterns study. Clin J Am Soc Nephrol. 2012;7(5):765–74.
25. Hercz G, Kraut JA, Andress DA, Howard N, Roberts C, Shinaberger JH, et al. Use of calcium carbonate as a phosphate binder in dialysis patients. Miner Electrolyte Metab. 1986;12(5–6):314–9.
26. Mactier RA, Van Stone J, Cox A, Van Stone M, Twardowski Z. Calcium carbonate is an effective phosphate binder when dialysate calcium concentration is adjusted to control hypercalcemia. Clin Nephrol. 1987;28(5):222–6.
27. Sawyer N, Noonan K, Altmann P, Marsh F, Cunningham J. High-dose calcium carbonate with stepwise reduction in dialysate calcium concentration: effective phosphate control and aluminium avoidance

in haemodialysis patients. Nephrol Dial Transplant. 1989;4(2):105–9.
28. Slatopolsky E, Weerts C, Norwood K, Giles K, Fryer P, Finch J, et al. Long-term effects of calcium carbonate and 2.5 mEq/liter calcium dialysate on mineral metabolism. Kidney Int. 1989;36(5):897–903.
29. Mountokalakis TD. Magnesium metabolism in chronic renal failure. Magnes Res. 1990;3(2):121–7.
30. Markell MS, Altura BT, Sarn Y, Delano BG, Ifudu O, Friedman EA, et al. Deficiency of serum ionized magnesium in patients receiving hemodialysis or peritoneal dialysis. ASAIO J. 1993;39(3):M801–4.
31. Gennari FJ. Acid-base balance in dialysis patients. Semin Dial. 2000;13(4):235–9.
32. Kopple JD, Kalantar-Zadeh K, Mehrotra R. Risks of chronic metabolic acidosis in patients with chronic kidney disease. Kidney Int Suppl. 2005;95:S21–7.
33. Leunissen KM, van den Berg BW, van Hooff JP. Ionized calcium plays a pivotal role in controlling blood pressure during haemodialysis. Blood Purif. 1989;7(5):233–9.
34. Wiegand C, Davin T, Raij L, Kjellstrand C. Life threatening hypokalemia during hemodialysis. Trans Am Soc Artif Intern Organs. 1979;25:416–8.
35. Hegbrant J, Sternby J, Larsson A, Martensson L, Lassen Nielsen A, Thysell H. Beneficial effect of cold dialysate for the prevention of hemodialysis-induced hypoxia. Blood Purif. 1997;15(1):15–24.
36. Hegbrant J, Martensson L, Ekman R, Nielsen AL, Thysell H. Dialysis fluid temperature and vasoactive substances during routine hemodialysis. ASAIO J. 1994;40(3):M678–82.
37. Sherman RA, Rubin MP, Cody RP, Eisinger RP. Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. Am J Kidney Dis. 1985;5(2):124–7.
38. Besarab A, Dorrell S, Moritz M, Michael H, Sullivan K. Determinants of measured dialysis venous pressure and its relationship to true intra-access venous pressure. ASAIO Trans. 1991;37(3):M270–1.
39. Besarab A, Al-Saghir F, Alnabhan N, Lubkowski T, Frinak S. Simplified measurement of intra-access pressure. ASAIO J. 1996;42(5):M682–7.
40. Besarab A, Sullivan KL, Ross RP, Moritz MJ. Utility of intra-access pressure monitoring in detecting and correcting venous outlet stenoses prior to thrombosis. Kidney Int. 1995;47(5):1364–73.
41. Schneditz D, Roob J, Oswald M, Pogglitsch H, Moser M, Kenner T, et al. Nature and rate of vascular refilling during hemodialysis and ultrafiltration. Kidney Int. 1992;42(6):1425–33.
42. Kim KE, Neff M, Cohen B, Somerstein M, Chinitz J, Onesti G, et al. Blood volume changes and hypotension during hemodialysis. Trans Am Soc Artif Intern Organs. 1970;16:508–14.
43. Hothi DK, Harvey E, Goia CM, Geary D. Blood-volume monitoring in paediatric haemodialysis. Pediatr Nephrol. 2008;23(5):813–20.
44. Patel HP, Goldstein SL, Mahan JD, Smith B, Fried CB, Currier H, et al. A standard, noninvasive monitoring of hematocrit algorithm improves blood pressure control in pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(2):252–7.
45. Dheu C, Terzic J, Menouer S, Fischbach M. Importance of the curve shape for interpretation of blood volume monitor changes during haemodiafiltration. Pediatr Nephrol. 2009;24(7):1419–23.
46. Leung KCW, Quinn RR, Ravani P, Duff H, MacRae JM. Randomized crossover trial of blood volume monitoring-guided ultrafiltration biofeedback to reduce intradialytic hypotensive episodes with hemodialysis. Clin J Am Soc Nephrol. 2017;12(11):1831–40.
47. Petitclerc T, Goux N, Reynier AL, Bene B. A model for non-invasive estimation of in vivo dialyzer performances and patient's conductivity during hemodialysis. Int J Artif Organs. 1993;16(8):585–91.
48. Polaschegg HD. Automatic, noninvasive intradialytic clearance measurement. Int J Artif Organs. 1993;16(4):185–91.
49. Grzegorzewska AE, Banachowicz W. Evaluation of hemodialysis adequacy using online Kt/V and single-pool variable-volume urea Kt/V. Int Urol Nephrol. 2008;40(3):771–8.
50. Locatelli F, Buoncristiani U, Canaud B, Kohler H, Petitclerc T, Zucchelli P. Haemodialysis with on-line monitoring equipment: tools or toys? Nephrol Dial Transplant. 2005;20(1):22–33.
51. Locatelli F, Andrulli S, Di Filippo S, Redaelli B, Mangano S, Navino C, et al. Effect of on-line conductivity plasma ultrafiltrate kinetic modeling on cardiovascular stability of hemodialysis patients. Kidney Int. 1998;53(4):1052–60.
52. Mercadal L, Challier E, Cluzel P, Hamani A, Boulechfar H, Boukhalfa Z, et al. Detection of vascular access stenosis by measurement of access blood flow from ionic dialysance. Blood Purif. 2002;20(2):177–81.
53. Hoenich NA, Woffindin C, Matthews JN, Goldfinch ME, Turnbull J. Clinical comparison of high-flux cellulose acetate and synthetic membranes. Nephrol Dial Transplant. 1994;9(1):60–6.
54. Craddock PR, Fehr J, Dalmasso AP, Brighan KL, Jacob HS. Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. J Clin Invest. 1977;59(5):879–88.
55. Chenoweth DE. Complement activation produced by biomaterials. Artif Organs. 1988;12(6):508–10.
56. Herbelin A, Nguyen AT, Zingraff J, Urena P, Descamps-Latscha B. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. Kidney Int. 1990;37(1):116–25.
57. Kaysen GA. Role of inflammation and its treatment in ESRD patients. Blood Purif. 2002;20(1):70–80.
58. Verresen L, Fink E, Lemke HD, Vanrenterghem Y. Bradykinin is a mediator of anaphylactoid reactions during hemodialysis with AN69 membranes. Kidney Int. 1994;45(5):1497–503.

59. Kammerl MC, Schaefer RM, Schweda F, Schreiber M, Riegger GA, Kramer BK. Extracorporal therapy with AN69 membranes in combination with ACE inhibition causing severe anaphylactoid reactions: still a current problem? Clin Nephrol. 2000;53(6):486–8.
60. John B, Anijeet HK, Ahmad R. Anaphylactic reaction during haemodialysis on AN69 membrane in a patient receiving angiotensin II receptor antagonist. Nephrol Dial Transplant. 2001;16(9):1955–6.
61. Fischbach M, Hamel G, Geisert J. Efficiency of high permeable membranes in hemodiafiltration in children: an optimal method of purification. Int J Pediatr Nephrol. 1985;6(4):251–6.
62. Fischbach M, Edefonti A, Schroder C, Watson A, European Pediatric Dialysis Working G. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.

21

Haemodiafiltration: Principles, Technique, and Advantages over Conventional Haemodialysis

Rukshana Shroff, Evgenia Preka, and Bruno Ranchin

Introduction and Defining a Need for Convective Clearance on Dialysis

In-center HD, performed three times is the conventionally used standard renal replacement therapy (RRT) for patients with end-stage kidney disease (ESKD). Standard HD clears uraemic toxins primarily through diffusion driven by the thermal energy of the uremic toxin molecules. Clearance is inversely proportional to the molecular size (expressed in daltons) of the toxin and also depends on its protein binding and tissue distribution. As a result, conventional HD does not clear large or protein-bound toxins effectively and fails to adequately correct the uraemic milieu [1–3]. Attempts to improve clearances on HD include initiation of dialysis at higher glomerular filtration rates, aiming for a single-pool Kt/V urea greater than 1.20 per session, increase in dialysis frequency and/or duration, use of high-flux membranes, or alternative haemofiltration. However, greater clearance of low-molecular-weight toxins or the use of high-flux membranes had no impact on patient mortality [4]. Moreover, patients on dialysis have a significantly higher cardiovascular mortality, and even amongst paediatric dialysis recipients, cardiovascular disease is the most common cause of death [5].

Children on dialysis have a very high burden of cardiovascular risk factors, including chronic fluid overload with hypertension and mineral dysregulation with hyperphosphatemia and hyperparathyroidism [6, 7]. Preclinical cardiovascular disease (CVD), measured through surrogate markers such as carotid intima-media thickness (cIMT), pulse wave velocity, and left ventricular hypertrophy, is prevalent in CKD [8, 9], with accelerated progression on dialysis [6–10]. Vascular calcification [7, 9–13], cIMT [13], and hypertension and cardiovascular function [14] worsen with increasing time on dialysis, implying that the dialysis milieu, including biochemical derangements and haemodynamic stresses, lead to a rapidly worsening cardiovascular risk profile; 18–40% of deaths in children [5, 15] and young adults [16] on dialysis are due to cardiovascular events. Even within a short period of 3 months on conventional haemodialysis (HD), biomarkers of inflammation, oxidative stress, and endothelial dysfunction were shown to increase [17]. Interventions that can improve outcomes in children on maintenance HD are

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urgently needed. Haemodiafiltration (HDF), which combines diffusive and convective clearance, was developed in the 1970s [2, 3, 18, 19] and may be a promising option.

Principles of Solute Clearance by HD and HDF

All forms of dialysis are characterised by three main principles that determine solute clearance: diffusion, convection, and ultrafiltration. These are discussed in detail in Chap. 2, and the relative contribution of these processes to HDF therapy is described below.

Haemodialysis (HD)

Solute clearance on HD is predominantly driven by diffusion. Diffusive small-solute transport involves the movement of molecules from an area of high concentration to an area of low concentration across a semipermeable membrane. The dialysis fluid flow and the dialyser surface area (which determines the mass transfer area coefficient (K_oA) and consequently, the solute permeability of the membrane) determine the quality of HD provided.

Haemodiafiltration (HDF)

Solute clearance on HDF involves a combination of diffusion and convection. HDF optimises the removal of middle (up to 300–500 dalton (Da) molecular weight) and larger molecules (greater than 15–50 kilo Da). If the clearance of low-molecular-weight solutes such as urea has reached maximal clearance by HD, then the addition of HDF will not improve the clearances further. With HDF there is no osmotic disequilibrium while arriving at a maximum urea clearance as the continuous iso-osmotic substitution fluid inflow maintains an osmotic stability throughout the whole dialysis session. The effectiveness of a membrane to ultrafiltrate fluid is described by the UF coefficient (K_{UF}), which is $Q_{UF}/\Delta P$ (volume of UF per unit time, divided by the pressure gradient across the membrane, also called the transmembrane pressure gradient [TMP]).

Haemofiltration (HF)

HF is mainly used in the acute setting in intensive care units for rapid fluid removal and allows convective transport of small- and medium-sized molecules, although solute clearance is not the primary goal of HF. HF should not be used as a modality of chronic dialysis and is not discussed further in this chapter.

Definition and Types of HDF Therapy

The European Dialysis Working Group (EUDIAL) has defined HDF as a blood purification therapy that combines diffusive and convective solute removal by ultrafiltration of 20% or more of the blood volume processed through a high-flux dialyser and maintenance of fluid balance by sterile replacement fluid infused directly into the patient's blood [20, 21]. In online HDF, large volumes of sterile replacement fluid are obtained by online filtration of standard dialysate though a series of bacteria- and endotoxin-retaining filters [21]. A high-flux membrane is defined as one that has an ultrafiltration coefficient greater than 20 mL/h/mmHg transmembrane pressure/m^2 and a sieving coefficient for β_2-microglobulin of greater than 0.6. HDF provides greater removal of middle-molecular-weight and protein-bound uraemic retention solutes than does conventional low- or high-flux HD [21].

A high convective volume is a fundamental requirement for HDF. The convective volume is the sum of the net ultrafiltration volume (i.e., the amount of fluid removed during a dialysis session based on the inter-dialytic weight gain) and the amount of substitution fluid (i.e., the sterile replacement fluid given as replenishment for the removal of extra fluid during HDF). Randomised controlled trials in adults [22–25] and a pooled individual participant data analysis [25] suggest that any improved survival associated with HDF occurs when the convective volume exceeds 20

liters/session. Therefore, the EUDIAL group felt that it was necessary to add a lower limit to ultrafiltration, below which the treatment would not qualify as HDF. An ultrafiltration volume equivalent to 20% of the total blood volume processed for the treatment was chosen as the lower limit because it is achievable with post-dilution HDF without excessive haemoconcentration, although with modern dialysis machines an ultrafiltration volume of 30–35% of the total blood volume can be achieved and should be aimed for in order to obtain optimal clearance. In theory, it would be more correct to prescribe convective volume as a proportion of plasma water volume processed rather than blood volume processed. However, as the blood volume processed, and not the plasma water volume processed, is displayed on the machine control panel, this term has been used to avoid confusion.

Modes of HDF

Depending on where in the dialysis circuit the replacement volume is infused, there are different modalities of HDF (Fig. 21.1).

Post-dilution HDF

In post-dilution HDF, the replacement fluid is infused downstream of the dialyser, usually into the venous bubble trap. For solutes which can pass the membrane unimpeded (sieving coefficient = 1), the concentration in the ultrafiltrate is the same as in the plasma water. A potential disadvantage is that haemoconcentration at high ultrafiltration rates can result in the deposition of plasma proteins on the membrane surface, clogging the membrane pores and occluding the blood channels of the dialyser. These effects can raise transmembrane pressure (TMP), causing alarms, reducing clearance, and possibly resulting in clotting of the extracorporeal circuit [21].

The degree of haemoconcentration is dependent on the filtration fraction (a practical clinical concept defined as the ratio of ultrafiltration rate to plasma water flow rate and described further in the next section), which in turn depends on haematocrit, protein concentration, and blood flow rate. Haemoconcentration generally limits the filtration fraction to 20–25% of the blood flow rate in post-dilution HDF. The ultrafiltration rate is controlled in proportion to the actual blood flow

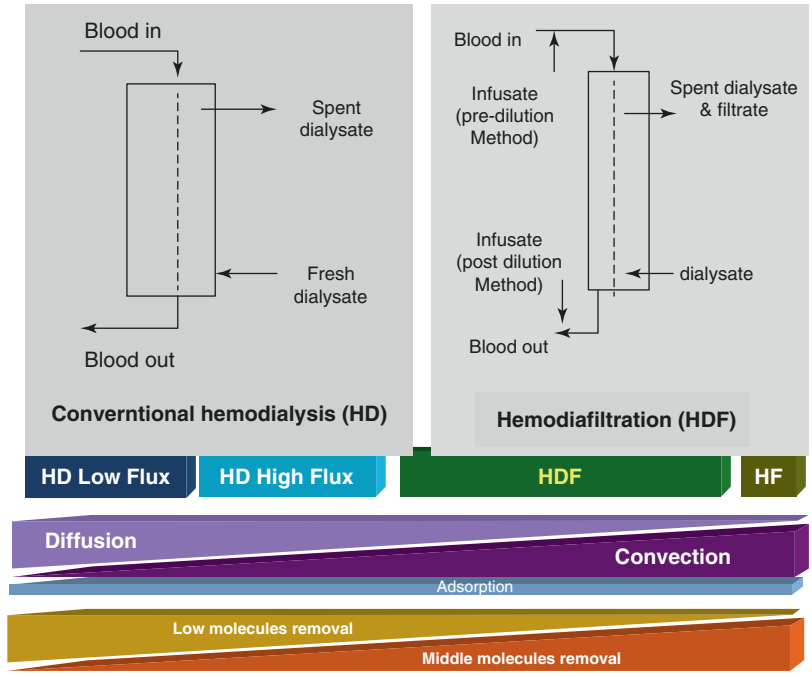

Fig. 21.1 Schematic presentation of HD and HDF therapies

rate or guided by TMP. A filtration fraction up to 35% of the blood flow rate is possible using systems designed to optimise filtration rate, based on automatic adjustment of TMP according to ultrafiltration flow rate measurements [26, 27].

Pre-dilution HDF

The haemoconcentration associated with post-dilution HDF can be avoided by infusing the replacement fluid upstream of the dialyser. With pre-dilution HDF, higher filtration rates are possible than with post-dilution HDF. Ultrafiltration rates up to 100% of the blood flow rate are used. However, pre-dilution reduces the efficiency of both the diffusive and convective components of solute removal by reducing solute concentrations in the blood compartment, and small solute clearance by pre-dilution HDF may be lower than conventional high-flux HD. For equivalent clearance, the convective volume needs to be two to three times greater for pre-dilution HDF than the post-dilution [28].

Mid-dilution HDF

The replacement fluid is infused part-way down the blood pathway using specially designed dialysers or systems. Thus, the first part of the blood circuit is operated in post-dilution mode and the second part in pre-dilution mode [29]. Very large filter sizes, up to 1.9 m^2, are required, and hence, this technique is not suitable for children.

Mixed Dilution HDF

In mixed dilution HDF, the replacement fluid is infused both upstream and downstream of the dialyser. The ratio of upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximising clearance and avoiding the consequences of a high TMP and haemoconcentration [30]. As with mid-dilution HDF, large filter sizes are required, so this technique is not feasible for children.

Choosing the Optimal HDF Modality

In theory, post-dilution is the most efficient mode of HDF for clearing middle- and large-molecular weight substances and is the routinely used HDF technique in adults and children. However, successful post-dilution HDF requires a high extracorporeal blood flow rate, a reliable vascular access, an ability to achieve adequate anticoagulation throughout the procedure, and the absence of any condition that increase blood viscosity (such as a high haematocrit). In children, the 3H study has shown that adequate blood flow rates can be achieved through both central venous catheters and arteriovenous fistulas in order to achieve a high convective volume and optimal HDF [31].

However, in patients with low blood flow rates (typically less than 200 mL/min in adults and comparative rates in children), pre-dilution HDF allows for adequately high volumes of substitution fluids. Compared with post-dilution HDF, pre-dilution HDF removes more low-molecular-weight proteins and protein-bound toxins and is associated with less bio-incompatibility (shear stress or membrane-cell or cell-cell activation) [32]. The Japanese Renal Data Registry compared the one-year prognosis of patients receiving pre-dilution HDF and standard HD using a propensity score-matched method. Pre-dilution HDF with a higher convective volume (more than 40 L/session) decreased all-cause mortality and cardiovascular mortality compared with standard HD or pre-dilution HDF with small convective volumes [33, 34]. Japanese experience shows an increase of adult patients' survival in pre-dilution HDF with an optimal substitution volume estimated to be 33 L/m^2/session in patients dialysed 3 times a week [35]. Pre-dilution HDF has been used effectively in children and is associated with excellent growth outcomes, especially when used in a frequent dialysis regimen (5 days per week) [36]; the authors have shown that for pre-dilution blood HDF, blood flow rates of 5–8 ml/min/kg body weight or 150–240 ml/m^2 body surface area were acceptable, with substitution volume of 75–100% of blood volume [37].

Requirements for HDF and Technical Aspects

Essential requirements for performing HDF include:

- 'Ultrapure' water for replacement of convective volume
- High-flux dialyser membranes
- Dialysis machines that allow careful regulation of UF

Important technical terms unique to HDF practice and equations for the calculation of solute clearances on HDF are also described here.

'Ultrapure' Water for HDF

The sterile, non-pyrogenic fluid used to maintain fluid balance, referred to as replacement fluid or substitution fluid, can be provided either as a terminally sterilised, packaged solution or as an online prepared solution. It is not practical to provide the volumes of replacement fluid used for the most effective forms of convective therapy using prepackaged solutions. Instead, replacement fluid is generated online by filtering dialysis fluid through bacteria- and endotoxin-retentive filters to prepare a sterile and pyrogen-free solution that is immediately infused into the patient. Therapies performed in this manner are referred to as online convective therapies. As large volumes of fluid are removed from, and added to, blood during online therapies, patients are exposed to risks beyond those associated with routine HD. Strict safety standards and regulatory oversight are required. Some recommendations related to HDF are also included in the European Best Practice Guidelines [38].

Water Purification Systems A standard water treatment device consists of a water softener, an activated carbon filter, a sediment filter, and a reverse osmosis system [39]. Water softeners contain a resin that exchanges sodium cations for calcium, magnesium, and other polyvalent cations. The effectiveness of softening is monitored by measuring the hardness of the effluent water. Water softening not only prevents hard water but also protects the reverse osmosis membrane which is used in the final step of water treatment from the build-up of scale and subsequent failure. The resin is regenerated periodically with concentrated sodium chloride solution, which also reduces bacterial growth in the resin bed. Activated carbon filters remove chloramines and organic solvents but tend to release carbon particles and therefore require a sediment filter placed downstream. The final purification step is performed by reverse osmosis where the water is forced through a semipermeable polyamide or polysulfone membrane at 14–28 bar. This step removes 90–99% of inorganic and organic substances, pyrogens, bacteria, and particulate matter. The purified water is pumped from the reverse osmosis module to the individual treatment stations in a recirculating ring loop which delivers the water produced in excess back to the reverse osmosis module, avoiding wastage of high-quality water. The ring loops themselves require regular disinfection, and this is performed either by heat or chemical disinfection.

Testing Water Quality The International Organization for Standardization (ISO) has published a series of standards addressing fluids for extracorporeal therapies. Specifically, ISO 11663:2009, *Quality of dialysis fluid for haemodialysis and related therapies*, requires that the replacement fluid used for HDF be sterile and pyrogen-free [40]. Typical testing for water quality follows the French regulations: 500 mL of replacement fluid is collected via the membrane filtration method and is cultured to determine endotoxin levels at least once every three months [41]. The currently accepted norms for ultrapure dialysate are defined as containing <0.1 colony-forming unit/ml and <0.03 endotoxin unit/ml. In addition, the chemical composition of water must be tested at least once per year.

Bacteria- and endotoxin-retentive filters installed on the inlet dialysis fluid circuit are the key components of the online HDF safety system. Those filters are disinfected after each dialysis treatment according to manufacturer's recommendations, and the repetitive disinfection

cycles can alter the membrane characteristics. Therefore, the filters should be replaced periodically to ensure proper operation of the cold sterilization process. The type of filter used and the frequency of replacement should comply with the HDF machine manufacturer's instructions. The integrity of the filters may also be assessed online by regular pressure testing or the use of other validated tests according to the manufacturer's instructions.

The dialysate can also be contaminated with other bioactive microbial contaminants, such as peptidoglycans [42] and fragments of bacterial DNA [43]. The extent to which the latter contaminants are removed by the techniques currently used for online preparation of replacement fluid is unclear, as are the consequences of inadequate removal.

High-Flux Membranes

Only highly permeable membranes are suitable for HDF in adults or children. Highly permeable membranes are defined as membranes characterised by a UF coefficient (K_{UF}) greater than 20 mL/hr/mmHg transmembrane pressure/m^2 and a sieving coefficient (S) for β2-m of greater than 0.6 [4, 21, 44]. The UF coefficient (K_{UF}) defines the hydraulic permeability of a membrane and is expressed in mL/min/mmHg transmembrane pressure. Whereas a low-flux membrane will allow only a small and undetermined convective flow and can be used for HD only, a high-flux membrane allows a larger and predefined convective flow as required for HDF. In practice, the KUF should be high enough to allow 50 mL/m/m^2 body surface area (equivalent to 2 mL/min/kg body weight) convective flow in post-dilution HDF. The albumin loss through a high-flux membrane should be <0.5 g in a 4-hour HD session [44, 45].

As with conventional HD, the dialyser surface area must be equal to (or slightly higher than) the body surface area for maintenance dialysis, so that the internal volume of the dialyser and blood lines is less than the safe extracorporeal blood volume permissible (i.e., less than 10 ml/kg body weight). Manufacturers provide an optimal range of blood flow for a given dialyser as a higher membrane surface is associated with the need for a higher blood flow in order to decrease the risk of coagulation and hollow-fibre obstruction [46, 47]. Theoretically, fiber length and diameter, as well as membrane material, membrane thickness, surface area, pore size, and pore density all may influence solute sieving and convective transport [44]. For HDF a biocompatible dialyser must be selected; biocompatibility is assessed by complement activation, thrombogenicity, contact activation, and cytokine generation [48]. European recommendations state that ultrapure dialysate must be used with synthetic high-flux membranes [21].

Dialysis Machines with Accurate Ultrafiltration Control

Today almost all new dialysis machines allow for both HD and HDF. In Europe, HDF machines suitable for children are manufactured by Gambro, Fresenius Medical Care, and Nikkiso. These machines are suitable for children from 10 to 17 kg body weight and require a paediatric circuit with low extracorporeal volumes.

Gambro AK 200™ ULTRA S and Artis® Dialysis System. These systems bear resemblances and dissimilarities. Both can be used in a pressure-control mode (fixed TMP and variable substitution flow rate) and a volume-control mode. In the latter, the target substitution volume must be set in the AK 200™ ULTRA S system, while the substitution flow rate must be set in the Artis® machine. In the AK 200™ ULTRA S, the actual convective volume and convective flow rate are also shown. Both machines display the FF value online (as 'QF/QB'), based on the real blood flow rate. The maximal value recommended by the manufacturer, however, is different for both systems. Of note, the older Gambro dialysis machine AK 200™ as well as their latest machine AK98™ do not perform HDF, and the AK 200™ is no longer manufactured. The Artis dialysis machine is only suitable for children above 20 kg.

Fresenius 5008 with ON-LINEplus™. This machine (*Fresenius Medical Care, Bad Homburg, Germany*) has an automatic substitution mode (AutoSub Plus™), in which the substitution rate is automatically regulated in response to variations in diverse patient- and treatment-related parameters throughout the session. The estimated final substitution volume is displayed on the monitor. When this mode is disabled, it is possible to set the substitution rate or target substitution volume manually. In this system, FF is automatically regulated but not displayed on the screen. A newer model of the Fresenius dialyser called the 6008 series is due to be launched very soon and will come with smaller paediatric lines that will allow HDF even in children from 10 kg in size.

Nikkiso DDB07 and DBB-EXA haemodialysis system. These machines enable HDF in children: the DDB07 system has low volume blood lines and requires a manual setting of FF, whereas the DBB-EXA can be used in children weighing more than 20 kg with an automatic substitution mode (i.e., the substitution rate is automatically regulated in response to TMP throughout the session).

Commonly used dialysis machines and blood line volumes are shown in Table 21.1.

Table 21.1 Blood line volumes for machines that perform HDF

Dialysis machine	Double needle	Single needle	Blood line volume (ml)	olHDF	BVM
Baxter Artis	Yes		132	Yes	Yes
		Yes	227		Yes
Braun Dialog iQ	Yes		122	Yes	Yes
		Yes	186		Yes
Fresenius 5008	Yes		108	Yes	Yes
	Yes		136	Yes	Yes
		Yes	142		Yes
		Yes	169		Yes
Fresenius 6008	Yes		83	Yes	Yes
	Yes		122	Yes	Yes
		Yes	137–187		Yes
Nikkiso DBB-07	Yes		56	Yes	No
	Yes		86	Yes	Yes
	Yes		113	Yes	Yes
		Yes	93		No
		Yes	123		Yes
		Yes	150		Yes
Nikkiso DBB-EXA	Yes		143	Yes	Yes
		Yes	202		Yes

olHDF online haemodiafiltration, *BVM* blood volume monitoring

Filtration fraction (FF) is a parameter unique to HDF as it quantifies the relation between convective flow rate and blood flow rate. It is also an important determinant for the amount of convective volume achieved [21]. FF is defined as the ratio of the ultrafiltration (UF) rate to the plasma water flow rate [21], where UF represents the total amount of plasma water removed from the patient. In clinical practice, however, blood flow rate (Q_b) is used as a surrogate for plasma water flow rate, as Q_b is indicated on all dialysis machines. The formula for calculating FF is:

$$\mathrm{FF} = \left[\left(Q_{\mathrm{subs}} + Q_{\mathrm{UF}} \right) / Q_b \right] \times 100$$

where $Q_{\mathrm{conv}} = Q_{\mathrm{subs}} + Q_{\mathrm{UF}}$

FF is in %, Q_{conv}, Q_{subs}, and Q_{UF} are the convective flow rate, substitution flow rate, and ultrafiltration flow rate, in mL/min (or L/h), respectively.

In clinical practice, net UF is the sum of the desired intradialytic weight loss in kilograms and the amount of fluids administered during treatment. The higher the FF, the greater the convective volume extracted from the blood. In post-dilution HDF because the substitution fluid is administered after the dialyser, haemoconcentration within the filter increases proportionately to the FF. As a result, filter clotting and loss of membrane integrity with altered dialyser performance may occur [30]. A filtration fraction up to 30–35% of the blood flow rate is possible using systems designed to optimise filtration rate, based on automatic adjustment of TMP.

It is important to keep in mind that the FF can vary based on several caveats:

(i) The true blood flow rate may vary from the set rate. This is particularly true at higher values of Q_b. If FF calculation is based on the set value, the real FF may be underestimated.
(ii) FF actually depends on the plasma water flow rate, but for practical purposes Q_b is used as surrogate. Unlike plasma water, Q_b depends on haematocrit (Ht) and total protein concentration.
(iii) Blood viscosity and clogging of membrane pores increase during the HDF session, so a high FF may be obtained at the start, but not at the end of a session. Thus, a higher TMP is needed to obtain the same substitution rate towards the end of the session.

Calculation of Solute Clearances in HDF

(i) The *diffusive component* (K_D) of clearance in HDF can be estimated using Michael's equations [49] from the blood flow rate (Q_b), the dialysis fluid flow rate (Q_d), and the solute-specific dialyser mass transfer – area coefficient (K_oA).

$$K_D = \frac{1 - e^{K_oA \times \left(\frac{Q_b - Q_d}{Q_b \times Q_d}\right)}}{\frac{1}{Q_b} - \frac{1}{Q_d} \times e^{K_oA \times \left(\frac{Q_b - Q_d}{Q_b \times Q_d}\right)}}$$

For pre-dilution, the actual blood and dialysis fluid flow rates at the inlet ports of the dialysers should be used by correcting for pre-dilution infusion, which will add to the blood flow rate and subtract from the dialysis fluid flow rate. For clearance of urea, Q_b is considered to be the blood water flow rate, while for other solutes, Q_b is considered to be the plasma water flow rate since only urea diffuses rapidly enough across erythrocyte membranes to allow erythrocyte water to be cleared [50, 51].

(ii) The *convective component* (K_C) is calculated using Ficheux's equation [52, 53] taking the sieving coefficient, S, into account.

$$K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S$$

where Q_f is the ultrafiltration rate.

(iii) The *total clearance,* K_T, is calculated by adding the diffusive and convective components and taking the dilution factor (DF) into account.

$$K_T = \left(K_D + K_C\right) \times \mathrm{DF}$$

The Concept of 'Backfiltration'

The concept of 'backfiltration' needs to be considered here. The hydrostatic pressure of both blood and dialysis fluid decrease as they pass through the dialysis filter. Since blood and dialysis fluid pass through the filter in counter-current directions, the resulting TMP may become negative at the venous side especially when the venous blood pressure is low. This phenomenon leads to influx of dialysis fluid into the blood compartment of the dialyser; this is called backfiltration. This phenomenon is a routine occurrence during high-flux HD [54], but not in low-flux HD. Therefore, a high internal ultrafiltration rate may increase the convective transport of middle molecules [46, 55]. In adults it has been shown that the convective volume achieved by backfiltration is no more than 1–10 L per session depending on the dialyser type and can vary throughout the dialysis session depending on TMP. Since the convective volume achieved by backfiltration is low and unreliable, it should not be considered a form of HDF and in fact is termed the 'poor man's HDF'!

Importantly, given the phenomenon of backfiltration, it has been suggested that dialysis fluid used for high-flux HD should also be sterile and pyrogen-free. Clinical experience suggests that the barrier provided by the dialysis membrane is

safe for backfiltration volumes of up to 8 L per treatment [38].

Writing a HDF Prescription

In addition to the routine management of any child on dialysis, the following points should be considered when writing an HDF prescription:

1. A *high-flux membrane* with surface area equal to the child's body surface area is used.
2. The total *extracorporeal circuit* should be less than 10 ml/kg body weight. Single- or double-needle circuits are available, although HDF is rarely ever performed with single-needle circuits. Paediatric blood lines (36–105 ml volume) with or without the possibility to do online HDF and to monitor blood volume variation are available (Table 21.1).
3. *Replacement fluid* that is generated online from the dialysate must be 'ultrapure' (<0.1 CFU/ml and <0.03 endotoxin unit/ml) as discussed earlier. The microbiologic purity (bacterial count and endotoxin level) should be determined regularly at intervals of 1–3 months.
   (European guideline Dialysate purity 2002, European Pharmacopoeia 2009).
4. *Blood flow*: HDF requires an optimal arterial blood flow of 5–8 mL/min/kg body weight or 150–250 mL/m^2 body surface area per minute. Both the diffusive clearance of molecules with a high K_0A and the substitution volume in post-dilution HDF depend on the blood flow rate. An optimal blood flow can be achieved through either a fistula or a central venous line, although in most cases a fistula allows a higher blood flow rate in order to (i) maintain arterial blood aspiration pressure of more than −150 to − 200 mmHg and venous restitution pressure of less than 200 mmHg and limit endothelial trauma, and (ii) vascular access recirculation of less than 10%. Vascular access recirculation can be measured by thermodilution (by dialysis machine), saline dilution, or ionic dialysance [56]. It is suggested that the blood flow rate is progressively increased from 90–100 mL/m^2/min in the first HDF sessions to 200–250 mL/m^2/min, increasing by 10 mL/min per week.
5. *Dialysate flow* of twice the blood flow is sufficient to optimise the diffusive blood purification process using highly permeable membranes for HDF. As with conventional HD, the dialysate runs counter-current to the blood flow. Modern dialysis machines control thermal exchanges during the dialysis session and perform isothermic dialysis, without changing the patient's body temperature.
6. *Convective flow* is equal to total UF flow, i.e., the sum of the desired ultrafiltration volume and the replacement fluid.
   - *Post-dilution HDF*: The convective flow needs to be maximal but is limited by the risk of the filter clotting. It typically decreases over the dialysis session. In order to maintain TMP within safe limits (usually TMP < 300 mmHg is suggested by manufacturers, but varies across dialyser), modern dialysis machines automatically adjust the convective volume throughout the session in order to optimise this convective flow without increasing the coagulation risk.
   - *Pre-dilution HDF*: The convective flow is set at 100% of the blood flow. This can be done despite the dilution of the blood potentially impacting negatively on urea clearance.

     β2-m and phosphate dialytic removal is optimised as is the clearance of uraemic protein-bound toxins.

     The actual substitution volume obtained per session has to be monitored regularly in order to ensure that the goal of 23 L/1.73m^2 per session in post-dilution and 75–100% of blood volume treated in pre-dilution is achieved.
7. The *dialysate* and substitution fluid are produced 'online' by the dialysis machine by dilution of acid concentrate and bicarbonate powder with dialysis water produced by the water treatment system. Dialysate composition is similar to that used in HD, but careful attention to dialysate sodium concentration is

important in order to maintain sodium balance and haemodynamic tolerance of the session [57]. To avoid the risk of positive sodium balance, the dialysate sodium concentration required is lower than in conventional HD, particularly when high convective volumes are infused, as with pre-dilution HDF. Sodium is predominantly drained in ultrafiltered water by convection. A low dialysate sodium enables additional sodium removal by diffusion, but it may be associated with a risk of intradialytic hypotension and disequilibrium syndrome. On the other hand, a high dialysate sodium increases haemodynamic tolerance but causes sodium and water overload that leads to hypertension and increased thirst post-session.

As with conventional HD, sodium profiling (high dialysate sodium at dialysis start with decrease during the session) with or without ultrafiltration profiling (high ultrafiltration rate at dialysis start and low at dialysis end) can help to correct fluid and sodium overload and maintain intradialytic haemodynamic stability and dialysis tolerance. This strategy needs to check that sodium delivered to the patient at session start is indeed drained at session end. Some new dialysis machines automatically modify the dialysate sodium concentration throughout the dialysis session in order to keep it equal to plasma sodium, delivering isonatraemic dialysis [57].

8. *Anticoagulation* is necessary to prevent filter clotting, particularly in post-dilution HDF. A single dose of low-molecular-weight heparin is effective for a 4-hour session. A starting dose of 50–100 U/kg of enoxaparin is suggested with a half dose added after 2 hours if the session lasts more than 4 hours. Alternatively, a continuous heparin infusion may be used.

Practical Guide for the Optimization of the Convective Volume

Just performing HDF does not automatically result in high convective volumes. For the optimization of convective volume, an understanding of its determining factors is essential. A post-hoc analysis of the CONTRAST study showed that treatment-related parameters, such as blood flow rate and treatment time, play a greater role in determining convective volume, rather than patient characteristics such as serum albumin, haematocrit, or body size [58–60].

To attain a high convective volume, one needs a high blood flow rate (because filtration fraction depends on blood flow and cannot be higher than 35%), optimization of substitution volume by automated programs in new dialysis machines and careful monitoring of the dialysis prescription and blood results to ensure that all dialysis-related parameters are achieved [61–63]. Practical problems and tips to optimise convective volume are discussed below.

(i) *Optimal vascular access* Both central venous catheters and fistulas can be used for HDF provided a good extracorporeal blood flow rate is achieved. The 3H study in children showed no difference in the blood flow achieved through either type of access [31, 64], although several studies in children report that a higher blood flow is usually achieved through a fistula [65, 66].

(ii) *Needle size* The choice of a fistula needle is based on the type, vintage and expansion of the access, bleeding susceptibility, and preference of patients. A common concern is that larger needles are associated with a poor shunt outcome. Although no specific recommendations can be made for needle size, with the exception of initial cannulation, the largest needle size suitable for the access type must be used.

(iii) *Avoid single-needle HDF* Given the high convective volume goals, single-needle HDF should not be performed. In single-needle systems, clamps on the arterial and venous lines are opened and closed alternately in order to pump blood from and to the patient through the same lumen. As a result, mean blood flow is lower than that with a double-needle procedure. Moreover, as a result of the variable blood flow, both transmembrane pressure and FF fluctuate

may lead to an inadequate and unpredictable convective volume [60].

(iv) *Access recirculation* When blood flow rate increases, recirculation may occur [63]. This phenomenon is especially prominent in case of an insufficient arterial inflow or obstruction in the venous outflow tract [62]. As an increase in the size of the convective volume by recirculation is inefficient and undesirable, regular monitoring is advisable.

(v) *Effective* versus *set blood flow rates* The true blood flow rate may often be somewhat lower than the set value, and the higher blood pump speed, the wider the difference [63, 67, 68]. This phenomenon is explained by partial collapse of the tubes at a more negative pre-pump pressure. In addition, the type of access may also influence this discrepancy: it has been shown that a set blood flow of 350 mL/min resulted in a markedly lower real blood flow in a CVC than in an AVF (316 ± 4 versus 342 ± 4 mL/min) [59].

(vi) *Anticoagulation* Because a high FF may induce considerable haemoconcentration and clotting within the dialyser, adequate anticoagulation with either unfractionated heparin or low-molecular-weight heparin (LMWH) is required. The optimal dose of these agents is unknown. Unfractionated heparins have a molecular weight in the range of 2–20 kDa, so large convective volumes are likely to alter their pharmacokinetics [69]. Higher doses than customary with both low-flux and high-flux HD may be required [70, 71].

Clinical Studies and Potential Advantages of HDF over Conventional HD

HDF: Potential Advantages over Conventional HD

HDF is thought to be superior to conventional HD in the following key areas:

I. *Improved dialysis efficiency and clearance of toxins across a wide molecular weight range* In HD circulating uraemic toxins, such as β2M, and other molecules, such as retinol-binding protein, adiponectin, leptin, ghrelin, cholecystokinin, and cystatin C, accumulate and are responsible for systemic inflammation, endothelial dysfunction, and oxidative stress [72, 73]. HDF has been shown to clear 70–80% of β2M compared to HD [72] and increase removal of inflammatory cytokines with reduction in inflammation and oxidative stress [17].

II. *Improved haemodynamic stability* HDF increases UF and improves intradialytic haemodynamic stability [74], leading to less intradialytic hypotension [75], reduced incidence of strokes [23], and faster recovery time post-dialysis [31].

III. *Biocompatibility and reduced inflammation* The use of 'ultrapure' dialysate and increased removal of inflammatory cytokines reduce inflammation and oxidative stress [17].

Studies in Adults

In adults on dialysis, the Estudio de Supervivencia de Hemodiafiltración On-line (ESHOL), one of the largest RCTs comparing HDF vs high-flux HD in adults and achieving convective volumes of 23 L/session, has shown a priori that patients on high-volume HDF have a survival benefit compared to those on high-flux HD [23]. Earlier RCTs including the CONvective TRAnsport STudy (CONTRAST) [22], Turkish Online Haemodiafiltration [24] studies, and French Convective versus Hemodialysis in Elderly (FRENCHIE) [75] aimed for lower convective volumes, and only a small proportion of their patients achieved these target volumes. Hence, these studies were not able to demonstrate an a priori benefit of HDF. However, on post-hoc analysis, the Turkish [24] and CONTRAST [22] studies also showed that HDF patients who achieved a higher convective volume (>17.4 L/session in the Turkish study [24] and >20 L/session in the CONTRAST study [22]) had lower all-cause and cardiovascular mortality. Pooled data [25] from the RCTs has indicated a critical dose-response relationship between the magnitude of the convective volume and

survival, with a goal of at least 23 L per session. Similarly, other RCTs, observational studies, and registries provide conflicting results, which to some extent can be explained by differences in the convective volume [63, 74, 76–80], with patients achieving the highest convective volumes benefiting most. A Cochrane review suggests that there is no clear benefit of HDF over HD, but these meta-analyses combine outcomes of both haemofiltration and HDF studies as 'convective therapies', and do not interpret outcomes based on convective volumes [81]. As stressed above, not all convective therapies are equal [82, 83].

HDF has been correlated with improved cardiovascular outcomes in adults [21], partly explained by improved haemodynamic stability, leading to less intradialytic hypotension and faster recovery time after dialysis [23, 24, 75]. ESHOL [23], FRENCHIE [75], and several observational studies have shown that HDF improves intradialytic haemodynamic stability compared to HD. Post-hoc analysis of the CONTRAST study showed that HDF helps improve phosphate control (more than 30%) when compared to HD [84], and fibroblast growth factor 23 has a 30% greater clearance by HDF [85]. In addition, patients on HDF compared to HD may have a lower erythropoietin resistance index, possibly associated with reduced inflammation, better biocompatibility, and reduced removal of erythropoiesis-inhibiting factors [78, 86].

Studies in Children

HDF is increasingly used in children, but until recently there have been few data on outcomes. Fischbach et al. showed improved nutrition and growth [36], reduced inflammation [87], regression of left ventricular hypertrophy [87, 88], improved anaemia control [87] and reduced post-dialysis recovery time [36] in a small number of children undergoing daily HDF. In the study by Fischbach et al. impressive catch-up growth, achieving a normal height, at/or above their target mid-parental height was shown [36]. However, this small single-centre study utilised 6 days per week HDF in the pre-dilution mode. Daily HDF improved appetite and corrected metabolic acidosis, but other hypothetical mechanisms for improved growth may also be involved. It is postulated that HDF may have a possible anabolic effect associated with the greater removal of uraemic toxins such as inflammatory cytokine and hormones that regulate appetite and growth, as well as superior clearance of accumulated endogenous somatomedin and gonadotropin inhibitors, improving target tissue sensitivity to growth hormone [73]. Further single-centre studies have shown improvements in left ventricular function within a short period of HDF therapy [89, 90]. A small single-centre study also suggests that switching children from nocturnal in-centre HD to nocturnal in-centre HDF may significantly improve BP, phosphate, and PTH control [31]. Recent studies from our group have shown that when HD patients are switched to HDF keeping all other dialysis-related parameters constant, a significant improvement in inflammation, antioxidant capacity, and endothelial risk profile is achieved within 3 months [17]. This study suggests that even in children who have a short anticipated time on dialysis, HDF is superior to conventional HD. Table 21.2 summarises paediatric studies on HDF and the key outcomes. A recent report from the Italian Registry suggests that HDF use in Italy has been limited to approximately a quarter of patients on extracorporeal dialysis, particularly those with high dialysis vintage, younger age, or a long expected waiting time to renal transplantation [91].

The International Pediatric Hemodialysis Network (IPHN) has recently performed a multicentre observational study to test the hypothesis that HDF improves the cardiovascular risk profile, growth and nutritional status, and health-related quality of life outcomes in children compared to conventional HD – the HDF, Hearts, and Height (3H Study) [31, 64]. 3H suggests that HDF halts the progression of increasing carotid intima-media thickness (Fig. 21.2), is associated with an increase in height standard deviation score, and improves patient-related outcomes compared to HD (Fig. 21.3) [31].

Table 21.2 Key studies in children on HDF

Outcomes	No. of participants/ (reference)	Conclusions
Uraemic toxin clearance, endothelial risk profile, inflammation	22 children (Agbas et al. [17])	Significant improvement in inflammation, antioxidant capacity, and endothelial risk profile achieved within 3 months of HDF compared to HD treatment: Reduction in b2M ($p < 0.001$), hCRP, ADMA, SDMA, AGEs, ox-LDL ($p < 0.01$ for all) Increase in total antioxidant capacity ($p < 0.001$) compared to HD
	30 children (Morad et al. [90])	HDF associated with decreased pro-inflammatory cytokine profile (IL-6, TNF-a, hsCRP) compared to conventional HD: hsCRP 3.41 μg/mL vs. 7.98, IL-6 11.44 pg/mL vs. 168.40 pg/mL ($p = 0.002$) TNF-a 11.45 pg/mL vs. 15.70 pg/mL ($p = 0.008$) in the HD vs. after 6 months on HDF
	33 children (Fadel et al. [89])	Significant decrease in hsCRP upon changing from HD to online HDF: hsCRP 7.9 ± 8.9 (range 0.3–35.7) μg/mL after 6 months of conventional HD vs. 3.4 ± 3 (range from 0.2 to 13) μg/mL after 6 months of online HDF ($p = 0.01$)
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	At 12-month follow-up, hsCRP levels increased in HD but remained static in HDF: Median CRP 3.9 vs. 0.9 mg/L ($p < 0.0001$)
Phosphate and PTH	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Serum phosphate levels similar between HD and HDF patients but significant difference in PTH: PTH levels declined in HDF cohort over 12 months ($p = 0.03$) but remained static in HD ($p = 0.13$), resulting in lower levels in HDF at 12 months (86 vs. 365 pmol/L, $p = 0.004$). No difference in the type of phosphate binders or cinacalcet use, serum and dialysate calcium, and 25-OH- vitamin D levels
Blood pressure and cardiovascular outcomes	33 children (Fadel et al. [89])	Improved systolic function of the myocardium in the group treated by HDF: mean systolic function in HD vs. HDF was 35 ± 5.6% vs. 39 ± 6% ($p = 0.007$) and mean ejection fraction 68 ± 8.5% vs. 72 ± 8% ($p = 0.05$). Significant reduction in diastolic dysfunction prevalence with HDF compared to conventional HD ($n = 25$ vs. $n = 19$, $p = 0.03$).
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Annualised change in cIMT-SDS was a median increase of 0.41 in the HD group and decrease −0.07 in the HDF group ($p = 0.02$), resulting in a significant difference between groups at 12 months ($p = 0.009$). On propensity score analysis, children on HD had a +0.47 greater increase in annualised cIMT-SDS change (95% CI 0.07–0.87; $p = 0.02$) compared to those on HDF. PWV-SDS higher in HD compared to HDF (2.07 vs. 0.68, $p = 0.002$) at baseline and at 12 months (1.43 vs. −0.31, $p = 0.0008$), but no difference in sensitivity analysis 24 h MAP-SDS higher in HD compared to HDF (2.75 vs. 0.98, $p < 0.0001$) at baseline and at 12 months (3.74 vs. 1.38, $p < 0.0001$). MAP-SDS increased from baseline to 12 months in HD ($p < 0.0001$) whereas unchanged in HDF ($p = 0.35$). *LVMI* at baseline comparable in HD and HDF ($p = 0.07$), but higher in HD at 12 months (47.4 vs. 39.3 g/[$m^{2.16 + 0.09}$], $p = 0.017$).

(continued)

Table 21.2 (continued)

Outcomes	No. of participants/ (reference)	Conclusions
Growth and nutrition	15 children switched to daily online HDF (Fischbach et al. [36])	Significant increase in growth velocity upon switching to daily online HDF, increase in height SDS from −1.5 ± 0.3 to +0.2 ± 1.1 SDS, $p < 0.05$ Increased appetite, decreased metabolic acidosis, BMI increase from 16.5 ± 2.0 to 18.0 ± 2.4, $p < 0.05$
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Small but statistically significant increase in the annualised change in height SDS in children on HDF ($\Delta = -0.16$; $p = 0.02$), whereas height SDS remained static in HD; HDF patients were taller than HD patients at 12 months ($p = 0.04$). Effect was independent of growth hormone therapy. In children above 13 years of age ($n = 49$ on HD and $n = 32$ on HDF), the median annualised change in height-SDS was significant between groups (HD $\Delta = -0.01$ and HDF $\Delta = +0.15$; $p = 0.005$).
Anaemia	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Median Hb levels (g/dL) at baseline: 10.3 vs. 10.9 ($p = 0.41$), after 12 months: 10.4 vs. 12.0 ($p = 0.001$) Haemoglobin levels comparable between groups at baseline, unchanged in HD but increased in HDF during treatment, resulting in significantly higher haemoglobin at 12 months in HDF group, with no difference in EPO dosage:

MBD metabolic bone disease, *RR* relative ratio, *CI* confidence interval, *B* regression coefficient, *RRF* renal residual function, *b2M* beta-2 microglobulin, *mo* month(s), *RCT* randomised-control trial, *hsCRP* high sensitivity C-reactive protein, *IL-6* interleukin 6, *IL-10* interleukin 10, *AGEs* advanced glycation end-products, *ox-LDL* oxidised low-density lipoprotein, *ADMA* asymmetric dimethyl arginine, *SDMA* symmetric dimethyl arginine, *BMI* body mass index, *OL-HDF* online haemodiafiltration, *pwv* pulse wave velocity, *MAP* mean arterial pressure, *SDS* standard deviation score, *LVMI* left ventricular mass index, *PTH* parathyroid hormone

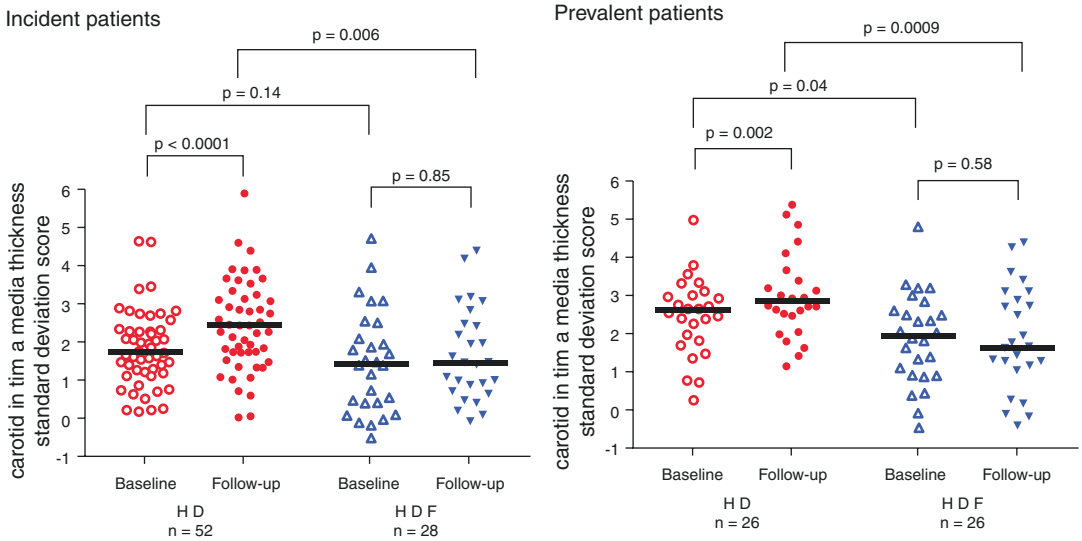

Fig. 21.2 Data from the 3H study showing the carotid intima-media thickness standard deviation score (cIMT-SDS) at baseline and 12 months in incident and prevalent HD and HDF patients. Data are shown as median and interquartile range. Incident patients on HD and HDF did not show any difference in cIMT-SDS at baseline ($p = 0.14$). Prevalent patients on HD had a significantly higher cIMT-SDS at baseline compared to HDF ($p = 0.04$). cIMT-SDS increased significantly from baseline in incident and prevalent HD patients ($\Delta = +0.64$; $p < 0.0001$ and; $\Delta = +0.34$, $p = 0.002$ respectively), but was static in HDF patients ($\Delta = -0.13$, $p = 0.85$ and $\Delta = -0.04$, $p = 0.58$ respectively)

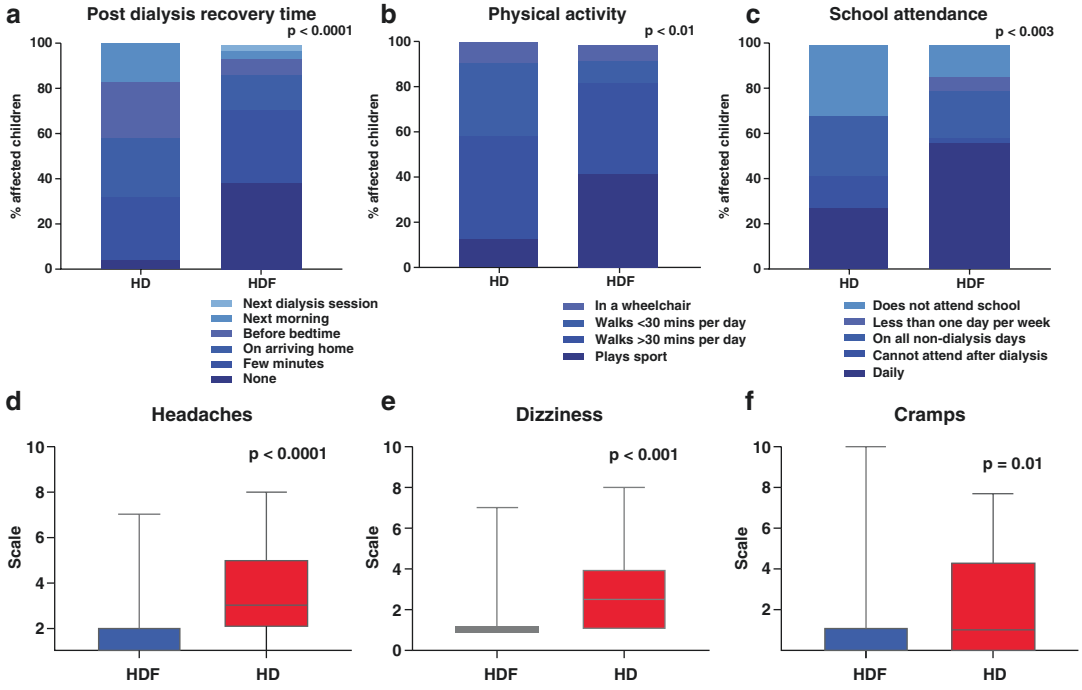

Fig. 21.3 Self-reported patient-related outcome measures. (**a**) Post-dialysis recovery time, (**b**) physical activity index, and (**c**) school attendance – individual scales for each measure shown on the figure. (**d**) Headaches, (**e**) dizziness, (**f**) cramps – graded on a scale of 1–5 (5 = most severe or frequent)

Children on HDF had improved blood pressure and haemodynamic stability, reduced inflammatory markers, and lower β2-microglobulin compared to children on HD [31]. The annualised change in vascular measures correlated with improved BP control and clearances on HDF. The 3H study demonstrated a very high prevalence of sub-clinical cardiovascular disease in children on dialysis and an attenuated progression of vascular changes in children receiving HDF compared to children receiving conventional HD [31]. Within 1 year of conventional HD, the cIMT increased by 0.41 SDS, whereas there was no change observed in HDF patients [31]. Improved fluid removal as well as clearance of middle-molecular-weight uraemic toxins by HDF were strongly correlated with improved vascular outcomes in HDF.

In the 3H trial, growth rate, a sensitive overall health parameter in children, was significantly higher in HDF compared to HD patients, independent of growth hormone treatment [31]. Convection may clear insulin-like growth factor-1-binding proteins and their metabolites that dampen the response to endogenous somatomedin and gonadotropins [73, 92]. Although mechanisms of improved growth in HDF are not clear, the 3H study showed an inverse correlation between height-SDS increase and β2-microglobulin, suggesting that clearance of middle-molecular-weight compounds may partly alleviate growth hormone resistance in dialysis patients.

Importantly, children treated with HDF rather than conventional HD reported a reduction in the frequency and/or severity of headaches, dizziness, and cramps on dialysis (Fig. 21.3), as well as a reduction in the post-dialysis recovery time, leading to an improvement in school attendance and physical activity [31]. Patient-related outcome measures that are primarily associated with fluid status, such as the post-dialysis recovery time, headaches, dizziness, and cramps, were less frequent and less severe in HDF compared to HD patients. Lower inter-dialytic weight gain on

HDF, implying lower ultrafiltration rates per session and greater haemodynamic stability, was strongly associated with fewer symptoms. Similar reports of fewer symptomatic intradialytic hypotensive episodes and muscle cramps were reported in a vulnerable population of elderly dialysis patients in the FRENCHIE study [75], and a lower risk of stroke, attributed to improved intradialytic haemodynamic stability in HDF patients, was reported in ESHOL [23, 93]. The Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) workgroup has identified fatigue as one of the most highly prioritised outcomes for dialysis patients and clinicians [94], and children value 'life participation' as their most important outcome measure.

In the 3H study, median convection volumes of 13.4 L/m^2 were achieved in children [64], which is comparable to the 23 L per 1.73 m^2 per session that proved beneficial in the pooled adult studies [25]. Importantly, the convection volume was independent of patient-related factors, such as age, gender, access type, or dialyser used, but strongly correlated with the blood flow rate [64], implying that convection volume is a modifiable factor that can be manipulated and optimised by the dialysis team.

Importantly, no reduction in serum albumin levels was observed with HDF, and no difference in the rate of change of residual renal function [31] was observed in children on either dialysis modality, implying that HDF is a safe treatment. Moreover, HDF patients who had a significant loss in residual renal function during the study period were able to maintain constant β2-microglobulin levels, whereas levels increased in HD patients [31]. Although the 3H study included over 40% of children on extracorporeal dialysis in Europe, it is not a randomised trial, so confirmation of the observed results through randomised trials is required.

Conclusions

HDF is a safe and effective dialysis therapy that has been shown to have significant benefits over conventional HD both in children and adults. Careful attention to the HDF technique, particularly focusing on achieving optimal convective volumes, is important in order to gain maximum benefit from this treatment.

References

1. Henderson LW, Silverstein ME, Ford CA, Lysaght MJ. Clinical response to maintenance hemodiafiltration. Kidney Int Suppl. 1975;7:58–63.
2. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med. 1975;85:372–91.
3. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Hemodiafiltration: a new alternative to hemofiltration and conventional hemodialysis. Artif Organs. 1978;2:150–3.
4. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010–9.
5. US Renal Data System, USRDS 2011 Annual Data Report. Atlas of chronic kidney disease and end-stage renal disease in the United States. 2011.
6. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol. 2012;23:578–85.
7. Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. J Am Soc Nephrol. 2013;24:179–89.
8. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, Wong C, Munoz A, Warady BA. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. Clin J Am Soc Nephrol. 2006;1:1006–15.
9. Schaefer F, Doyon A, Azukaitis K, Bayazit A, Canpolat N, Duzova A, Niemirska A, Sozeri B, Thurn D, Anarat A, Ranchin B, Litwin M, Caliskan S, Candan C, Baskin E, Yilmaz E, Mir S, Kirchner M, Sander A, Haffner D, Melk A, Wuhl E, Shroff R, Querfeld U. Cardiovascular phenotypes in children with CKD: the 4C study. Clin J Am Soc Nephrol. 2017;12:19–28.
10. Shroff RC, McNair R, Figg N, Skepper JN, Schurgers L, Gupta A, Hiorns M, Donald AE, Deanfield J, Rees L, Shanahan CM. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation. 2008;118:1748–57.
11. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478–83.

12. Litwin M, Wuhl E, Jourdan C, Niemirska A, Schenk JP, Jobs K, Grenda R, Wawer ZT, Rajszys P, Mehls O, Schaefer F. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant. 2008;23:2552–7.
13. Shroff RC, Donald AE, Hiorns MP, Watson A, Feather S, Milford D, Ellins EA, Storry C, Ridout D, Deanfield J, Rees L. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol. 2007;18:2996–3003.
14. Mitsnefes M, Stablein D. Hypertension in pediatric patients on long-term dialysis: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Am J Kidney Dis. 2005;45:309–15.
15. Chesnaye NC, Schaefer F, Groothoff JW, Bonthuis M, Reusz G, Heaf JG, Lewis M, Maurer E, Paripovic D, Zagozdzon I, van Stralen KJ, Jager KJ. Mortality risk in European children with end-stage renal disease on dialysis. Kidney Int. 2016;89:1355–62.
16. Modi ZJ, Lu Y, Ji N, Kapke A, Selewski DT, Dietrich X, Abbott K, Nallamothu BK, Schaubel DE, Saran R, Gipson DS. Risk of cardiovascular disease and mortality in young adults with end-stage renal disease: an analysis of the US Renal Data System. JAMA Cardiol. 2019;4:353–62.
17. Agbas A, Canpolat N, Caliskan S, Yilmaz A, Ekmekci H, Mayes M, Aitkenhead H, Schaefer F, Sever L, Shroff R. Hemodiafiltration is associated with reduced inflammation, oxidative stress and improved endothelial risk profile compared to high-flux hemodialysis in children. PLoS One. 2018;13:e0198320.
18. Colton CK, Henderson LW, Ford CA, Lysaght MJ. Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. J Lab Clin Med. 1975;85:355–71.
19. Henderson LW, Colton CK, Ford CA, Bosch JP. Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. 1975. J Am Soc Nephrol. 1997;8:494–508.
20. Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. Kidney Int. 2010;77:581–7.
21. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28:542–50.
22. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Levesque R, Nube MJ, Ter Wee PM, Blankestijn PJ. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol. 2012;23:1087–96.
23. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
24. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.
25. Peters SA, Bots ML, Canaud B, Davenport A, Grooteman MP, Kircelli F, Locatelli F, Maduell F, Morena M, Nube MJ, Ok E, Torres F, Woodward M, Blankestijn PJ. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. Nephrol Dial Transplant. 2016;31:978–84.
26. Teatini U, Steckiph D, Romei LG. Evaluation of a new online hemodiafiltration mode with automated pressure control of convection. Blood Purif. 2011;31:259–67.
27. Ledebo I, Blankestijn PJ. Haemodiafiltration-optimal efficiency and safety. NDT Plus. 2010;3:8–16.
28. Canaud B, Levesque R, Krieter D, Desmeules S, Chalabi L, Moragues H, Morena M, Cristol JP. On-line hemodiafiltration as routine treatment of end-stage renal failure: why pre- or mixed dilution mode is necessary in on-line hemodiafiltration today? Blood Purif. 2004;22(Suppl 2):40–8.
29. Maduell F, Arias M, Vera M, Fontsere N, Blasco M, Barros X, Garro J, Elena M, Bergada E, Cases A, Bedini JL, Campistol JM. Mid-dilution hemodiafiltration: a comparison with pre- and postdilution modes using the same polyphenylene membrane. Blood Purif. 2009;28:268–74.
30. Pedrini LA, De Cristofaro V, Pagliari B, Sama F. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int. 2000;58:2155–65.
31. Shroff R, Smith C, Ranchin B, Bayazit AK, Stefanidis CJ, Askiti V, Azukaitis K, Canpolat N, Agbas A, Aitkenhead H, Anarat A, Aoun B, Aofolaju D, Bakkaloglu SA, Bhowruth D, Borzych-Duzalka D, Bulut IK, Buscher R, Deanfield J, Dempster C, Duzova A, Habbig S, Hayes W, Hegde S, Krid S, Licht C, Litwin M, Mayes M, Mir S, Nemec R, Obrycki L, Paglialonga F, Picca S, Samaille C, Shenoy M, Sinha MD, Spasojevic B, Stronach L, Vidal E, Vondrak K, Yilmaz A, Zaloszyc A, Fischbach M, Schmitt CP, Schaefer F. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, heart and height study. J Am Soc Nephrol. 2019;30:678–91.
32. Tsuchida K, Minakuchi J. Clinical benefits of predilution on-line hemodiafiltration. Blood Purif. 2013;35(Suppl 1):18–22.
33. Masakane I, Sakurai K. Current approaches to middle molecule removal: room for innovation. Nephrol Dial Transplant. 2018;33:iii12–21.
34. Masakane I, Kikuchi K, Kawanishi H. Evidence for the clinical advantages of predilution on-line hemodiafiltration. Contrib Nephrol. 2017;189:17–23.
35. Kikuchi K, Hamano T, Wada A, Nakai S, Masakane I. Predilution online hemodiafiltration is associated

with improved survival compared with hemodialysis. Kidney Int. 2019;95:929–38.
36. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
37. Fischbach M, Fothergill H, Seuge L, Zaloszyc A. Dialysis strategies to improve growth in children with chronic kidney disease. J Ren Nutr. 2011;21:43–6.
38. Tattersall J, Martin-Malo A, Pedrini L, Basci A, Canaud B, Fouque D, Haage P, Konner K, Kooman J, Pizzarelli F, Tordoir J, Vennegoor M, Wanner C, ter Wee P, Vanholder R. EBPG guideline on dialysis strategies. Nephrol Dial Transplant. 2007;22(Suppl 2):ii5–21.
39. Boccato C, Evans D, Lucena R, Vienken J. Good dialysis practice, vol. 8. Lengerich: Pabst Science Publishers; 2015.
40. European Directorate for the Quality of Medicines. Purified water .In :European Pharmacopoeia 9.4. 5665–5667; 2018. https://www.edqm.eu/sites/default/files/institutional-brochure-edqm.pdf. Accessed 7.7.2019
41. Agence Francaise de Securite Sanitaire des Produits de Sante. Circulaire N°DHOS/E4/AFSSAPS/DGS/2007/52 du 30 janvier 2007 relative aux spécifications techniques et à la sécurité sanitaire de la pratique de l'hémofiltration et de l'hémodiafiltration en lignedans les établissements de santé. https://solidarites-sante.gouv.fr/fichiers/bo/2007/07-03/a0030058.html. Accessed 7.7.2019.
42. Tsuchida K, Takemoto Y, Yamagami S, Edney H, Niwa M, Tsuchiya M, Kishimoto T, Shaldon S. Detection of peptidoglycan and endotoxin in dialysate, using silkworm larvae plasma and limulus amebocyte lysate methods. Nephron. 1997;75:438–43.
43. Schindler R, Beck W, Deppisch R, Aussieker M, Wilde A, Gohl H, Frei U. Short bacterial DNA fragments: detection in dialysate and induction of cytokines. J Am Soc Nephrol. 2004;15:3207–14.
44. Ronco C, Clark WR. Haemodialysis membranes. Nat Rev Nephrol. 2018;14:394–410.
45. Ward RA, Beck W, Bernardo AA, Alves FC, Stenvinkel P, Lindholm B. Hypoalbuminemia: a price worth paying for improved dialytic removal of middle-molecular-weight uremic toxins? Nephrol Dial Transplant. 2019;34:901–7.
46. Ronco C, Brendolan A, Lupi A, Metry G, Levin NW. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58:809–17.
47. Boure T, Vanholder R. Which dialyser membrane to choose? Nephrol Dial Transplant. 2004;19:293–6.
48. Consensus conference on biocompatibility. Nephrol Dial Transplant. 1994;9(Suppl 2):1–186.
49. Michaels AS. Operating parameters and performance criteria for hemodialyzers and other membrane-separation devices. Trans Am Soc Artif Intern Organs. 1966;12:387–92.
50. Gotch FA, Panlilio F, Sergeyeva O, Rosales L, Folden T, Kaysen G, Levin N. Effective diffusion volume flow rates (Qe) for urea, creatinine, and inorganic phosphorous (Qeu, Qecr, QeiP) during hemodialysis. Semin Dial. 2003;16:474–6.
51. Bergstrom J, Wehle B. No change in corrected beta 2-microglobulin concentration after cuprophane haemodialysis. Lancet. 1987;1:628–9.
52. Ficheux A, Argiles A, Bosc JY, Mion C. Analysis of the influence of the infusion site on dialyser clearances measured in an in vitro system mimicking haemodialysis and haemodiafiltration. Blood Purif. 1999;17:10–8.
53. Ficheux A, Argiles A, Mion H, Mion CM. Influence of convection on small molecule clearances in online hemodiafiltration. Kidney Int. 2000;57:1755–63.
54. Ronco C. Backfiltration: a controversial issue in modern dialysis. Int J Artif Organs. 1988;11:69–74.
55. Ronco C, Orlandini G, Brendolan A, Lupi A, La GG. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. Kidney Int. 1998;54:979–85.
56. Badr B, Bories P, Marais R, Frat B, Seigneuric B, Longlune N, Kamar N, Maggioni S, Rostaing L. Transonic, thermodilution, or ionic dialysance to manage vascular access: which method is best? Hemodial Int. 2014;18:127–35.
57. Canaud B, Kooman J, Selby NM, Taal M, Francis S, Kopperschmidt P, Maierhofer A, Kotanko P, Titze J. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. Kidney Int. 2019;95:296–309.
58. Chapdelaine I, Mostovaya IM, Blankestijn PJ, Bots ML, van den Dorpel MA, Levesque R, Nube MJ, Ter Wee PM, Grooteman MP. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. Blood Purif. 2014;37:229–37.
59. Mostovaya IM, Blankestijn PJ. What have we learned from CONTRAST? Blood Purif. 2013;35(Suppl 1):39–44.
60. Penne EL, van der Weerd NC, Bots ML, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, Ter Wee PM, Blankestijn PJ. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. Nephrol Dial Transplant. 2009;24:3493–9.
61. Chapdelaine I, de Roij van Zuijdewijn CL, Mostovaya IM, Levesque R, Davenport A, Blankestijn PJ, Wanner C, Nube MJ, Grooteman MP, Blankestijn PJ, Davenport A, Basile C, Locatelli F, Maduell F, Mitra S, Ronco C, Shroff R, Tattersall J, Wanner C. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. Clin Kidney J. 2015;8:191–8.
62. Mostovaya IM, Grooteman MP, Basile C, Davenport A, de Roij van Zuijdewijn CL, Wanner C, Nube MJ, Blankestijn PJ. High convection volume in online

post-dilution haemodiafiltration: relevance, safety and costs. Clin Kidney J. 2015;8:368–73.
63. Penne EL, van Berkel T, van der Weerd NC, Grooteman MP, Blankestijn PJ. Optimizing haemodiafiltration: tools, strategy and remaining questions. Nephrol Dial Transplant. 2009;24:3579–81.
64. Shroff R, Bayazit A, Stefanidis CJ, Askiti V, Azukaitis K, Canpolat N, Agbas A, Anarat A, Aoun B, Bakkaloglu S, Bhowruth D, Borzych-Duzalka D, Bulut IK, Buscher R, Dempster C, Duzova A, Habbig S, Hayes W, Hegde S, Krid S, Licht C, Litwin M, Mayes M, Mir S, Nemec R, Obrycki L, Paglialonga F, Picca S, Ranchin B, Samaille C, Shenoy M, Sinha M, Smith C, Spasojevic B, Vidal E, Vondrak K, Yilmaz A, Zaloszyc A, Fischbach M, Schaefer F, Schmitt CP. Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children – the HDF, heart and height (3H) study. BMC Nephrol. 2018;19:199.
65. Borzych-Duzalka D, Shroff R, Ariceta G, Yap YC, Paglialonga F, Xu H, Kang HG, Thumfart J, Aysun KB, Stefanidis CJ, Fila M, Sever L, Vondrak K, Szabo AJ, Szczepanska M, Ranchin B, Holtta T, Zaloszyc A, Bilge I, Warady BA, Schaefer F, Schmitt CP. Vascular access choice, complications, and outcomes in children on maintenance hemodialysis: findings from the International Pediatric Hemodialysis Network (IPHN) Registry. Am J Kidney Dis. 2019;74(2):193–202.
66. Shroff R, Calder F, Bakkaloglu S, Nagler EV, Stuart S, Stronach L, Schmitt CP, Heckert KH, Bourquelot P, Wagner AM, Paglialonga F, Mitra S, Stefanidis CJ. Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group. Nephrol Dial Transplant. 2019;34(10):1746–65.
67. Canaud B, Leray-Moragues H, Kerkeni N, Bosc JY, Martin K. Effective flow performances and dialysis doses delivered with permanent catheters: a 24-month comparative study of permanent catheters versus arterio-venous vascular accesses. Nephrol Dial Transplant. 2002;17:1286–92.
68. Leblanc M, Bosc JY, Vaussenat F, Maurice F, Leray-Moragues H, Canaud B. Effective blood flow and recirculation rates in internal jugular vein twin catheters: measurement by ultrasound velocity dilution. Am J Kidney Dis. 1998;31:87–92.
69. Klingel R, Schaefer M, Schwarting A, Himmelsbach F, Altes U, Uhlenbusch-Korwer I, Hafner G. Comparative analysis of procoagulatory activity of haemodialysis, haemofiltration and haemodiafiltration with a polysulfone membrane (APS) and with different modes of enoxaparin anticoagulation. Nephrol Dial Transplant. 2004;19:164–70.
70. Sombolos KI, Fragia TK, Gionanlis LC, Veneti PE, Bamichas GI, Fragidis SK, Georgoulis IE, Natse TA. The anticoagulant activity of enoxaparin sodium during on-line hemodiafiltration and conventional hemodialysis. Hemodial Int. 2009;13:43–7.
71. McMahon LP, Chester K, Walker RG. Effects of different dialysis membranes on serum concentrations of epoetin alfa, darbepoetin alfa, enoxaparin, and iron sucrose during dialysis. Am J Kidney Dis. 2004;44:509–16.
72. Cheung AK, Rocco MV, Yan G, Leypoldt JK, Levin NW, Greene T, Agodoa L, Bailey J, Beck GJ, Clark W, Levey AS, Ornt DB, Schulman G, Schwab S, Teehan B, Eknoyan G. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17:546–55.
73. Schaefer F. Daily online haemodiafiltration: the perfect 'stimulus package' to induce growth? Nephrol Dial Transplant. 2010;25:658–60.
74. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, Basile C, David S, Feriani M, Montagna G, Di Iorio BR, Memoli B, Cravero R, Battaglia G, Zoccali C. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol. 2010;21:1798–807.
75. Morena M, Jaussent A, Chalabi L, Leray-Moragues H, Chenine L, Debure A, Thibaudin D, Azzouz L, Patrier L, Maurice F, Nicoud P, Durand C, Seigneuric B, Dupuy AM, Picot MC, Cristol JP, Canaud B. Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. Kidney Int. 2017;91:1495–509.
76. Maduell F, Varas J, Ramos R, Martin-Malo A, Perez-Garcia R, Berdud I, Moreso F, Canaud B, Stuard S, Gauly A, Aljama P, Merello JI. Hemodiafiltration reduces all-cause and cardiovascular mortality in incident hemodialysis patients: a propensity-matched cohort study. Am J Nephrol. 2017;46:288–97.
77. Nube MJ, Peters SAE, Blankestijn PJ, Canaud B, Davenport A, Grooteman MPC, Asci G, Locatelli F, Maduell F, Morena M, Ok E, Torres F, Bots ML. Mortality reduction by post-dilution online-haemodiafiltration: a cause-specific analysis. Nephrol Dial Transplant. 2017;32:548–55.
78. Pedrini LA, Zawada AM, Winter AC, Pham J, Klein G, Wolf M, Feuersenger A, Ruggiero P, Feliciani A, Barbieri C, Gauly A, Canaud B, Stuard S. Effects of high-volume online mixed-hemodiafiltration on anemia management in dialysis patients. PLoS One. 2019;14:e0212795.
79. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, Bots ML, Blankestijn PJ, Ter Wee PM. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
80. Penne EL, van der Weerd NC, Blankestijn PJ, van den Dorpel MA, Grooteman MP, Nube MJ, Ter Wee PM, Levesque R, Bots ML. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol. 2010;5:80–6.

81. Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, Strippoli GF. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. Cochrane Database Syst Rev. 2015;(5):CD006258.
82. Grooteman MP, Blankestijn PJ, Nube MJ. Not all convective dialysis therapies are equal. Am J Kidney Dis. 2014;64:819–20.
83. Marshall MR. Measuring the patient response to dialysis therapy: hemodiafiltration and clinical trials. Kidney Int. 2017;91:1279–82.
84. Locatelli F, Altieri P, Andrulli S, Sau G, Bolasco P, Pedrini LA, Basile C, David S, Gazzanelli L, Tampieri G, Isola E, Marzolla O, Memoli B, Ganadu M, Reina E, Bertoli S, Ferrara R, Casu D, Logias F, Tarchini R, Mattana G, Passaghe M, Fundoni G, Villa G, Di Iorio BR, Pontoriero G, Zoccali C. Phosphate levels in patients treated with low-flux haemodialysis, predilution haemofiltration and haemodiafiltration: post hoc analysis of a multicentre, randomized and controlled trial. Nephrol Dial Transplant. 2014;29:1239–46.
85. Bacchetta J, Sellier-Leclerc AL, Bertholet-Thomas A, Carlier MC, Cartier R, Cochat P, Ranchin B. Calcium balance in pediatric online hemodiafiltration: beware of sodium and bicarbonate in the dialysate. Nephrol Ther. 2015;11:483–6.
86. Movilli E, Camerini C, Gaggia P, Zubani R, Feller P, Salviani C, Facchini A, Cancarini G. Total convection affects serum beta2 microglobulin and C-reactive protein but not erythropoietin requirement following post-dilutional hemodiafiltration. Am J Nephrol. 2015;41:494–501.
87. Fischbach M, Attal Y, Geisert J. Hemodiafiltration versus hemodialysis in children. Int J Pediatr Nephrol. 1984;5:151–4.
88. Fischbach M, Terzic J, Menouer S, Dheu C, Soskin S, Helmstetter A, Burger MC. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21:1746–52.
89. Fadel FI, Makar SH, Zekri H, Ahmed DH, Aon AH. The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis. Saudi J Kidney Dis Transpl. 2015;26:39–46.
90. Morad AA, Bazaraa HM, Abdel Aziz RE, Abdel Halim DA, Shoman MG, Saleh ME. Role of online hemodiafiltration in improvement of inflammatory status in pediatric patients with end-stage renal disease. Iran J Kidney Dis. 2014;8:481–5.
91. Paglialonga F, Vidal E, Pecoraro C, Guzzo I, Giordano M, Gianoglio B, Corrado C, Roperto R, Ratsch I, Luzio S, Murer L, Consolo S, Pieri G, Montini G, Edefonti A, Verrina E. Haemodiafiltration use in children: data from the Italian Pediatric Dialysis Registry. Pediatr Nephrol. 2019;34:1057–63.
92. Blum WF, Ranke MB, Kietzmann K, Tonshoff B, Mehls O. Growth hormone resistance and inhibition of somatomedin activity by excess of insulin-like growth factor binding protein in uraemia. Pediatr Nephrol. 1991;5:539–44.
93. Farrington K, Davenport A. The ESHOL study: hemodiafiltration improves survival-but how? Kidney Int. 2013;83:979–81.
94. Ju A, Unruh M, Davison S, Dapueto J, Dew MA, Fluck R, Germain M, Jassal SV, Obrador G, O'Donoghue D, Josephson MA, Craig JC, Viecelli A, O'Lone E, Hanson CS, Manns B, Sautenet B, Howell M, Reddy B, Wilkie C, Rutherford C, Tong A. Establishing a core outcome measure for fatigue in patients on hemodialysis: a standardized outcomes in nephrology-hemodialysis (SONG-HD) consensus workshop report. Am J Kidney Dis. 2018;72:104–12.

Maintenance Hemodialysis During Infancy

22

Sarah J. Swartz and Fabio Paglialonga

Introduction

Over the last decades, the number of infants with ESKD has significantly increased [1, 2]. These infants frequently have other comorbidities. Although preemptive renal transplantation is the best treatment strategy, it is usually necessary to postpone transplantation until the infant has gained weight and grown to body weight of 8–10 kg and length 75–80 cm. While peritoneal dialysis (PD) remains the dialytic modality of choice in this age group, hemodialysis (HD), either as a bridge to peritoneal dialysis or as a long-term modality, is required in selected cases. The provision of HD during infancy is characterized by some peculiarities in terms of technical details and long-term clinical management due to the infant's small size.

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Epidemiology/Indications

Data from different large international registries show that most infants and small children requiring dialysis are currently treated with PD; only 8.7–13.5% of the patients below 1 year of age undergo maintenance HD [1–5]. Main indications for HD in infants are anatomical contraindications for PD (gastroschisis, omphalocele, bladder exstrophy) and primary oxalosis. In addition, there is a small subset of infants with neonatal ESKD who either require HD as a bridge to PD initiation or following failure of PD [6]. Psychosocial problems can be considered relative indications to chronic HD as well [6].

Technical Issues

Vascular Access

Central venous catheter (CVC) is used as vascular access in almost 100% of infants needing hemodialysis. Although the use of arteriovenous fistula is associated with lower complication rate and longer access survival than CVC in children on maintenance HD, the placement of an AVF in infants requires specific surgical skills, and it is currently feasible in only a few selected centers with great expertise in microsurgical techniques for children 10–20 kg. Different types of catheters are used in infants on HD with huge differences in terms of outcome with mean CVC

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survival rates ranging from 21 to 390 days according to the available reports [7–16]. Given that uncuffed catheters are associated with lower survival and a higher incidence of infectious and noninfectious complications, their use should be reserved for acute HD only. Catheter selection is driven by infant size with the goal to avoid endothelial damage and development of venous stenosis. Appropriate catheter selection is paramount but limited by available products. Both 8 Fr double-lumen cuffed CVCs and 6.5 single-lumen cuffed CVCs are currently available in most countries and are appropriate for the majority of infants requiring long-term HD. The CVC should be placed in preferably the right internal jugular vein by percutaneous cannulation or surgical approach by specialized experts and managed by trained personnel only.

Central line use is hampered by the risk of malfunction, central vein thrombosis, and infections. Unfractionated heparin is the most frequently used lock solution; heparin concentration should not exceed 1000 U/ml to avoid the risk of systemic anticoagulation, and 500 U/ml is adequate for most of the infants. Urokinase or rtPA and sodium citrate are possible alternatives with good results in older children but without specific studies in infants. Frequently limited vascular access is a leading cause of morbidity and mortality in this population. Central vein thrombosis occurs in a high (but difficult to estimate) proportion of patients starting HD in the first years of life; data from the Italian Pediatric Dialysis Registry showed that radiologic evidence of central vein thrombosis was found in 38% of children treated with chronic HD in the first 2 years of life, with two out of four deaths due to lack of vascular access [14]. Doppler ultrasound central vein monitoring can be of some help to diagnose thrombosis as early as possible allowing for appropriate treatment. A small single center study proposed the use of sodium warfarin to improve CVC survival in children on HD [17]. Some centers have used prophylactic enoxaparin with success in older infants with frequent catheter dysfunction. Data assessing these strategies to prevent central vein thrombosis in infants are significantly lacking.

The incidence of CVC infections is highly variable in different studies, ranging from 0.3 to 10 episodes per 1000 CVC days [7–16]: an infection incidence lower than 1/1000 CVC days can be considered an acceptable target. Standardized bundle practices are frequently used for catheter care and maintenance to prevent infection [18]. Strict sterile technique for CVC management by experienced nurses is the cornerstone of CVC infection prevention in infants as in older children.

Equipment (Machines/Dialyzers/Blood Lines)

Machines designed for adult patients are used in most centers for infant HD, but their relatively low accuracy in measuring ultrafiltration volume and large extracorporeal blood volume (EBV) is an important limitation. It is well demonstrated that adult dialysis machines are subjected to an ultrafiltration error of ±30–50 ml/h, with possible significant discrepancies between the prescribed and actual fluid removal. Hence close monitoring to reassess volume status throughout the treatment is paramount.

To prevent hemodynamic imbalances, EBV should ideally be maintained lower than 10% of patient blood volume (BV), which is difficult to achieve with most of the currently available machines, dialyzers, and blood lines. Total EBV is the sum of the hemofilter blood compartment and blood lines (plus CVC lumens). The infant's blood volume is approximated by 80 ml/kg * body weight. Dialyzer selection in an infant population involves choosing a combination of filter and blood lines which will impart the lowest EBV to minimize hemodynamic imbalances while providing adequate surface area for clearance and fluid removal. In regard to the dialyzers, the smallest filters available in Europe are the Gambro Polyflux 2H and Fresenius FX Paed, both of which have a surface of 0.2 m^2 and an EBV of 17 and 18 ml, respectively. In the USA, the smallest available filter is the Fresenius Hemoflow F3 with a surface area 0.4 m^2 and EBV 24 ml (Table 22.1).

Table 22.1 Hemofilters for infant hemodialysis

Dialyzer	Distribution	Surface (sqm)	Blood volume (ml)	Membrane	Urea clearance (ml/min)	Kuf (ml/h/mmHg)
Gambro Polyflux 2H	Europe	0.2	17	Polyamix	72*	15
Fresenius FX Paed	Europe	0.2	18	Helixone	76*	7
Fresenius Hemoflow F3	USA	0.4	24	Polysulfone	125**	1.7
Gambro CA50	USA	0.5	35	Cellulose acetate	130**	2.5

*Qb 100 ml/min, Qd 300 ml/min
**Qb 200 ml/min, Qd 500 ml/min

In regard to blood lines, the available selection is also quite limited. The Gambro neonatal lines for AK200 are the smallest lines on the market in Europe, with a BV of 33 ml. However, this machine is no longer produced, and the same will soon become true for the blood lines. In the USA, low volume blood lines are available from Medisystems (2.6 mm and 4.8 mm) with BV of 29 ml and 52 ml, respectively, and Cobe (neonatal and pediatric) lines with BV 40 ml and 75 ml, respectively. The low-volume Medisystems lines however are without arterial line pressure monitoring capabilities.

In the more recent years, two new hemodialysis machines have been specifically designed for extracorporeal renal replacement therapy in neonates and small children. This technology is currently available in Europe but not yet in the USA. The CARDIO-RENAL PEDIATRIC DIALYSIS EMERGENCY MACHINE (CARPEDIEM) is a device developed at the International Renal Research Institute in San Bortolo Hospital in Vicenza, Italy [19, 20]. It has the ability to provide continuous veno-venous hemofiltration and continuous veno-venous HD in neonates and children weighing less than 10 kg. The system offers a miniaturized version of conventional adult continuous renal replacement therapy machine with the availability of three different sized hemodialyzers ranging from 0.075 to 0.25 m^2 with the total circuit EBV from 27 to 42 ml. Blood flow rate and dialysate-substitution flow rate can be set at 2–50 ml/min and 1–10 ml/min, respectively; the maximum fluid removal is 1000 ml per session with an accuracy of 1 ml per h. Although CARPEDIEM is designed for continuous renal replacement therapy, the first experiences have recently been published reporting its use for intermittent HD in neonates and infants with ESKD [20]. The Newcastle Infant Dialysis and Ultrafiltration System (Nidus) is a miniaturized machine which uses two syringes to pump blood. Its circuit volume is less than 10 ml and only a single-lumen line is needed to provide the therapy. It has the capability to provide a prescribed blood flow rate between 20 and 45 ml/min and accurate ultrafiltration down to the microliter. It was developed for renal replacement therapy in infants weighing between 800 grams and 8 kg. The first reports on this machine are really promising [21].

Blood Flow

The dialysis prescription should be tailored to the size of the infant. Ideally blood flow rates (Qb) should be kept at 3–8 ml/kg/min. The following formula can also be used to calculate the ideal Qb: (body weight + 10) × 2.5 ml/min. Frequently however higher Qb (~15 ml/kg/min or 30 ml/min) is required due to the limitations of current available technology. The optimal Qb should however be established slowly over multiple sessions and during each treatment to prevent hemodynamic compromise.

Connection and Disconnection

In case of ECV/BV > 10%, priming with either blood or albumin is usually suggested to avoid hemodynamic problems at the beginning of the treatment. Blood priming with pure red blood cells

diluted to hematocrit 35% is required to prevent hemodynamic changes until the ECV/BV is closer to 10–15%. Blood prime however can be associated with an increased risk of sensitization, hyperkalemia, and hypocalcemia especially in the smaller infants. Due to the disproportionally large EBV, when the circuit is primed with blood, it should not be returned to the infant at the end of the session due to the acute risk of volume overload and hence hemodynamic instability, hypertension, and cardiac failure. When priming with albumin, the EBV should be returned to the infant slowly (typically slower than 20% treatment Qb) balancing the need to limit the amount of saline administered at the end of treatment and the importance of clearing the dialyzer when returning to the EBV to reduce anemia from chronic blood loss.

Anticoagulation

Sodium heparin is the preferred anticoagulant for HD in infants. The standard dose is 10–20 U/kg as initial bolus followed by 10–30 U/kg/h as continuous infusion, maintaining a target activated clotting time (ACT) of 180–220 s. The dose required is dependent on several factors, but low Qb, high hematocrit levels, and significant hemoconcentration due to ultrafiltration are known risk factors for clotting, which could require an increase in heparinization. Lower ACT targets may be suggested for neonates and very small infants, in particular in case of arterial hypertension, to reduce the risk of intracranial hemorrhage. If the circuit is primed with heparinized saline, the amount of heparin administered with the connection at the beginning of dialysis should be modified to take heparin exposure from the prime into account.

Ultrafiltration (UF) and Dry Weight Assessment

Cardiovascular complications are a leading cause of hospitalization and death in children with ESKD, and in particular in infants on chronic HD. Volume control is the mainstay of cardiovascular protection in this population, as both chronic and intermittent volume overload can lead to hypertension and cardiac impairment. On the other hand an excessive or too fast UF rate should also be avoided as it is associated with intradialytic morbidity, loss of residual renal function, and myocardial stunning. The first step in improving volume management is to accurately assess dry weight (DW), which is a difficult task particularly in small children and infants as anticipated true weight gain needs to be differentiated from fluid gains. The clinical assessment of DW is important but often misleading. In this population, the presence of edema is not a sensitive marker of volume overload. An accurate assessment of DW replies on a comprehensive evaluation that includes more parameters. Among the available techniques, blood volume monitoring is the best method to guide UF goals in children on HD [22, 23]. Bioimpedance analysis, inferior vena cava diameter, lung ultrasound, and brain natriuretic peptide monitoring can be helpful although serial assessment and longitudinal follow-up are needed to provide patient-specific comparative values [23]. However, the reliability of these techniques can be influenced by the expertise of the center.

Intradialytic hypotension is frequently exacerbated by anemia and carnitine deficiency, both of which are common in infants with ESKD. To reduce the risk of intradialytic complications, the UF rate should be lower than 0.2 ml/kg/min or 4% of body weight per session. Carnitine and serum albumin levels should be monitored regularly and replaced if deficient. Despite correction, intradialytic hypotension may recur limiting UF, and infant may need alpha agonist such as midodrine for cardiovascular support during HD treatments. Frequently UF rates need to be modified throughout the HD treatment. In case of intradialytic hypovolemia or hypotension, UF must be stopped and normal saline (5 ml/kg) or albumin (0.25 g/kg) administered.

HD Schedule

Frequent hemodialysis is often required during the first year of life for infants who are unable to transition to peritoneal dialysis. Several factors

other than adequacy (kt/v) need to be taken into account when prescribing the dialysis dose in terms of session number and duration, including UF need, metabolic control, growth, primary renal disease, and residual urine output. The smallest infants typically require daily HD to meet the infant's nutritional needs to promote growth and maintain metabolic and volume control. Overall the dialysis frequency tends to be most influenced by the infant's fluid requirements. Thus, a standard thrice weekly HD schedule is often inadequate for infants; more than 60% of children younger than 2 years of age received ≥4 sessions/week according to the Italian Pediatric Dialysis Registry [14].

Clinical Problems

Growth

Nearly 30% of postnatal growth occurs during the first 2 years of life, which implies that a special attention should be paid to this issue in infants with ESKD. Growth retardation is epidemic in small children on HD, occurring in 22–90% of infants according to the different reports. Growth hormone however is not typically recommended until after the first year of life. During the first year of life, growth tends to be dependent on providing adequate caloric and protein intake. An infant's nutritional needs to promote growth can however vary. It is suggested that the initial dietary prescription for infants on HD should provide at least 100% of dietary reference intake (DRI) for healthy peers. The DRI accounts for 100% of the dietary energy intake and dietary protein intake required to promote growth as no evidence exists that infants with ESKD have different nutritional requirements compared with healthy children. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF K/DOQI) recommendations, infants on HD require 1.6 grams/kg/day of protein if <6 months and 1.3 grams/kg/day of protein between 7 and 12 months of age [24] . The amount of protein provided in the diet should be adjusted based on serum BUN, albumin levels, calculated nPCR, and linear growth and can vary between 1.1 and 2.2 grams/kg/day.

Formulas provided to meet the nutritional requirements of an infant with ESKD frequently need to be adjusted to prevent hyperkalemia while providing adequate calories. Frequently standard formulas such as Nephea Infant (Europe only), Kindergen (Europe only), Similac PM 60/40 (the USA only), Renastart (the USA only), or breast milk are used as a base. These formulas are characterized by reduced potassium and phosphate levels. In infants with oligoanuria, these formulas typically need to be concentrated with addition of carbohydrate and protein modifiers to provide adequate calories in a reduced volume. On the other hand, infants with polyuric renal failure such as renal dysplasia with renal salt wasting frequently require increased free water and/or sodium chloride supplements to maintain both euvolemia and metabolic control.

Frequently infants with ESKD have anorexia and oral aversion requiring either gastrostomy or nasogastric tube to ensure delivery of nutritional needs. Metabolic acidosis also exerts a detrimental effect on growth and nutritional status and, if present, should be corrected with sodium bicarbonate supplements to maintain serum HCO3 ≥ 22 mmol/L. In case of growth failure despite adequate dietary intake and good metabolic control, the use of growth hormone should be considered based on small trials of infants with CKD which have demonstrated improvement in growth velocity with use of growth hormone [25, 26].

Anemia

Anemia in infants with ESKD is frequently multifactorial and related to combination of prematurity, physiologic nadir, erythropoietin (EPO) deficiency associated with CKD, and blood loss. Although there are no set recommendations around goal hemoglobin levels in infants with ESKD, healthy infants typically have higher hemoglobin than healthy children (Table 22.2). Uncontrolled anemia can frequently lead to hemodynamic instability during hemodialysis

Table 22.2 Normal values for hemoglobin and hematocrit in infants

Age	Hemoglobin (g/dL)	Hematocrit (%)
Term birth	16.5 ± 3.0	51 ± 9
2–6 months	11.5 ± 2.5	35 ± 7
6 months–2 years	12.0 ± 1.5	36 ± 3

resulting in frequent need for blood transfusions to maintain hemoglobin at least 8.5–9 grams/dl. In addition to blood exposure for circuit prime, the percentage of infants on hemodialysis who need blood transfusions ranged in the published reports between 56% and 90%, with most of the infants requiring multiple transfusions. Feinstein demonstrated that infants starting HD during the first year of life required a median of 25 ml/kg/month of blood in the first three months of dialysis [12]. Blood loss was mainly attributable to residual volume in the dialysis system (15.7 ml/kg/month) and frequent blood tests (12.1 ml/kg/month). Attempting to limit exposure to blood however is key in this population due to the long-term sequelae of blood product exposure including risk of HLA sensitization with the consequent risk of prolonged waiting times for renal transplantation and antibody-mediated rejection.

To reduce the need for blood transfusions, iron supplement and rhEPO are needed in almost all infants on chronic HD. Frequently infants require higher doses of rhEPO when compared with older children if normalized for body weight (usually >400 U/kg/week). Typically rhEPO is initiated at 50–150 units/kg/dose or 150–450 U/kg/week, administered intravenously, and titrated monthly based on response. Iron administration is required via enteral or intravenous route to optimize rhEPO efficacy; iron dose also requires titration based on response for goal transferrin saturation >20% and ferritin >200 ng/ml. Enteral iron supplementation is typically started at 3 mg/kg/dose and titrated to 6 mg/kg/dose of elemental iron. Intravenous ferrum (ferric gluconate or iron sucrose) can be administered starting at 1 mg/kg weekly. Blood loss should be minimized by limiting unnecessary laboratory screening and optimizing anticoagulation to prevent loss of circuits.

Hypertension

High blood pressure affects almost 80% of infants on chronic HD. Hypertension is typically secondary to volume overload or renin mediated due to underlying renal disease.

As previously mentioned, volume control is the cornerstone of BP management in all patients with ESKD and particularly in infants. Appropriate fluid restrictions and frequency of dialysis need to be instituted to allow for adequate nutritional intake in conjunction with low interdialytic weight gains (ideally <4% of body weight) and slow ultrafiltration. In addition, frequent reassessment of dry weight is needed to account for expected weight gain. Antihypertensive medications are often needed in infants on HD to maintain BP within age-appropriate norms. ACE inhibitors should be considered the first-line agents if antihypertensive therapy is needed. Cardiac function should be monitored closely with frequent echocardiograms.

CKD/MBD

Mineral bone disorder is very common in infants with ESKD and a main cause of growth retardation related to uncontrolled secondary hyperparathyroidism. Infants are at high risk of skeletal pain, bone deformities, and pathological fractures in setting of uncontrolled MBD. Infants require both higher calcium and phosphorus levels for bone formation in the setting of rapidly growing bones. Hence unlike children who struggle with hyperphosphatemia and require phosphate binding drugs, infants on hemodialysis, especially if receiving frequent HD, often require phosphorus supplement to avoid hypophosphatemia and maintain serum phosphorus ≥4.5 mg/dl or 1.5 mmol/L. In those patients with high phosphate levels despite dietary and dialysis optimization, calcium carbonate or sevelamer carbonate can safely be used. In addition, infants require a positive calcium balance via a combination of dietary intake, calcium supplement, and high calcium concentrations in the dialysate (2.5–3 meq/L or 1.25–1.5 mmol/L). Parathyroid hormone (PTH) levels should be checked at least once per month in infants. There is no consensus on optimal PTH tar-

gets in infants on chronic HD, but levels of intact PTH between 100 and 200 pg/ml are usually suggested. Treatment with native vitamin D if deficient or activated vitamin D analogue such as calcitriol or paricalcitol if high PTH should be initiated. Frequently infants require supplements with both. Activated vitamin D analogues can be administered enterally or intravenously; if given enterally however, medication should be administered by mouth as it frequently will adhere to plastic resulting in ineffective administration.

Psychosocial Impact

Chronic HD in infancy is associated with significant psychological stress for the child and the family due to frequent in-center treatments, multiple hospitalizations, invasive procedures, and various medical problems resulting in significant care complexity. Moreover, infants with ESKD often experience significant development delays associated with chronic illness and have an increased risk of neurologic deficit compared to their healthy peers. Each dialysis treatment can be difficult and stressful as the infant is unable to understand the procedure and requires a continuous presence of a caregiver. Frequently not only is a parent required for distraction but additional members of the interdisciplinary team including the child life specialist or music therapist. In addition a 1:1 nurse to patient ratio is usually needed to ensure the infant's safety especially as they become more mobile. A psychologist and social worker are also instrumental in aiding the family in the adjustment process for caring for an infant with complex medical needs. Hence, the provision of psychosocial support is an integral part of the care of these patients.

Outcomes

Infants maintained on chronic HD have a mortality rate 14–30% with those with comorbidities having the greatest risk according to available reports [1–5, 7–14]. Cardiovascular complications and infections remain the leading causes of death for this age. Lack of vascular access is a huge problem in the long term [14]. HD however can provide a successful bridge to transplant for those infants that are unable to be maintained on peritoneal dialysis. Successful transplantation is reported in a variable percentage ranging from 28% to 82% of patients according to different studies [1–5, 7–14]. In a study of the ERA/ESPN registry, Vidal recently compared the outcome of 917 infants who initiated dialysis with PD to 146 infants who initiated dialysis with HD; the 5-year cumulative incidence of death and of transplantation in HD cohort was 16.3% and 69%, respectively [5]. Interestingly, the mortality risk and the likelihood of transplantation were not different between the modalities. Notably, however infants on HD had a higher risk for changing dialysis modality (at 5 years 30.9 vs 24.6%) (Fig. 22.1).

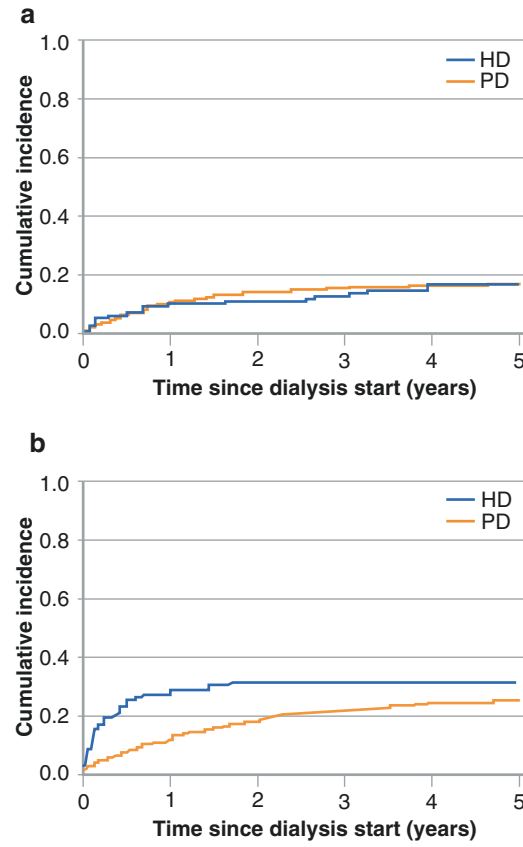

Fig. 22.1 Cumulative incidence curves for (**a**) death (with transplantation as a competing risk); (**b**) modality switching (with both death and transplation as competing risks); and (**c**) transplantation (with death as competing risk). (Modified from Ref. [5])

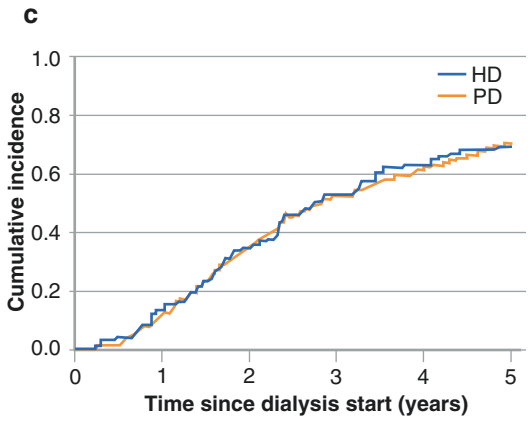

Fig. 22.1 (continued)

Developmental delay is a major issue in infants undergoing chronic dialysis irrespective of dialysis modality. Infants require early physical and occupational therapy to help promote appropriate development. Infants on hemodialysis however are at increased risk for brain injury associated with alterations in blood pressure with repeated episodes of both hypotension and hypertension as well as potential hypoxemia, hypoperfusion, and temperature dysregulation during HD sessions.

Conclusions

Although PD is the most appropriate renal replacement therapy modality for infants requiring dialysis, maintenance hemodialysis can provide an alternative management strategy to bridge an infant to the ultimate goal of renal transplantation for management of ESKD. Hemodialysis is feasible in infants with ESKD. Notwithstanding significant advances in the last decades, the provision of hemodialysis for infants is still hampered by technical challenges including the limitation of the available equipment and need for a CVC with its short- and long-term complications and clinical challenges including poor growth, anemia, and blood pressure variability. Infants with ESKD should be treated in very specialized centers with a skilled multidisciplinary team, which must include pediatric nephrologists, nurses, psychologists, dieticians, child life specialists, play therapists, and social workers as well as other pediatric subspecialists.

References

1. 2017 Annual data report: atlas of pediatric end-stage renal disease in the United States. United States Renal Data System (USRDS). 2017. Available from: https://www.usrds.org/2017/view/v2_07.aspx.
2. North American Pediatric Renal Trials and Collaborative Studies. NAPRTCS 2011 annual dialysis report. The EMMES Corporation. 2012. Available at: http://www.emmes.com/study/ped/annlrept/annualrept2011.pdf.
3. Carey WA, Talley LI, Sehring SA, Jaskula JM, Mathias RS. Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American Pediatric Renal Trials and Collaborative Studies special analysis. Pediatrics. 2007;119:e468–73.
4. van Stralen KJ, Borzych-Dużalka D, Hataya H, Kennedy SE, Jager KJ, Verrina E, et al. ESPN/ERA-EDTA registry; IPPN registry; ANZDATA registry; Japanese RRT registry. Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. Kidney Int. 2014;86:168–74.
5. Vidal E, van Stralen KJ, Chesnaye NC, Bonthuis M, Holmberg C, Zurowska A, et al. ESPN/ERA-EDTA Registry. Infants requiring maintenance dialysis: outcomes of hemodialysis and peritoneal dialysis. Am J Kidney Dis. 2017;69:617–25.
6. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ, on behalf of the European Paediatric Dialysis Working Group. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). Pediatr Nephrol. 2013;28:1739–48.
7. Sousa CN, Gama M, Andrade M, Faria MS, Pereira E. Haemodialysis for children under the age of two years. J Ren Care. 2008;34:9–13.
8. Quinlan C, Bates M, Sheils A, Dolan N, Riordan M, Awan A. Chronic hemodialysis in children weighing less than 10 kg. Pediatr Nephrol. 2013;28:803–9.
9. Kovalski Y, Cleper R, Krause I, Davidovits M. Hemodialysis in children weighing less than 15 kg: a single-center experience. Pediatr Nephrol. 2007;22:2105–10.
10. Shroff R, Wright E, Ledermann S, Hutchinson C, Rees L. Chronic hemodialysis in infants and children under 2 years of age. Pediatr Nephrol. 2003;18:378–83.
11. Al-Hermi BE, Al-Saran K, Secker D, Geary DF. Hemodialysis for end-stage renal disease in

children weighing less than 10 kg. Pediatr Nephrol. 1999;13:401–3.
12. Feinstein S, Rinat C, Becker-Cohen R, Ben-Shalom E, Schwartz SB, Frishberg Y. The outcome of chronic dialysis in infants and toddlers—advantages and drawbacks of haemodialysis. Nephrol Dial Transplant. 2008;23:1336–45.
13. Pollack S, Eisenstein I, Tarabeih M, Shasha-Lavski H, Magen D, Zelikovic I. Long-term hemodialysis therapy in neonates and infants with end-stage renal disease: a 16-year experience and outcome. Pediatr Nephrol. 2016;31:305–13.
14. Paglialonga F, Consolo S, Pecoraro C, Vidal E, Gianoglio B, Puteo F, et al. Chronic haemodialysis in small children: a retrospective study of the Italian Pediatric Dialysis Registry. Pediatr Nephrol. 2016;31:833–41.
15. Paul A, Fraser N, Manoharan S, Williams AR, Shenoy MU. The challenge of maintaining dialysis lines in the under twos. J Pediatr Urol. 2011;7:48–51.
16. Lopez PJ, Troncoso B, Grandy J, Reed F, Ovalle A, Celis S, et al. Outcome of tunnelled central venous catheters used for haemodialysis in children weighing less than 15 kg. J Pediatr Surg. 2014;49:1300–3.
17. Paglialonga F, Artoni A, Braham S, Consolo S, Giannini A, Chidini G, et al. Vitamin K antagonists in children with central venous catheter on chronic haemodialysis: a pilot study. Pediatr Nephrol. 2016;31:827–32.
18. Eisenstein I, Tarabeih M, Magen D, Pollack S, Kassis I, Ofer A, et al. Low infection rates and prolonged survival times of hemodialysis catheters in infants and children. Clin J Am Soc Nephrol. 2011;6:793–8.
19. Ronco C, Garzotto F, Brendolan A, Zanella M, Bellettato M, Vedovato S, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM). Lancet. 2014;383:1807–13.
20. Vidal E, Cocchi E, Paglialonga F, Ricci Z, Garzotto F, Peruzzi L, et al. Continuous veno-venous hemodialysis using the Cardio-Renal Pediatric Dialysis Emergency MachineTM: first clinical experiences. Blood Purif. 2018;31:1–7.
21. Coulthard MG, Crosier J, Griffiths C, Smith J, Drinnan M, Whitaker M, et al. Haemodialysing babies weighing <8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): comparison with peritoneal and conventional haemodialysis. Pediatr Nephrol. 2014;29:1873–81.
22. Patel HP, Goldstein SL, Mahan JD, Smith B, Fried CB, Currier H, et al. A standard, noninvasive monitoring of hematocrit algorithm improves blood pressure control in pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2:252–7.
23. Hayes W, Paglialonga F. Assessment and management of fluid overload in children on dialysis. Pediatr Nephrol. 2019;34:233–42.
24. National Kidney Foundation Disease Outcomes Quality Initiative. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53:S11–S104.
25. Mencarelli F, Kiepe D, Leozappa G, Stringini G, Cappa M, Emma F. Growth hormone treatment started in the first year of life in infants with chronic renal failure. Pediatr Nephrol. 2009;24:1039–46.
26. Santos F, Moreno ML, Neto A, Ariceta G, Vara J, Alonso A, et al. Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. Clin J Am Soc Nephrol. 2010;5:1190–7.

Home Haemodialysis in Children

23

Daljit K. Hothi and Claus Peter Schmitt

Introduction

Haemodialysis as a chronic maintenance therapy for end-stage renal disease (ESRD) started in the early 1960s with groups in Boston, London, Seattle and Hokkaidō providing 8–12 hours of dialysis two to three times/week. These patients were dialysed at home and perceived fewer restrictions on their daily lives with liberalisation of fluid and dietary restrictions compared to non-dialysed patients. In 1962, Scribner started the world's first outpatient dialysis facility in Seattle. As news of the successful dialysis programs spread, very quickly demand exceeded capacity necessitating difficult decisions about patient selection. Consequently, numerous dialysis centres were established in the 1970s and 1980s. Home haemodialysis (HHD) declined, owing to the significant burden reported by families and the difficulties with practicalities and resource commitments that were arising from managing both a home program and an in-centre unit. With improving survival data of in-centre patients, questions arose about the benefit of prolonged dialysis sessions, which resulted in in-centre, 4 hours, three times per week, 'conventional' dialysis prescriptions in parallel with a consensus on defining 'adequate' dialysis through blood urea purification, namely, Kt/V_{urea}. In spite of this trend, some groups continued to deliver extended HD regimens and demonstrated improved outcome [1].

In the 1990s, there was a renewed interest in HHD prescriptions, predominantly driven by an operational need to meet the rising demand for dialysis with a fixed in-centre capacity and the option of intensifying HD with low psychosocial patent burden seen with prolonged in-centre HD times. As this dialysis cohort started to grow, the collective narrative from these patient series also triggered a desire to understand and build an evidence base on the potential health and psychosocial benefits of HHD prescriptions.

Rationale for Augmented Home HD

Dialysis is a life-saving procedure, but the inherent limited purification and buffering capacity remains a major risk factor for morbidity and mortality in children and adults. The USRDS Registry data for patients on conventional HD with datasets up to 2003 indicated that the lifespan of a child on dialysis was 40–60 years less than the general population whilst that of a paediatric transplant recipient was 20–30 years less than the general population [2]. Thus, the effect of increasing dialysis

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dose has repeatedly been studied. In the HEMO trial, patients on a higher-dose HD with a urea-reduction ratio of 75.2%, i.e. a single pool Kt/V (spKt/V) of 1.71, experienced a minor mortality risk reduction only (relative risk 0.96) compared with standard dose HD (urea-reduction ratio of 66%, sp Kt/V of 1.32) [3]. On a secondary analysis, women on higher-dose dialysis had a significantly lower mortality risk. Wolfe et al. demonstrated that patients treated with URR >75% had a substantially lower relative risk of mortality than patients treated with URR 70 to 75% ($P < 0.005$ each, for medium and small BMI groups) [4]. According to the DOPPS review of 22,000 HD patients from seven countries, a higher Kt/V was an independent predictor of lower mortality with a synergistic survival advantage with treatment time. Survival was most pronounced by combining a higher Kt/V with longer treatment time. For every 30 minutes longer on HD, the relative risk of mortality was reduced by 7% [5]. An ANZDATA analysis of 4193 patients found that the optimal dialysis dose for survival was a Kt/V greater or equal to 1.3 and a dialysis session greater or equal to 4.5 hours. A duration less than 3.5 hours was associated with a higher mortality risk [6].

Targeting HD according to Kt/V does not take into account the removal of middle molecules or phosphate, pathogenic mediators of uraemic morbidity and mortality. For both, purification is poor with conventional dialysis. Middle molecules are more effectively removed by convective dialysis modalities such as haemodiafiltration (HDF), but in the absence of increased convection, increased time on HD is beneficial. Phosphate clearance is best achieved by increasing the total weekly dialysis time.

Traditionally, paediatric dialysis units have set maximum UF targets as a total UF volume per dialysis session, with ranges between 5% and 8% of the dry weight. However, tolerance of UF can vary between patients and amongst patients. Studies in adults have shown an association between UF rate and mortality. Movilli et al. demonstrated a critical safe point, with improved survival with UF rates less than 12.37 mls/kg/h [7]. Patients that frequently exhibit intradialytic hypotension are at a higher risk of mortality compared to those that experience no hypotension [8]. A higher UF rate places patients at higher risk of intradialytic hypotension and multi-organ ischaemia. The consequence of a high UF rate in the heart is myocardial ischaemia causing reversible, regional, left ventricular dysfunction, a phenomena called myocardial stunning which further aggravates intradialytic cardiovascular instability [9]. Regional myocardial dysfunction and ischaemia have been demonstrated in children during conventional HD prescriptions. The degree of myocardial dysfunction correlated with the UF rate and intradialytic blood pressure change [10]. In young children with a higher dependency on liquid feeds and in adolescents prone to non-adherence to salt and fluid restrictions, UF requirements can be particularly high. The impact of UF rate on outcome in children has not been systematically studied, but a negative impact is likely and thus low UF rates are advised. Setting an upper UF rate limit of 12 mls/kg/h will necessitate longer or more frequent dialysis sessions in oligo-anuric paediatric patients.

Taken together, current evidence suggests that HD outcomes can be improved in children and adults through longer dialysis sessions that deliver a larger dose whilst reducing UF rates and maintaining intradialytic blood pressures.

Home HD Prescriptions

Dialysis in the home creates an opportunity for delivering augmented dialysis treatments, prescribed as an intended weekly dose. Then, in partnership with the patient and their carers, a realistic goal for each individual dialysis session within the week can be formulated. As a general rule, the paediatric dialysis community would consider ‘conventional HD’ as up to 5 hours of dialysis three times per week. A weekly dialysis prescription that comprises more than 15 hours falls under the remit of ‘intensified’ or ‘augmented’ HD. The augmented HD regimens are further classified according to their duration

(treatment hours per session), frequency (alternate days or four to seven times per week), their location (in-centre or at home) and timing (daytime or nocturnal).

There is no doubt that augmented prescriptions translate to patients needing to spend more time per week on dialysis. However, by delivering this at home, with parents or carers being trained to deliver the dialysis, a degree of flexibility is allowed around when the dialysis takes place. In addition, it removes the need to travel to hospital several times per week and offers families the opportunity to establish new routines both for the patient, such as returning to school, and also for the entire family. This helps restore the balance between benefit and burden of augmented HD.

Over the years several hybrids of HHD prescriptions have emerged. We have summarised the potential gains and considerations of some of the most commonly adopted prescriptions in Table 23.1.

Table 23.1 Essential considerations of different intensified HD prescriptions in children [11]

Prescription	Session duration [hours]	Sessions per week	Patient or family considerations	Prescription considerations
Short daily	2–3	6–7	Helpful for working/busy parents with a limited window for dialysing Best for young children who cannot tolerate long sessions Higher frequency best for children unable to tolerate aggressive UF or poorly adherent to fluid restrictions	Most expensive due to higher dialysis consumables cost Dialysis and blood flow typically unchanged from conventional HD Seldom allows discontinuation of phosphate binders Improved BP control, lower antihypertensive requirement
Extended	4.5–5.5	≥Alternate days	Alternate-day therapy offers greater respite time for the caregiver Teenagers become increasingly frustrated sacrificing their evenings and social events to HD	Dialysis and blood flow rates typically 20–30% lower than conventional prescriptions Often allows liberalisation of dietary and fluid restrictions Improved BP control, lower antihypertensive requirement
Nocturnal	7–12	≥Alternate days	Dialysing overnight can induce anxiety in caregivers and children from fear of disconnection or not hearing machine alarms Virtually eliminates adverse intradialytic symptoms Greatest chance of achieving complete freedom from dietary and fluid restrictions possible	Requires additional safety considerations Patients may develop persistently low BP. Clinicians may wish to consider prophylactic midodrine at the start of dialysis to support the BP for UF Dialyse against 1.75 mmol/L dialysate calcium to protect against a negative calcium balance Higher frequency nocturnal HD may cause hypophosphatemia Treat with oral supplements and/or add phosphate to the dialysate concentrate (such as a sodium phosphate enema preparation) Risk of dialysis-induced deficiencies. Some have advocated a daily dose of renal multivitamins

These considerations are based on expert personal opinion
BP blood pressure, *HD* haemodialysis, *UF* ultrafiltration

Setting Up a Paediatric Home HD Program

Patient Selection Criteria

The reasons for selecting a HHD treatment can be multiple, including medical, social, education or families exercising their rights to choose a unit where HHD is an option. At the earlier stages of a HHD program, it is advisable to set conservative selection criteria until the team's experiences and confidence grows. A suggested patient selection criteria are listed in Table 23.2, but the specifics should be determined in the planning stage of a home HD program by a multidisciplinary team.

With growing confidence and experiences, the team at Great Ormond Street Hospital has gradually moved away from a lengthy list of inclusion criteria to a few exclusion criteria that mainly comprise (i) a lack of a home or home base to accommodate the dialysis treatment and (ii) lack of commitment to deliver the agreed dialysis schedule reliably and consistently. Failed home PD does not necessarily preclude the possibility of HHD.

Table 23.2 Key selection criteria for paediatric home HD

Patient and family commitment to delivering the dialysis schedule consistently at home
Patient cut-off weight determined by home dialysis system
Well-functioning vascular access
Absence of or controlled psychosocial concerns
Sufficient room within the family home to accommodate the dialysis equipment and 1-month supply of dialysis consumables
If reverse osmosis dialysis system required, permission and ability to modify the home water source
Adequate family household hygiene that does not increase the patient's risk of infection
Family home is not located in an area with frequent and prolonged electricity supply disruptions or an emergency source of power is not available at all times
Patient is medically stable despite clinical manifestations of multi-disease or multi-organ involvement

Infrastructure

Developing a HHD program requires careful planning, resources, a commitment to safety and risk management and dedicated staff. The service delivery model can vary considerably and is largely influenced by four factors:

- Resources and existing expertise
  - Is the ambition to be fully independent or will a partnership with a neighbouring paediatric or adult service become necessary?
- Spectrum of dialysis prescriptions to be offered
  - Will routine prescriptions include daytime and nocturnal treatments?
  - How many sessions will be routinely prescribed per week?
- Preferred dialysis system
  - What home modifications will be required?
  - How familiar is the in-centre dialysis team with the home dialysis system?
  - Which dialysis consumables will be delivered to the home and how often?
  - How will the dialysis machines and dialysate system be serviced and maintained?
- Training patients and their carers
  - Will training take place on the dialysis unit or within a dedicated facility?
  - Is a training program available or will it need to be designed?

Finances and Business Case

A dialysis team wishing to develop a program will need to prepare a robust business case for the hospital board or executive team. A key requirement of a business case is a risk-benefit analysis.

Geary et al. have explored the cost of delivering HHD in children and reported a 27% saving after comparing the cost of delivering a HD treatment at home compared to a dialysis unit [12]. Cost saving was largely from removing the cost of the hospital bed and dialysis staff. The latter is particularly relevant in paediatrics owing to the recommended 1:1 or 1:2 nurse-to-patient ratio when delivering HD treatments in hospital. To

establish the potential cost savings for a HHD program, each unit needs to predict the projected size of the program and multiply that by an accurate cost-saving calculation when patients transition home. This financial 'gain' must then be offset against the cost pressures of delivering a home HD program. These include:

- Staffing the multidisciplinary team required to deliver the program
- Lease, rental or purchase of dialysis machines alongside service and maintenance costs
- Home conversions or modifications to accommodate the dialysis systems
- Dialysis consumables and drugs cost which will be proportionally higher as the prescribed weekly treatment frequency often increases
- Establishing and maintaining a training facility
- The resultant and unintended bed vacancies as in-centre patients transition home

In adult programs the potential savings from a home dialysis program can be significant as the HD patient pool may be in the hundreds and thousands. In comparison the size of paediatric HD programs typically range from 4 to 25 patients. Thus, the potential cost benefit of a paediatric HHD program will depend on the number of children that transition home and in real terms will be small. In comparison, the financial risk and investment to establish a HHD program is significant and probably higher than adult programs owing to the larger multidisciplinary team requirement. Thus, in the first few years the financial risk to benefit analysis of a paediatric HHD program will feature risk dominance as the program attempts to establish itself and gain momentum. Further difficulties of convincing policy makers and insurance companies may arise from the fact that for the majority of children HD is a short-term bridging therapy to transplantation. It is estimated that HHD with a home conversion only becomes more cost-effective than in-centre HD when patients remain on treatment for more than 14 months [13]. In Europe median waiting time for deceased donor kidney transplantation in Europe is still about 15 months [14].

If one was to broaden the financial case of paediatric HHD to the health economics related to the life of a patient, the narrative should be more favourable. Children on HHD should typically have improved health outcomes and thus a lower medical burden. Access to school and education has the potential to improve future career prospects and the subsequent financial contribution to society. Truth to be told, similar to many paediatric case studies, building a population-based financial case for HHD is challenging and less convincing than the emotive case around the potential gain for an individual child.

Safety

HHD in children remains a relatively new therapy that places a high-risk clinical procedure directly under the care of patients and their families within their homes. Therefore, safety should be the central focus point of any program design with mitigations in place to minimise the potential to cause harm. The greatest sources of risk fall under four broad categories.

Vascular Access

Children can be dialysed at home through a central venous line or preferably an arteriovenous fistula (AVF). Whilst training for home dialysis, families need to develop an understanding of the common complications related to the vascular access and the appropriate response. Central line malfunction and infection risk are attenuated with weekly alteplase locks [15]. At minimum, weekly dressing changes are recommended with monthly surveillance for exit site infections. Patients with fistulae are advised to check them at minimum daily. For buttonhole needling, we encourage needling by the same person, to promote good health of the fistula. At Great Ormond Street Hospital, where possible we actively promote older children or young adults to become the primary person who needles their fistulae. Any major change in blood flow rates and system pressures should be reported to the centre. We suggest functional ultrasound surveillance of the

fistulae every 3 months for early and timely detection of issues.

Anticoagulation

Clotting in an HD circuit can affect the quality and quantity of dialysis provided. Children at home can use unfractionated heparin (UFH), often as an initial bolus dose and then a continuous infusion [16] in line with in-centre prescribing practices. Alternatively, a low-molecular-weight heparin (LMWH) can be prescribed. Lutkin et al. have reported their experience using dalteparin, a LMWH, for children on home HD. Each child was started on a single intravenous dose of 50 IU/kg through the arterial arm of the dialysis circuit within 15 minutes of the treatment starting. The dose was increased if clots were repeatedly visible in the circuit and dialyser and reduced if there was any evidence of bleeding events or prolonged bleeding from an AVF in children dialysed in this way. The dalteparin dose was routinely increased if a child was moving from daytime to nocturnal home HD. The median dalteparin dose at 12-month follow-up was 40 IU/kg (range 8–142 IU/kg). Factors associated with higher dalteparin dosing requirements included a younger age of the child ($p < 0.01$), a lower blood flow rate ($p < 0.01$) and the use of a central venous line for dialysis access ($p = 0.038$). No children had evidence of bioaccumulation of dalteparin or inadequate clearance. No significant bleeding or adverse events were reported [17]. Therefore, for children on augmented HHD prescriptions, both UFH and LMWH are feasible options.

Family Centric Remote Monitoring and Support

The motivation to dialyse at home will differ amongst families as will the perceived risks and sources of stress. In the 1970s paediatric HHD was replaced by in-centre dialysis largely due to carer burden. Families reported feeling lonely and struggling to cope with the medical and technical responsibilities [18]. This is not too dissimilar today. Therefore, it is absolutely essential to be proactive in creating an individualised risk management and support system for all families dialysing at home to minimise their perceived carer burden as much as possible whilst maximising the family's positive experiences of dialysing at home. The key components of this are:

- A home assessment prior to committing to a home therapy to assess the suitability of the home environment for dialysis and to align child and family expectations of HHD.
- Access to clinical and technical support 24/7, especially if families are dialysing in the evenings after school or overnight.
- Written guidelines for the family describing normal ranges for dialysis parameters including BP, HR, temperature, UF rates and venous pressures, with clear instructions on how and when to seek help if parameters fall out of the normal range.

Remote monitoring is not universally employed, but if available can alleviate family anxieties. A growing plethora of telehealth platforms is making it feasible for the exchange of treatment data real time between families and their medical teams. This is another source of reassurance that also provides the opportunity for the medical team to intervene earlier and make adjustments to treatments outside the hospital clinic reviews. Currently haemodialysis machines are not equipped with digital telecommunication devices. Internet-based online functions may be applied, but require careful consideration of reliability and data safety. *For further detail, please refer to the Chap. 18 on Remote Patient Monitoring.*

Dialysing overnight introduces additional risks and induces anxiety both in caregivers and children due to the potential risk of needle dislocation with AV fistulas and AV grafts, central line disconnection or not hearing machine alarms whilst everybody is sleeping. It is recommended to address these additional measures. In our experience at Great Ormond Street Hospital, a simple and familiar device such as a baby monitor can be a useful strategy to amplify the sound of the alarms overnight. Monitoring for

access-related blood leaks is essential and can be effectively achieved through enuresis alarm pads; more sophisticated monitors such as HEMOdialert™ that are sensitive to fluid and the colour red are now available. For the NxStage™ system, a cycler base fluid detector is available to detect any circuit water leaks.

Effective Training and Education Program

Training programs can vary considerably between teams and are important for aligning expectations. Ideally it is advisable to train two people from the outset and involve the child or adolescent as much as age appropriate. Families should be offered repeated opportunities to enhance their knowledge and skills once they are home especially following (1) an adverse event such as a central line infection, (2) a change in treatment or (3) a change in dialysis access such as switching from central lines to fistulae.

Companies supplying the dialysis equipment often provide considerable teaching materials and expertise. However, in paediatrics adaptation is often necessary. To ensure families have totally understood the content, a trainee's competency should be formally assessed and signed off both by the trainee and trainer. Prior to discharge an adherence contact signed by the child and their carers can be extremely important at formalising and thus reinforcing the decision taken by the medical team and family to delegate responsibility for providing the dialysis treatment to the family within their home; any deviation will be taken very seriously.

Training can take place in the HD unit or within a separate training facility. Ideally, prior to going home, families should have the option to 'step down' within an environment co-located within hospital grounds but separate from the dialysis unit, in order to simulate the home environment as much as possible. Following discharge, it is advisable for one of the HHD nurses to be present for the first dialysis treatment in the patient's home. This provides reassurance and also provides the opportunity to coordinate and connect the family with their community teams. Regular, four to six weekly outpatient visits are recommended for detailed history, physical examination and biochemical work-up.

Staffing

In order to provide safe, effective care, a HHD program needs to be staffed by a skilled multidisciplinary team. The composition of the team can vary depending on resources and whether you are operationally independent. At minimum access to or recruitment of a HD nurse, nephrologist, dietician, dialysis technician, pharmacist and social worker is necessary. Collaborating with other allied health professionals such as a psychologist, community nurses, local paediatricians and general practitioners is desirable for optimal support.

Families at home will be expected to communicate with a number of professionals, but to ensure their safety and trust, clear communication pathways need to be developed and explicitly laid out to the families. It is important to establish a reliable communication channel between the core HHD team and the families for assurance that all is well. As families become more confident at home, communication with the hospital team can become less frequent, but it is important to invest in maintaining that contact.

Dialysis Equipment

Dialysis Systems Requiring Home Water Conversions

The majority of commercially available HD machines that are suitable for paediatric HHD require home water conversions to produce the large volumes of high-quality dialysate necessary for the dialysis treatment. This cost can sometimes become a barrier for transitioning children to HHD, especially when it is a bridging therapy for a renal transplant. Water conversions can also be a source of additional work and anxiety for families as complications such as leaks and blocked drains can occur and need to be addressed as a matter of urgency. Dialysate fluid needs to be tested on a regular basis.

Water conversion requires the installation of a cold water outlet and a drain to allow the carbon filter, reverse osmosis unit and dialysis machine to be fitted.

- A system for testing the water quality needs to be put in place.
- Typically, families test their water for chloride every session.
- In addition, they bring a sample for advanced testing to their monthly hospital clinic visit. The dialysis technician will test for chemicals, endotoxins and microbiology.

Mobile HD System: NxStage™

The NxStage System One™ is a portable home dialysis machine that functions without home water modifications. Dialysate is prepared from ordinary tap water in batches of up to 60 litres using the NxStage PureFlow™ SL integrated water purification and dialysate production system. Water is mixed with sterile-filtered concentrate, to produce lactate-buffered dialysate. Premixed bagged dialysate is also available for home patients in sterile, 5 L bags, with a variety of fluid configurations.

- Three different NxStage™ circuits have been used at Great Ormond Street London: CAR-172-C is the standard circuit with a pre-attached polysulfone dialyser. The extracorporeal circuit volume is 163 mls.
- CAR-124-C, a modified CVVH circuit with an extracorporeal volume of 97 mls (minus dialyser) that can house any appropriately sized dialyser.
- CAR-125-B, with an extracorporeal circuit volume minus the dialyser of 55 mls to treat children weighing 10 kg and above.

Prescribing dialysis treatment using the NxStage™ system is different from standard HD prescriptions with respect to the volume of dialysate utilised during each dialysis session. In conventional HD dialysate, volumes of 200–500 mls/minute are typically prescribed. In comparison, during treatment with the NxStage™ system, dialysate volumes are typically less than 60 litres per session and thus the spent dialysate is highly saturated. The prescribed dose is altered by adjusting the 'flow fraction' which is the ratio of effluent flow (spent dialysate plus ultrafiltration) divided by blood flow rate and corresponds to the degree of dialysate saturation. Compared to the more conventional machines that are also used in centre, the NxStage™ system offers some advantages in the home setting. It takes 30–40 minutes to set up from start to finish, with the option to partially set up the machine for convenience. Owing to the freedom from home conversions, families are mobile and thus able to transport the dialysis machine and consumables between family homes and on holiday. The machine has been designed to be used by patients; whilst its simplicity means that additional technical capabilities are absent, in the home environment in the hands of patients this can be an advantage.

Adult Home HD Experience

Experience with HHD is substantially greater in adults. Data on clinical outcomes and patient experiences amongst adults is increasing. We can learn from this experience as we build our paediatric experience.

Adults on augmented home dialysis regimes have demonstrated several health benefits, and the effect is the most pronounced with nocturnal prescriptions. Patients switching to short-daily 33% survived at 6 years and demonstrated reduced hospitalisation [19], fewer vascular access problems, reduced antihypertensive medication burden, lower incidence of left ventricular hypertrophy, improved anaemia control and a reduction in the use of phosphate binders as a consequence of the improved phosphorus clearance [20]. Nocturnal HD is associated with significant reduction in the risk for mortality or major morbid events when compared to conventional HD. During a matched cohort study comparing survival between nocturnal HHD and deceased and living donor kidney transplantation, there was no difference in the adjusted survival between nocturnal HHD and deceased donor renal transplantation. The proportion of

deaths amongst the three was 14.7% for nocturnal HHD, 14.3% for deceased donor transplantation and 8.5% for live donor transplantation [21]. This is very reassuring for patients who are not eligible for transplantation or those waiting for a transplant.

On a more granular level, patients on nocturnal HHD demonstrate improved cardiovascular outcomes with superior blood pressure control; regression of left ventricular hypertrophy, improvement in left ventricular systolic function and ejection fraction; an overall improvement in haemodynamic status; a more responsive endothelial-mediated vasodilation; an improvement in lower extremity peripheral arterial disease [22, 23]; and a slowing in the rate of calcification progression [24]. Potential biochemical benefits include normalisation of the blood urea, serum creatinine, albumin, B2 microglobulin, homocysteine and triglyceride levels and other nutritional markers. Patients have a lower medication burden with a reduced dependency on antihypertensives, freedom from phosphate binders, reduced iron supplementation [22] and a lower dose and occasionally discontinuation of erythropoietin [25]. Quality of life is improved owing to removal of fluid and dietary restrictions, the capacity for full-time employment and for women the ability to become pregnant and deliver healthy babies. Despite receiving treatment overnight, patients report an improved quality of life and sleep patterns and a resolution of sleep apnoea [22]. In a comparison with peritoneal dialysis, patients reported a similar perception of control over their kidney disease and did not consider home HD as a more intrusive treatment [26].

Despite the positive narrative, a number of concerns remain. Firstly, dialysis equates to the non-selective, measured and unmeasured removal of solutes, minerals and trace elements from the blood compartment. Thus, unknowingly or unintentionally dialysis may cause deficiencies, the so-called dialysis deficiency syndrome. This has already received the attention of dieticians supporting vulnerable groups such as pregnant women and children. Secondly, owing to the increased requirement for needling fistulae or accessing central lines during augmented HD prescriptions, there have been concerns that both the frequency and the home setting may cause additional access-related complications. The results however are conflicting, and causality to the home setting is difficult to prove, as both frequency and expertise are likely to be confounders applicable to the home and hospital setting. Finally, concerns remain over the burden placed on carers for patients dialysing at home. Reports have repeatedly highlighted the cognitive burden carers perceive from taking on the responsibility for a complex treatment normally delivered by nurses and doctors in hospital on their loved ones. This concern is real and cannot be obliterated, but steps can be taken to both monitor and reduce the cumulative impact. Successful interventions include respite care or spreading the burden by training multiple people to deliver the treatment at home.

Paediatric Home HD Experience

Literature on paediatric home HD is scarce and limited to experiences from a handful of specialist centres worldwide. Reassuringly the results are similar to the larger adult literature.

Simonsen et al. were the first to describe their experience of HHD in four children, age 10–19 years, who were treated with slow nocturnal HD for 7–8 hours, six nights each week, for a period of 5–55 months. Achieving a weekly Kt/V of 7.2–13.6, these children had no fluid or dietary restrictions, but actually required phosphate supplements orally to avoid hypophosphatemia. Catch-up growth was achieved and quality of life improved markedly [27].

Geary et al. reported on six patients on nocturnal HHD aged 11–17 years. The first two patients were transitioned to an augmented home program after all previous dialysis options had failed. The following four patients had requested HHD. One patient switched to a hybrid program comprised of three consecutive days of home nocturnal HD combined with one in-centre 4-hour HD session per week after 1 year of dialysing exclusively at home. No dropouts from the

program or patient deaths were reported. One patient developed a fistula aneurysm in the absence of steal syndrome, but no line disconnections were reported [28]. Measured subjectively, appetite improved in all patients. One patient converted from being completely G-tube dependent to increasing her oral intake to 50% of her dietary requirements. Blood pressure control was variable with two patients who had native kidneys still requiring antihypertensives, whilst three anephric patients became hypotensive requiring intradialytic midodrine to support their BP. All patients were free from fluid and dietary restrictions, and phosphate binders were discontinued. Normal calcium and phosphate levels were achieved by increasing the dialysate calcium to 1.75 mmol/L (3.5 mEq/L) and through the addition of approximately 1 mmol/L (3 mg/dL) of phosphate to the acid bath using a Fleet®'s enema. PTH values fell within or below the normal range [29]. School attendance improved substantially in all children. Physical and psychological HRQoL scores improved in all patients in addition to a general feeling of well-being. However, the parents' feedback did highlight the burden they perceived in undertaking HD at home. They reflected on the increased intensity of their workload that initially disrupted other family members and necessitated establishing a new routine within the home. The impact of the additional responsibilities evoked anxiety. The mother of one patient was psychologically and emotionally worn out after 1 year and moved to a hybrid program when her son refused to revert back to in-centre dialysis [28].

The paediatric HHD program at Great Ormond Street Hospital (GOSH) started in October 2010 and to date has trained and transitioned 40 patients home, aged from 2 to 17 years. Children typically start on a weekly program of 5 hours of dialysis, four times/week in the evenings, except for infants who start on 4 hours, four times/week owing to the challenges of keeping them entertained during longer sessions. The weekly program is then adapted according to individual needs. Aside from the infants and younger children, most patients transition to a nocturnal program. The only patients receiving five or more times per week dialysis are children with co-existing heart failure or at high risk of cardiac failure where we have attempted to modify the dialysis prescription to minimise intradialytic cardiac injury. In one patient with severe dilated biventricular cardiomyopathy, the heart was functionally and structurally normal following 3 months of 25–30 hours per week HD followed by 3 months of 40–48 hours per week of home HD, despite almost 1 year of receiving frequent and extended in-centre HD previously [30]. Only one patient has dropped out of the program secondary to rising psychosocial issues, whilst the remaining patients left the program after receiving a renal transplant. The GOSH experience with vascular access certainly is reassuring with a central line-related bacteremia event rate of 0.3 per 1000 patient days, whilst IPHN reported a CVL infection rate of 1.3 per 1000 days for those on in-centre dialysis. Similar to the adult and previously described paediatric experiences, the patients on HHD have better BP control, reduced or no dependency on antihypertensives and resolution of left ventricular hypertrophy. No patient from the GOSH cohort has required intradialytic midodrine to support their BP during dialysis.

Maintaining bone health across the cohort has been more challenging. During periods of accelerated growth such as infancy and puberty, patients have required oral calcium supplementation, a higher calcium dialysate bath of 1.75 mmol/l and higher doses of vitamin D to maintain normal plasma calcium, phosphate, PTH and alkaline phosphatase levels. All patients have reported more energy, some have an improved appetite and oral intake and we have observed an increased growth velocity and catch-up growth in those started on growth hormone. As the weekly hours of dialysis increase, the fluid and dietary restrictions are incrementally lifted. The extended and thus gentler dialysis sessions have resulted in virtually eliminating intradialytic symptoms, and the dialysis recovery time is reduced from hours to minutes.

The carer burden of HHD is a constant presence for all our families treated at GOSH, but the benefits afforded by HHD have almost made it an accepted and tolerable norm that the families are

not willing to give up. The flexibility of home treatments means that parents can return to work and children can return to school. This has increased the opportunities for social and recreational activities for the whole family. Children at GOSH are dialysed on the NxStage™ dialysis system, and, as a result, families are travelling within the UK or abroad on holiday. This ability to travel has been a huge factor in recruiting families to HHD. Adverse events are inevitable and reassuringly infrequent, with 16 events recorded from 11762 HD sessions. These include line dislodgement, extravasation from needling a fistula, prolonged bleeding times after removing fistula needles, allergic reactions, access-related bacteremia and thrombophlebitis and suspected air embolus from incompetent tego bung valves. Each has become a learning experience for the program, and we continue to reform our safety infrastructure to ensure that families do not feel isolated or unsupported but are constantly connected to a larger home HD community and the hospital.

Summary

HHD is slowly gaining momentum, driven by individual patient requests and clinicians who believe in the benefits of augmented HD prescriptions within the home setting. The evidence from adult and paediatric literature demonstrates the feasibility, safety and improved quality of care and outcomes for patients on dialysis. However, access and acceptance of HHD varies internationally. Thus, most children are still living their lives around their dialysis as opposed to dialysing around their lives. This in the very least deserves a call for action. Regardless of the modality, as a paediatric community we need to actively promote and support home dialysis therapies in children. Through clinical communities of practice, we can provide mentorship and support to those wishing to start their journey on paediatric HHD. For those who remain sceptical, in order to further understand the value and limitations of HHD treatments, we need greater commitment to organise ourselves into collaboratives such as the International Pediatric Dialysis Network, to advance our practices through benchmarking, and increase our knowledge by determining trends and patterns that inform future practice and encouraging research including multicentre, international studies.

References

1. Buoncristiani U, Quintaliani G, Cozzari M, Giombini L, Ragaiolo M. Daily dialysis: long-term clinical metabolic results. Kidney Int Suppl. 1988;24:S137–40.
2. US Renal Data System: USRDS (2003) Annual Report. Bethesda, The National Institute of Diabetes and Digestive and Kidney Diseases. 2003.
3. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R, Haemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance Haemodialysis. N Engl J Med. 2002;347:2010–9.
4. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA. Dialysis dose and body mass index are strongly associated with survival in Haemodialysis patients. J Am Soc Nephrol. 2002;13:1061–6.
5. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, Kimata N, Gillespie BW, Combe C, Bommer J, Akiba T, Mapes DL, Young EW, Port FK. Longer treatment time and slower ultrafiltration in Haemodialysis: associations with reduced mortality in the DOPPS. Kidney Int. 2006;69:1222–8.
6. Marshall MR, Byrne BG, Kerr PG, McDonald SP. Associations of Haemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int. 2006;69:1229–36.
7. Movilli E, Gaggia P, Zubani R, Camerini C, Vizzardi V, Parrinello G, Savoldi S, Fischer MS, Londrino F, Cancarini G. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant. 2007;22(12):3547–52.
8. Chou JA, Streja E, Nguyen DV, Rhee CM, Obi Y, Inrig JK, Amin A, Kovesdy CP, Sim JJ, Kalantar-Zadeh K. Intradialytic hypotension, blood pressure changes and mortality risk in incident Haemodialysis patients. Nephrol Dial Transplant. 2018;33(1):149–59.
9. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Haemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4(12):1925–31.
10. Hothi DK, Rees L, Marek J, Burton J, McIntyre CW. Pediatric myocardial stunning underscores the

cardiac toxicity of conventional Haemodialysis treatments. Clin J Am Soc Nephrol. 2009;4(4):790–7.
11. Hothi D, Sinnott K, Stronach L. Home Haemodialysis in children. Hemodial Int. 2016;20(3):349–57.
12. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, Harvey EA. Home nocturnal Haemodialysis in children. J Pediatr. 2005;147:383–7.
13. Mackenzie P, Mactier RA. Home haemodialysis in the 1990's. Nephrol Dial Transplant. 1998;13:1944–8.
14. Hogan J, Couchoud C, Bonthuis M, Groothoff JW, Jager KJ, Schaefer F, Van Stralen KJ, ESPN/ERA-EDTA Registry. Gender disparities in access to pediatric renal transplantation in Europe: data from the ESPN/ERA-EDTA Registry. Am J Transplant. 2016;16(7):2097–105.
15. Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, LeBlanc M, Faris P, Barre P, Zhang J, Scott-Douglas N, for the Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin (PreCLOT) Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med. 2011;364:303–12.
16. Sagedal S, Hartmann A, Sundstrom S, et al. A single dose of dalteparin effectively prevents clotting during haemodialysis. Nephrol Dial Transplant. 1999;14:1943–7.
17. Lutkin M, Stronach L, Yadav P, Hothi DK. Dalteparin anticoagulation in paediatric home haemodialysis. Pediatr Nephrol. 2018;33(12):2337–41.
18. Reichwald-Klugger E, Tieben-Heibert A, Korn R, Stein L, Weck K, Maiwald G, Mehls O, Diekmann L, Müller-Wiefel DE, Jochmus I. Psychosocial adaptation of children and their parents to hospital and home Haemodialysis. Int J Pediatr Nephrol. 1984;5(1):45–52.
19. Ting GO, Kjellstrand C, Freitas T, Carrie BJ, Zarghamee S. Long-term study of high-comorbidity ESRD patients converted from conventional to short daily Haemodialysis. Am J Kidney Dis. 2003;42:1020–35.
20. Puñal J, Lema LV, Sanhez-Guisande D, Ruano-Ravina A. Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: a systematic review. Nephrol Dial Transplant. 2008;23:2634–46.
21. Pauly RP, Gill JS, Rose CL, Asad RA, Chery A, Pierratos A, Chan CT. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. Nephrol Dial Transplant. 2009;24:2915–9.
22. Agar J. Nocturnal haemodialysis in Australasia. Nephrology. 2005;10:222–30.
23. Bergman A, Fenton SS, Richardson RM, Chan CT. Reduction in cardiovascular related hospitalization with nocturnal home Haemodialysis. Clin Nephrol. 2008;69(1):33–9.
24. Yuen D, Pierratos A, Richardson RMA, Chan CT. The natural history of coronary calcification progression in a cohort of nocturnal haemodialysis patients. Nephrol Dial Transplant. 2006;21(5):1407–12.
25. Chan CT, Liu PP, Arab S, Jamal N, Messner HA. Nocturnal Haemodialysis improves erythropoietin responsiveness and growth of hematopoietic stem cells. J Am Soc Nephrol. 2009;20(3):665–71.
26. Fong E, Bargman JM, Chan CT. Cross-sectional comparison of quality of life and illness intrusiveness in patients who are treated with nocturnal home Haemodialysis versus peritoneal dialysis. Clin J Am Soc Nephrol. 2007;2:1195–200.
27. Simonsen O. Slow nocturnal dialysis as a rescue treatment for children and young patients with end-stage renal failure. J Am Soc Nephrol. 2000;11:327A.
28. Geary DF, Piva E, Gajaria M, Tyrrel J, Picone G, Harvey E. Development of a nocturnal home haemodialysis (NHHD) program for children. Semin Dial. 2004;17(2):115–7.
29. Hothi DK, Piva E, Keating L, Secker D, Harvey E, Geary D. Calcium and phosphate balance in children on home nocturnal hHaemodialysis. Pediatr Nephrol. 2006;21:835–41.
30. Melhem NZ, Yadav P, Stronach L, Hothi DK. Intensified home haemodialysis for managing severe cardiac failure. Pediatr Nephrol. 2015;30(3):533–6.

24 Infectious Complications of Hemodialysis in Children

Ali Mirza Onder and Michael J. G. Somers

Hemodialysis Access in Children

Practice guidelines strongly recommend the use of an arteriovenous fistula (AVF) or an arteriovenous graft (AVG) for chronic dialysis access [1]. Despite such recommendations, tunneled cuffed catheters (TCC) remain a common choice for dialysis access in children [2, 3]. Although AVFs can be successfully created and maintained in almost all children needing chronic hemodialysis, local dialysis culture and the acceptance of a dialysis catheter as typical care lead to long-term catheter rates exceeding 50% in many pediatric centers [3, 4].

HD Catheters and Infection: Greater Risks with Children

Infection is second only to cardiovascular disease as a cause of death in chronic dialysis patients [5–8]. Sepsis and septic shock account for the overwhelming majority of infection-associated HD deaths [9–12]. Presence of an HD catheter is the most important risk factor for bacteremia, septic shock, and hospitalization due to infection [13, 14].

With the high prevalence of long-term tunneled cuffed catheters in children on HD, the scope of concern for catheter-related bloodstream infections (CRBSI) is greater in the pediatric dialysis unit. Moreover, cognitive and behavioral differences between an adult and pediatric population may also exacerbate catheter-related infection risk in children, with some reports documenting how pediatric HD patients are more likely to expose catheter exit sites or catheter hubs outside of the dialysis unit [15–19].

Changes in the configuration and composition of long-term HD catheters have been proposed as ways to reduce infection rates. Unlike acute HD catheters that are typically made of stiffer materials, uncuffed, and placed in an untunneled fashion with an insertion site in close proximity to the vessel lumen, long-term HD catheters tend to be made of more pliable material, are cuffed, and are placed in a tunneled fashion. Since these "permanent" HD catheters benefit from both the physical barrier that the cuffs provide between the exit site and the more distal catheter and the distance the tunnel provides between the exit site and the catheter insertion site into the vessel, they should help to reduce dialysis catheter-related infections [20].

Despite such strategies related to the actual physical characteristics of the HD catheter, the incidence of BSI with a hemodialysis catheter remains significantly higher than with AVF or

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AVG dialysis access [13, 14, 18, 21]. Accordingly, there is increased focus on preventive strategies to reduce CRBSI for both adults and children receiving HD [19, 22]. For example, in the US catheter-related infection is the focus of the Choosing Dialysis Wisely initiatives by the Centers for Disease Control and Prevention as well as several national quality improvement initiatives such as the Standardizing Care for Outcomes in Pediatric Dialysis (SCOPE) consortium.

Given that many children on chronic HD will have a catheter as dialysis access, the focus of this chapter will be on infections related to the dialysis catheter and most notably catheter-related bloodstream infections (CRBSI). These infections are most commonly encountered in children on hemodialysis and are the most significant potentially modifiable cause of morbidity and mortality. Additionally, catheter infections increase the likelihood that a catheter may need to be replaced, and infected catheters tend to have shorter overall survival times than uninfected catheters, leading to more access-related procedures and potential adverse effects on long-term vascular access (Fig. 24.1).

Catheter-Related Bloodstream Infections

Incidence and Epidemiology of CRBSI

There is noteworthy variability in CRBSI rates in children on HD, ranging from 1.2 to 5.7 episodes/1000 HD catheter days [2, 6, 7, 19, 23–26], but consistently higher than the CRBSI rates typically reported in adult HD [5, 12, 14]. Many pediatric reports come from single centers, and unique aspects of particular pediatric HD patient

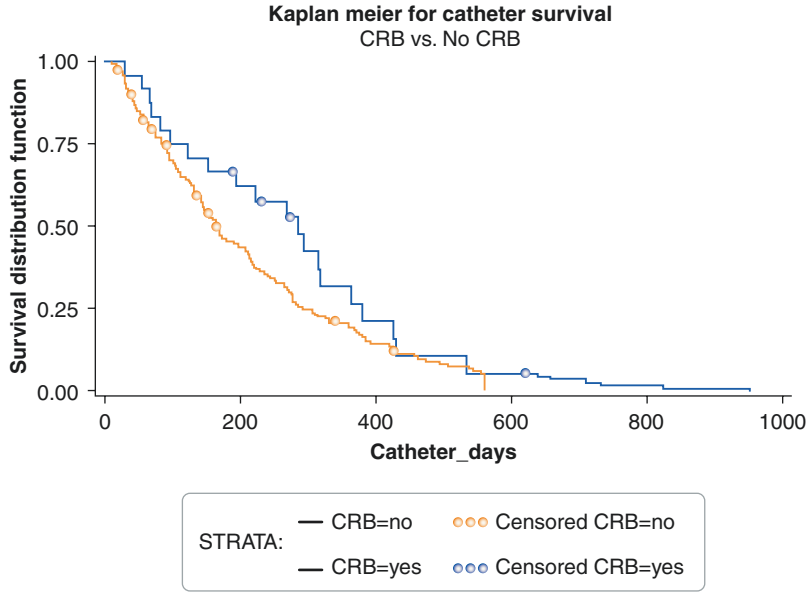


Fig. 24.1 Hemodialysis catheter survival and CRBSI. Hemodialysis catheters with no documented CRBSI in a pediatric dialysis unit trended toward longer overall catheter survival when compared to catheters with at least one documented infection ($p = 0.1042$ by Wilcoxon test). The curve on the left represents catheters with infections, with 50% of these catheters lost by 200 days after placement, compared to catheters on the right that were uninfected, with 50% catheter loss being reached several months later. All catheter infections were treated with antibiotic locks (ABL) and systemic antibiotics. Subjects with recurrent or life-threatening infections were treated with prophylactic ABL. Removal of the catheter was at discretion of the treating physician. (Modified from: Onder et al. [106])

populations, catheter care protocols, or local infection treatment or prevention strategies make generalization of findings difficult.

Additionally, when assessing published rates, it is important to be aware of the variability that also exists in the time span used to report CRBSI rates. Although CRBSI rates are often provided as number of infection episodes per 1000 HD catheter days, there are also reports using CRBSI episodes per 100 patient months. Since 100 months is nearly equivalent to 3000 days, a factor of three can be used to convert between these rates.

Experience also seems to suggest that CRBSI rates in pediatric HD patients can be reduced effectively with strict attention to catheter care. Eisenstein et al. showed that a standardized catheter care protocol in a single center resulted in a low CRBSI rate of 0.52 episodes/1000 HD catheter days [23]. More recently, the SCOPE consortium demonstrated a reduction from 1.1 episodes/1000 HD catheter days to 0.26 episodes/1000 HD catheter days with implementation of a standardized HD catheter care bundle across 15 pediatric dialysis units [27].

In most series of pediatric CRBSI, gram-positive microorganisms constitute up to 70% of episodes [6, 7]. *Staphylococcus epidermidis* or another coagulase-negative staphylococcus is the most frequent infecting microorganism, with *Staphylococcus aureus* also being common [6, 28–30]. *Enterococcus* is a less common gram-positive isolate. Over time, an increasing portion of gram-positive isolates from CRBSI have shown resistance to oxacillin and methicillin, up to 40% for *Staphylococcus aureus* and up to 50–75% for coagulase-negative *Staphylococcus* species [29, 31, 32]. Similarly, rates of vancomycin or gentamicin resistance for *Enterococcus* have also been increasing [29, 32, 33].

Gram-negative microorganisms make up 15–25% of CRBSI in children, with another 10–15% accounted for by polymicrobial bacteremia. Tobramycin resistance is seen in up to a quarter of gram-negative isolates but can be as high as 50–75% for polymicrobial infections. There are also increasing reports of CRBSI secondary to expanded spectrum beta-lactamase-producing bacteria [29, 32]. CRBSI secondary to fungal infections is rare in pediatric HD patients, ranging from 0% to 3% in most series, and fungal infections are generally a *Candida* isolate.

For clinicians caring for children on HD, familiarity with local infection profiles and local rates of antibiotic resistance should help inform empiric treatment. Increasing rates of antibiotic resistance also underscore the importance of collaboration between dialysis facilities and infection prevention programs and consideration of the strategies outlined in antibiotic stewardship guidelines and policies.

Pathogenesis and Risk Factors for CRBSI

Although risk of CRBSI increases with duration of HD catheter use [34], protocols designed to decrease CRBSI in both children and adults most often focus on appropriate insertion and initial handling of the catheter, attention to aseptic technique when accessing or de-accessing catheters, and exit site care [23, 27, 35]. Guidelines such as those published under the auspices of the Centers for Disease Control and Prevention (CDC), the Kidney Disease Outcomes Quality Initiative (KDOQI), and the American Society of Nephrology (ASN) are aimed at optimizing the infection-free use of a catheter for chronic HD, with the understanding that AVF or AVG creation is still the better long-term strategy to minimize infection, regardless of the positive impact of these catheter-focused initiatives [36–38].

Microbial Colonization and Biofilm

Generally, microbial colonization of the HD catheter is thought to pre-date most CRBSI episodes [39–41]. HD catheter colonization typically comes about in three ways: microbial contamination through an open HD catheter hub onto the intraluminal surface; migration of microbial flora at the exit site onto portions of the extraluminal catheter surface that is tunneled subcutaneously; and direct seeding of the cathe-

ter due to transient and potentially asymptomatic episodes of bacteremia [42–45].

With colonization, the subsequent formation of biofilm on or within the catheter further predisposes to CRBSI. Biofilm functions as an exopolysaccharide matrix that can both harbor microorganisms and protect them from host immune system response and systemic antibiotics [45–47]. Once microbial colonies reach a certain size or receive a key signal, they can convert from sessile to planktonic form, with single bacteria or bacterial aggregates detaching from the biofilm, entering into the bloodstream, and causing bacteremia [42–44].

Biofilm on both the external and internal surfaces of intravascular catheters is generated by microorganisms that can colonize such catheters, generally from entry through the exit site or the catheter hub [48, 49]. Biofilms have been found as quickly as 24 hours after insertion [41, 45], with extraluminal catheter colonization and biofilm tending to occur more acutely than biofilm on the inner surface of the catheter.

Biofilms can become more established and extend over time, primarily a result of the fibrin-protein ultrastructure of the biofilm protecting the microorganisms [41, 46–48, 50] and the microorganism switching from planktonic to sessile phases while resting in the biofilm. The biofilm matrix also can physically protect embedded microorganisms from contact with antimicrobial therapy or decrease the degree of effective contact, all factors that may help contribute to antibiotic resistance [42, 43]. Biofilm formation is more common in areas where there has been catheter surface erosion, increasing its likelihood in older catheters and catheters made of less durable material [51]. Episodes of bacteremia and prolonged exposure to high concentrations of antibiotics such as seen with antibiotic catheter locks (ABL) can also affect biofilm distribution and characteristics [52, 53].

Clinical Risk Factors for CRBSI

Studies in adults have outlined several modifiable clinical risk factors for CRBSI. HD patients with untunneled or uncuffed catheters have higher infection rates [54–56]. Previous bacteremia episodes, ongoing immunosuppressive therapy, nasal carriage of *Staphylococcus aureus*, and ongoing anemia requiring intravenous iron therapy have also been associated with CRBSI [54–63]. There are more limited studies identifying clinical risk factors in children that suggest that young age, an immunodeficient state, and a prior infection of a current HD catheter may be concerning [6, 64]. There are no studies thus far linking hemoglobin level or IV iron provision in children to CRBSI even though anemia, IV iron use, and iron overload states seem to be risk factors in adults [65–69].

Clinical Presentation of CRBSI

New onset fever, often accompanied by chills or even rigor during an HD treatment, is a typical clinical presentation of CRBSI in a child at risk [5–7]. The presenting symptoms can be nonspecific, however, and infection needs to be considered in any pediatric patient with an HD catheter who manifests a change in vital signs during dialysis not readily attributable to ultrafiltration [70]. Although rare, full-blown sepsis physiology can also be the first presentation, with tachycardia, widening pulse pressure, hypotension, and altered mental status [6, 7, 71].

There should be a higher clinical index of suspicion for potential CRBSI in children with HD catheters who may have had recent difficulties obtaining or maintaining prescribed blood flows. Such flow issues often arise because of intraluminal clotting or obstructing fibrin sheaths, and prior transient asymptomatic bacteremia may have seeded these sites, subsequently establishing a locus of ongoing bacterial infection. Moreover, the presence of an actual concomitant exit site or tunnel infection substantially increases concerns for CRBSI.

A child with an HD catheter is more likely to manifest signs and symptoms of a catheter-related infection during the actual course of an HD treatment, when there are high flow rates of blood through an infected nidus. Regardless, any

child with a HD catheter presenting with fever at home needs complete assessment for potential HD line infection [5–7].

Diagnosis of CRBSI

With concern for a CRBSI, CBC and blood cultures are obtained as standard of care, with other studies such as chest radiograph, influenza swab, or urine culture to be obtained as indicated. Empiric antibiotics should then be provided through the HD catheter, with ongoing antibiotic coverage until all bacterial cultures are negative [71–73].

Practically, CRBSI is defined as an episode of bacteremia in a patient with an HD catheter who has concomitant clinical signs and symptoms of infection, such as fever, chills, nausea, vomiting, headaches, or dizziness, all in the absence of an obvious alternative source of symptomatic infection [73, 74]. Fungemia can also present in a similar fashion, though it is far less common in the average child on chronic HD without a risk factor for fungal disease.

In distinction to an acute bacterial CRBSI, bacterial colonization of the catheter can also potentially result in positive HD catheter cultures, but colonization by itself usually manifests no clinical signs or symptoms of active infection, and there is no common clinical practice to do surveillance blood cultures of asymptomatic children with HD catheters. Peripheral cultures done simultaneously with catheter cultures should always be negative with colonization [5]. As noted earlier, an interplay exists between colonization and eventual CRBSI, but the factors promoting both colonization and then infection need further elucidation.

With the suspicion of a CRBSI, the catheter exit site and tunnel should also be examined to assess for signs or symptoms of concomitant infection. An exit site infection is generally defined by tenderness, erythema, warmth, purulent discharge, or induration within 2 cm of the catheter exit site [73, 74]. Such findings beyond 2 cm from the exit site and along the subcutaneous tunnel from the exit site to the catheter's insertion in a central vein characterize a tunnel infection [73, 74]. A discussion specifically about exit site and tunnel infections in pediatric HD patients can be found later in this chapter.

To correctly diagnose CRBSI, most guidelines recommend that at least two blood cultures be obtained, one from the HD catheter and a second from a peripheral vein or from blood in the dialysis circuit [1, 73, 74]. In clinical practice in many pediatric dialysis units, blood cultures are obtained from both arterial and venous limbs of the HD catheter, but a peripheral culture is not as routinely sent. Blood cultures should be obtained prior to the first doses of any empiric systemic antibiotics.

In the event that catheter and peripheral cultures are obtained and all cultures do show subsequent bacterial growth, CRBSI should reveal the same microorganism from all sources [74–76]. Considering various combinations of HD catheter, HD circuit, and peripheral cultures, a longitudinal study in an adult dialysis center showed that the greatest sensitivity, specificity, and accuracy for CRBSI were found to come from blood cultures obtained through the catheter hub or the HD circuit, disregarding peripheral culture results [77].

In children on HD, given the lifetime need for vascular access and concerns for complications such as venous stenosis that ensue with repeated interventions in large central veins, there also tends to be reluctance to remove most infected HD catheters without some initial attempt to clear the infection with antibiotic therapy [78, 79]. In recognition of the differences in approach between dialysis patients and other patients with central lines, the Infectious Diseases Society of America (IDSA) has begun to include nephrologists in the committees composing guidelines for the management of vascular catheter-associated infections [73].

Initial Clinical Management of Suspected CRBSI

Figure 24.2 outlines an approach to clinical care in the setting of a presumed or confirmed CRBSI.

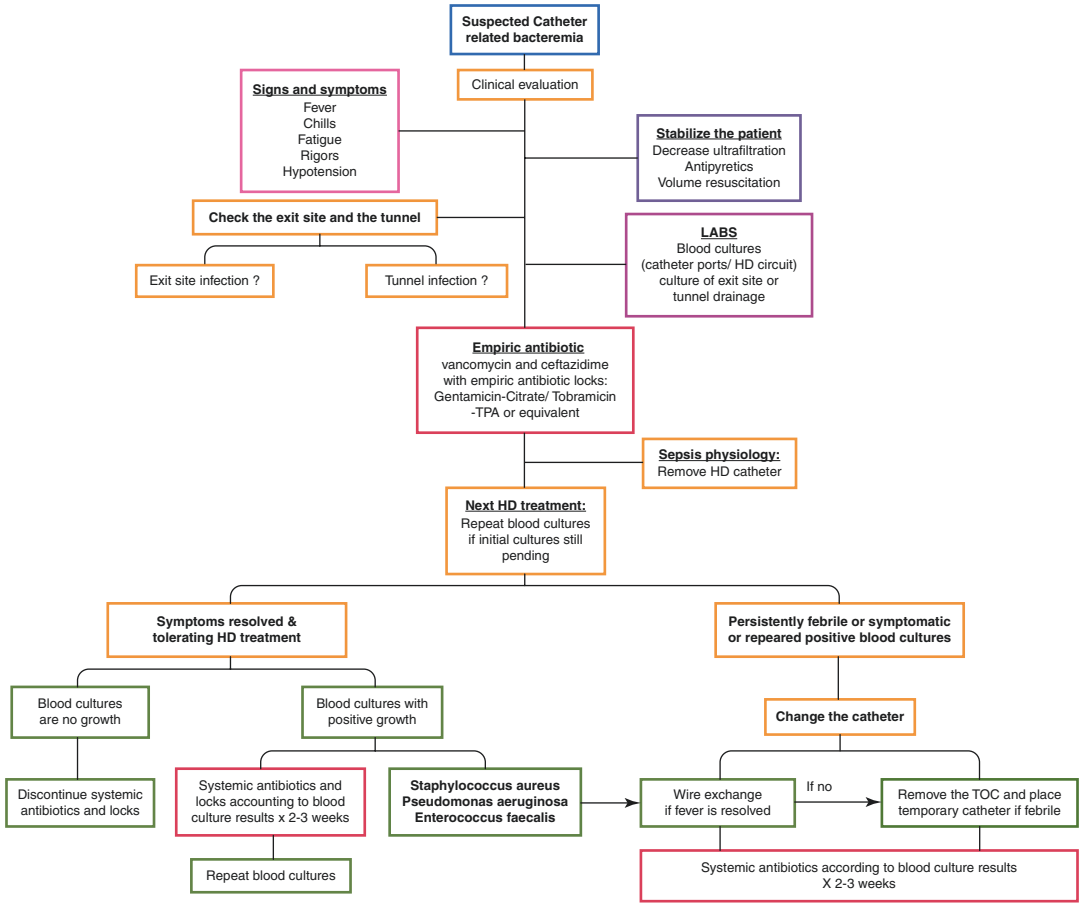


Fig. 24.2 Suggested treatment algorithm for catheter-related bloodstream infection. TPA Tissue plasminogen activator

When CRBSI is suspected, the dialysis clinician and staff need to be vigilant for clinical deterioration related to bacteremia or even evolving sepsis during the HD treatment, even after antibiotic therapy has been initially provided. Judicious rates of ultrafiltration, preparation for fluid resuscitation, and anti-pyretic administration should all be considered. Along with blood cultures, with the initial presentation, most clinicians will also obtain a complete blood count (CBC) and some may look at C-reactive protein (CRP) as a marker of acute inflammation.

Empiric systemic antibiotics should be broad spectrum and especially effective against the most likely potential microorganisms responsible for CRBSI. In general, about 75% of HD catheter-related infections are caused by gram-positive organisms and 25% by gram-negatives [6, 7, 29]. As discussed earlier, *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species are the most common gram-positive microorganisms, with sensitivity patterns affected by usual resistance factors.

Typically, vancomycin is used as empiric gram-positive coverage because of potential methicillin-resistant species [6, 80]. A 10–20 mg/kg/dose loading dose up to 1 gram is followed by further doses at subsequent dialysis sessions based on blood levels obtained [73, 81]. The absence of effective native GFR obviates the need for interdialytic dosing. Vancomycin is, however, nephrotoxic and may deleteriously affect residual renal function. Both third-generation cephalosporin and aminoglycosides

are reasonable options for empiric gram-negative coverage. Many centers use ceftazidime (50 mg/kg/dose or 1 gram maximum), given its good *Pseudomonas* species coverage and pharmacokinetics in end-stage kidney disease that allow administration every 48 hours after HD sessions. Aminoglycoside use requires checking serum levels prior to subsequent doses and has the potential risk of adversely affecting any residual kidney function and contributing to ototoxicity. The use of vancomycin along with aminoglycosides may increase these toxicities.

Antimicrobial locks used during treatment for CRBSI can also improve rates of successful clearance of HD catheter infection [72, 81]. Various antimicrobial agents have been used for antimicrobial locks, including an empiric combination of vancomycin-ceftazidime-heparin, with the ability to then narrow coverage based on culture results. In addition to heparin, both citrate and tissue plasminogen activator have also been used as anticoagulants in locking solutions [72, 81].

If the initial blood cultures show no growth and the child's symptoms have abated, then empiric antibiotics are usually stopped [1, 5, 6, 73]. It typically takes one to two subsequent HD treatments after presentation before final blood culture results are reported. If the child's symptoms are persistent, then ongoing evaluation and potential extension of antibiotic treatment may be needed, while occult HD catheter infection is being ruled out and other infectious etiologies are being considered.

Catheter Replacement

When there is confirmation of a CRBSI with a positive blood culture in a child on chronic hemodialysis, in addition to choices regarding ongoing antibiotic therapy, there needs to be a decision as to whether the HD catheter must be removed for successful eradication of bacteremia or if catheter in situ treatment can be attempted [81]. Decisions about the HD catheter disposition typically weigh the clinical severity of the CRBSI episode, the presence or persistence of life-threatening symptoms, the microorganism identified and pertinent antimicrobial sensitivities, the persistence of positive blood cultures during the course of treatment [73, 81], and whether this CRBSI episode represents a recurrent infection.

It is uncommon for a child on dialysis with a suspected CRBSI to need immediate removal of a tunneled cuffed catheter and placement of a temporary HD catheter, outside of situations where there is some defect with the integrity of the catheter or concern for its use because of a severe concomitant tunnel or exit site infection. Given the focus on preserving long-term vascular access in children with end-stage kidney disease, there is generally empiric treatment with antibiotics while awaiting culture results and following the clinical response to initial therapy. If there is prompt resolution of all given symptoms after antibiotic provision and follow-up blood cultures are without any growth, this is considered indication of successful treatment without need for any early catheter manipulations [6, 78].

The persistence of fever 48–72 hours after initiation of systemic antibiotics or ongoing positive blood cultures from the HD catheter are considered indications of persisting bacteremia [5–7]. With ongoing bacteremia, there is increased concern for seeding new sites of infection (endocarditis, osteomyelitis), and consideration must be given to catheter removal or exchange [59, 62]. Infection with fungus or a microorganism such as *Pseudomonas* that will not be readily cleared by antibiotic provision alone also requires consideration of HD catheter removal.

HD catheter replacement can occur either by wire-guided exchange (WGE). or by actual surgical removal and replacement [82]. With WGE, the infected catheter is removed over a guide wire, and a new catheter placed into the same vessel through the existing exit site and tunnel catheter. The advantage of WGE is using the same large vessel for the new catheter and sparing other vessels while exchanging the catheter in one procedure [64, 83, 84]. Even after placement of the new catheter, systemic antibiotics are provided to complete a full treatment regimen. When compared to surgical removal and replacement of an infected catheter, HD patients undergoing

WGE have similar mean times to achieving an afebrile state and to experiencing an asymptomatic HD treatment, and they have similar rates of remaining infection free after the completion of their CRBSI treatment [64, 71].

In some instances, WGE cannot be technically accomplished, or there is concern for an exit site infection or tunnel infection mediating the CRBSI and contraindicating catheter exchange. In those cases, the HD catheter is surgically removed and replaced by a new catheter, using a new exit site or new vessel as needed. Especially with the more invasive surgical approach, a concern is replacement of the catheter in the setting of ongoing bacteremia and the potential re-infection of the new catheter. When there is greater concern about re-infection, the infected catheter may be removed, and then a new catheter placed in 48–72 hours when dialysis is required again. A tunneled cuffed catheter may on occasion also be removed and replaced with an acute HD catheter, with plans to eventually place a new tunneled cuffed catheter once the bacteremia and any other associated infected sites have been fully treated. Although this is the approach most likely to prevent re-infection of the new HD catheter, it involves multiple procedures and potentially the use of multiple vessels.

Recurrence of a positive blood culture anytime during treatment or shortly following antibiotic discontinuation should prompt removal of the dialysis catheter [61, 64, 73]. Figure 24.3 outlines the efficacy of various treatment strategies in clearing CRBSI.

Catheter In Situ Treatment: Antimicrobials for Empiric and Calculated Therapy

Generally, in the child with a CRBSI who responds quickly to provision of systemic antibiotics with subsequently negative blood cultures and no further fever or symptoms of infection, intravenous antibiotics will be maintained for at least 2–3 weeks, with consideration of ongoing use of antibiotic locks if these had also been started at presentation. Culture and sensitivity results should guide choice of therapy for both ongoing systemic antibiotics and any antibiotic locks.

As discussed earlier in the chapter, empiric antibiotic therapy, most often with vancomycin (daptomycin if vancomycin allergic) and ceftazidime, is then narrowed as blood culture results return. Choice of initial empiric therapy may also depend on local practice, with the need for any empiric agent to be effective in coverage of common isolates from the local dialysis unit. Unless there are no other therapeutic options, antibiotics with end-stage kidney disease pharmacokinetics that forgo dosing outside of dialysis sessions should be chosen. Table 24.1 lists frequently provided antimicrobial agents with dosing ranges and target levels.

The increasing emergence of vancomycin-resistant organisms in dialysis patients underscores the importance of judicious provision of vancomycin [85, 86] and consideration of empiric cefazolin use where there is limited methicillin resistance in *Staphylococcus* species. Methicillin-sensitive *Staphylococcus* species can be successfully treated using cefazolin, typically 20 mg/kg/dose to a maximum of 2 grams, given every 48 hours at dialysis. Some investigators recommend a higher dose of cefazolin (30 mg/kg/dose, maximum 3 grams) when there will be a 72-hour period between HD treatments. Cefazolin therapy not only reduces ongoing vancomycin exposure and the potential induction of vancomycin resistance, but its administration is easier, and its dosing does not require checking drug levels. There is also some data to suggest that MSSS and MSSA bacteremia may be eradicated more efficaciously with cefazolin in comparison to vancomycin [87]. Nafcillin and oxacillin are not good alternatives to vancomycin in dialysis patients as they need to be dosed more frequently than every 48 hours.

In HD patients with CRBSI, most gram-negative isolates are sensitive to ceftazidime, and

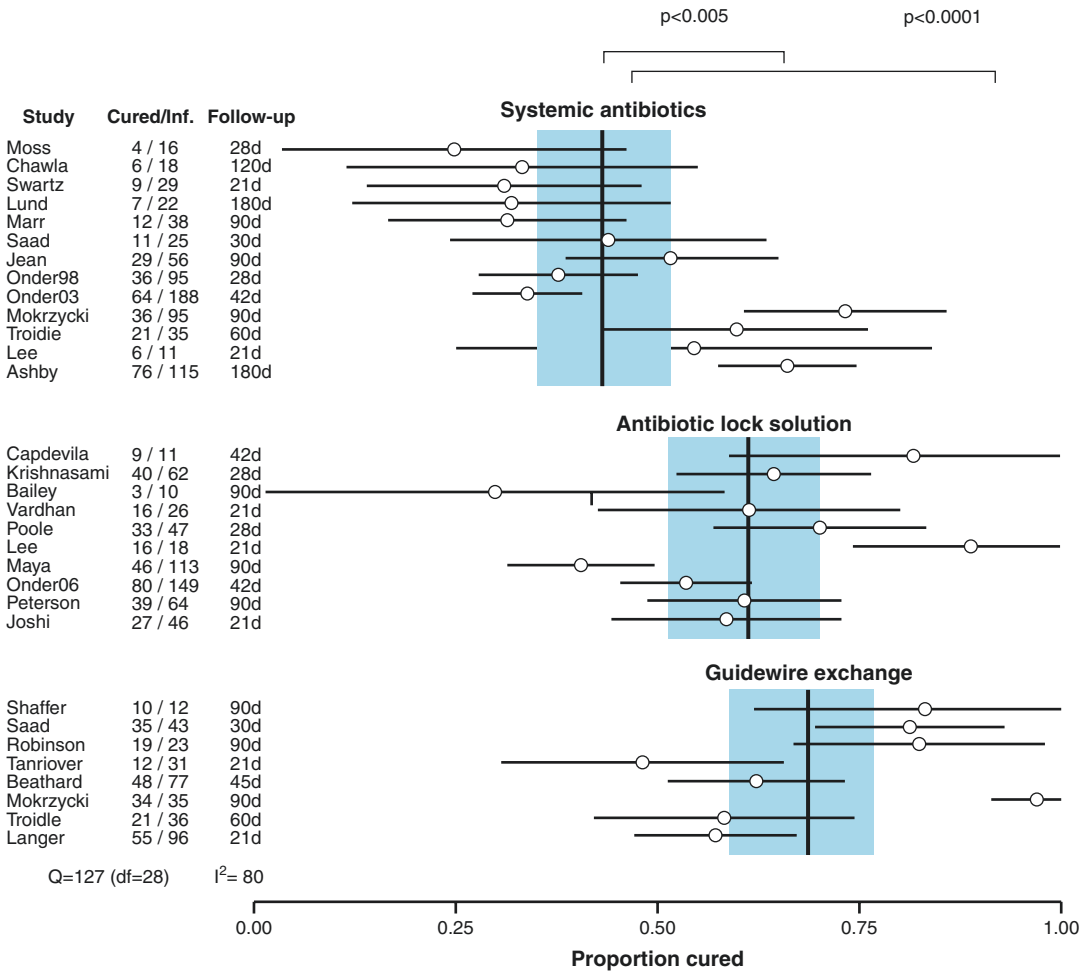


Fig. 24.3 Success rates for clearance of CRBSI stratified according to treatment strategies. The vertical lines demonstrate the mean clearance rates (with 95% confidence bands as shaded area) for each treatment strategy, across all studies reviewed for this treatment. Next to each study, specific data for the number of cured and infected subjects is provided. Outcomes were significantly better for patients treated with antibiotic locks (ABL) and with wire-guided exchange (GWX) in combination with systemic antibiotics when compared to systemic antibiotics alone (SABX). Odds ratio for CRBSI clearance for ABL versus SABX was 2.08 (95% CI, 1.25–3.45; $p < 0.01$) and, for GWX versus SABX, 2.88 (95% CI, 1.82–4.55; $p < 0.001$). There was no statistical difference for clearance of infection when GWX was compared to ABL; odds ratio, 1.39 (95% CI, 0.78–2.46; $p = 0.27$). (Modified from: Aslam et al. [105])

treatment can be continued at a dose of 50 mg/kg/dose, maximum 1 gram, infused during the last 30 minutes of the HD treatment. Alternatively, aminoglycosides can be chosen, though their use requires drug levels to guide dosing, and their ototoxicity and potential adverse effect on residual renal function must also be considered [88]. With gentamicin, a dose of 2 mg/kg to a maximum of 80–100 mg is typically provided, with documentation of a level <3–5 mcg/ml at the start of the next HD session.

Fungal CRBSI is an extremely rare event, constituting 0–3% of most series, and almost always a consequence of a *Candida* infection. Fungal

Table 24.1 Antimicrobials for treatment of CRBSI in children

Antimicrobial agent	Initial dose	Maximal dose	Safe random level to re-dose
Vancomycin	10–15 mg/kg	1 gram	<10 mcg/ml
Ceftazidime	50 mg/kg	1 gram	NA
Cefazolin	20–30 mg/kg	2 grams	NA
Daptomycin	4–9 mg/kg	NA	NA
Gentamicin	2 mg/kg	100 mg	<2 mcg/ml
Fluconazole[a]	12 mg/kg	800 mg	NA

Systemic antimicrobials should be administered after every HD treatment, according to levels if applicable. Suggested dosing and targeted levels may need adjustment according to specific clinical conditions, local laboratory ranges, or recommendations of infectious disease consultants

[a]Some recommend that fluconazole be dosed at 6 mg/kg after the initial dose, with doses provided daily rather than just after dialysis

infection requires prompt HD catheter removal [89]. Treatment can be initiated with intravenous fluconazole on dialysis days, though consultation with an infectious disease specialist to guide specifics and duration of antimicrobial therapy with fungemia is strongly recommended.

Antibiotic Therapy: Specifics of Provision

Unless the catheter is no longer functioning, it should be used for the infusion of antibiotics, with the purpose of exposing the site of infection to the highest concentration of medication, though medication provision into the dialysis circuit during the last portion of a dialysis treatment also effectively exposes the catheter and is the general practice during an ongoing antibiotic course [87]. The duration of antibiotic treatment will be guided by concomitant clinical circumstances and the actual microbial isolate. Most often, treatment continues for at least 2–3 weeks after documentation of the first of two consecutive negative blood cultures [6, 59, 62]. Such practice necessitates serial cultures from the HD catheter at each dialysis. There are some practice recommendations to repeat a blood culture 1 week after the first negative blood culture and within 2 weeks after the completion of the antibiotic treatment when a CRBSI is treated without catheter removal [6, 64], though this longer-term surveillance is not widely practiced.

Certain isolates or polymicrobial infections may require longer treatment or guidance from infectious disease specialists. If the CRBSI is complicated by endocarditis, osteomyelitis, discitis, septic arthritis, or epidural abscess, then the duration of treatment will depend on response of this condition to antibiotics and often results in therapy for at least 6–8 weeks [85, 86, 88]. Such complications are seen less often in children than adults, likely related to other underlying health concerns found more commonly in an older population [90, 91]. These complications are also more common if an infected catheter with persistent positive blood cultures continues to be used rather than removed or replaced [92–95].

Antimicrobial Locks in CRBSI

Recognition of the role of intraluminal biofilm in HD catheter bacterial colonization and infection has led to a more widespread approach in CRBSI to supplement intermittent systemic antibiotic provision with use of antibiotic locks. The purpose of this approach is to provide a high concentration of antibiotic within the catheter lumen during the entire interdialytic period, increasing the chances of eradicating any pathogen within the biofilm [8, 45, 49, 96, 97]. It is estimated that antibiotic concentrations from 10 to 100 times the minimal inhibitory concentration (MIC) can be achieved in an antibiotic lock, far exceeding the ongoing antibiotic concentration achieved by infusion of systemic antibiotics alone [81, 98–100].

Most HD catheter antibiotic locks consist of an antimicrobial-anticoagulant mixture. Commonly used antibiotics include vancomycin, gentamicin, tobramycin, cefazolin, minocycline, and ceftazidime, though antimicrobials such as ethanol, EDTA, taurolidine, and methylene blue have also been used [72, 73, 81, 101]. The most common anticoagulants in HD catheter locks are

heparin and citrate, though use of urokinase or tissue plasminogen activator (TPA) has also been described [30, 72, 101]. The anticoagulant is just as important as the antibiotic/antimicrobial component to the overall effect of the lock, maintaining catheter patency and affecting biofilm integrity [102].

Supplementing intermittent systemic antibiotic infusion with interdialytic antibiotic lock use has significantly improved the likelihood of clearing an infected HD catheter and preventing catheter replacement [30, 103–105]. In one pediatric series of 188 CRBSI episodes, 34% responded to initial systemic antibiotics, with the later addition of an interdialytic antibiotic lock clearing a further 23% of infections [6, 64]. In another series with 76 CRBSI episodes, 83% cleared with concomitant systemic antibiotics and antibiotic locks, with most catheters not responding to this therapy manifesting polymicrobial infections and needing replacement by WGE [30]. During the follow-up period, there was no difference in the rate of recurrent infection between the two groups.

Early use of antibiotic locks also seems to be more efficacious than their later introduction. In a report of 264 episodes of bacteremia in 79 children with HD catheters, early antibiotic lock use along with initiation of systemic antibiotics was compared to late lock implementation in the setting of persistent bacteremia despite use of systemic antibiotics [72]. Children with antibiotic locks added late were found to require WGE significantly more frequently because of persistent bacteremia than the children treated with early antibiotic locks. Recurrence of catheter-related bacteremia during the follow-up period was similar in both groups.

In terms of other factors that affect the efficacy of antibiotic lock use, a study of 149 CRBSI episodes found that children infected with coagulase-negative *Staphylococcus* were significantly more likely to respond during the first 2 weeks of concomitant systemic antibiotics and antibiotic locks [106]. Children infected with *Staphylococcus aureus*, *Enterococcus* species, and *Pseudomonas* species were all significantly more likely to have persistent bacteremia. Although not reaching statistical significance, infection with *Klebsiella* or *Enterobacter* species had rates of failure up to three times higher. This same study showed that younger children and those with higher baseline phosphorus levels were more likely to get re-infected during the 6-week follow-up period, whereas other clinical factors such as need for catheter replacement during the initial CRBSI, prior catheter vintage, concomitant exit site infection, serum albumin level, HIV infection, or immunosuppressive therapy were unrelated to the risk of recurrent infection.

The apparent increased efficacy of combining use of antibiotic locks with systemic antibiotic provision has led some to recommend that CRBSI should not be treated with systemic antibiotics alone and that an antibiotic lock should always be added [81]. There is still limited data comparing various treatment strategies for CRBSI, though one meta-analysis looked at 28 publications encompassing nearly 1600 HD patients with tunneled cuffed catheters, nearly 30% of whom were pediatric patients [105]. Three potential treatment strategies were compared: systemic antibiotics alone, systemic antibiotics and an antibiotic lock, and wire guided exchange of the infected HD catheter for a new catheter with systemic antibiotic therapy. The primary end point assessed was clearance of the bacteremia, with secondary analyses considering complications from the CRBSI and recurrent infection. Both antibiotic locks and wire guided exchange were statistically superior to antibiotic therapy alone in clearing the bacteremia and in staying infection free during the follow-up period. There were no differences between the three therapies in terms of CRBSI complications. As has been reported in the past, infections with certain gram-negative organisms or with *Staphylococcus aureus* were more difficult to clear without catheter replacement. This meta-analysis would suggest that antibiotic locks can be used to improve outcomes with systemic antibiotics without increasing the rates of complications related to therapy, though some cases will still require catheter exchange as part of overall management.

Role of Strategies to Prevent CRBSI

Infections of HD catheters can occur at the time of insertion due to a lapse in aseptic technique but more commonly come about during the course of ongoing use of the catheter. Infections related to contamination of dialysate fluid or dialysis equipment are very rare if commercially available products are being used and expected equipment sanitization procedures are followed. Most HD catheter infections can be traced back to bacterial flora on the patient's own skin, from bacterial contamination from a health worker's hands delivering dialysis care, or from bacterial contamination of the catheter hubs.

Both the Centers for Disease Control and Prevention (CDC) and the Kidney Disease Outcomes Quality Initiative (KDOQI) have created care practice recommendations aimed to decrease infections in patients with HD catheters [35, 36, 38]. These guidelines focus especially on maneuvers to optimize hand hygiene, exit site care, and accessing and disconnecting catheters. Much of the evidence supporting these recommendations originally came from studies of central venous catheter care in the intensive care unit setting [23, 107] but have in large part been substantiated by studies and experiences in the dialysis unit setting. Moreover, there is evidence from single centers and from the SCOPE consortium that following such recommended bundles of care can reduce hemodialysis infections in children in pediatric dialysis facilities [23, 27].

All guidelines that are aimed at reducing dialysis-related infections are grounded on good hand hygiene prior to any handling of the HD catheter, as well as before and after taking off gloves for catheter connection or disconnection. Masks are typically worn for HD catheter connection or disconnection, and although not stipulated in CDC guidelines, they are recommended by KDOQI and by the Centers for Medicare & Medicaid Services.

Staphylococcus Colonization

In terms of respiratory tract carriage of bacteria that may contribute to dialysis infection, *Staphylococcus aureus* has been reported to colonize 10–50% of patients in various dialysis cohorts [108]. Infections of the HD catheter with *Staphylococcus aureus* can be problematic, since these infections are typically harder to clear than coagulase-negative staphylococcal strains or gram-negative organisms (Fig. 24.4). *Staphylococcus aureus* strains are more drug resistant than other staphylococcal species, thereby contributing to significant HD patient morbidity and healthcare costs [109]. This virulence may in part be a function of the predisposition for *Staphylococcus aureus* to form biofilm and accounts for why *Staphylococcus aureus* infection results in higher rates of catheter removal or replacement [99, 106, 110, 111]. Since skin folds are especially prone to colonization with *Staphylococcus*, femoral catheters are considered to be at higher risk than catheters placed in the neck or chest.

Since nasal carriage of *Staphylococcus aureus* has been associated with higher rates of staphylococcal infections, eradication by a 5-day course of topical intranasal mupirocin has been utilized. Some reports in HD patients show efficacy in three-quarters of colonized individuals, though re-colonization is common and requires re-treatment [112–115]. A concern for widespread or repeated mupirocin exposure, however, is the development of resistant bacteria, as has been found in both HD and peritoneal dialysis patients using long-term mupirocin for exit site care [116–119]. Alternatively, a brief course of oral rifampin is also effective in eradicating nasal *Staphylococcus aureus* carriage for up to 3 months [115]. Some have also suggested that intermittent baths with chlorhexidine-based soaps may also decrease *Staphylococcus* colonization on the skin.

Currently, there are no recommendations for widespread testing or treatment of nasal carriers

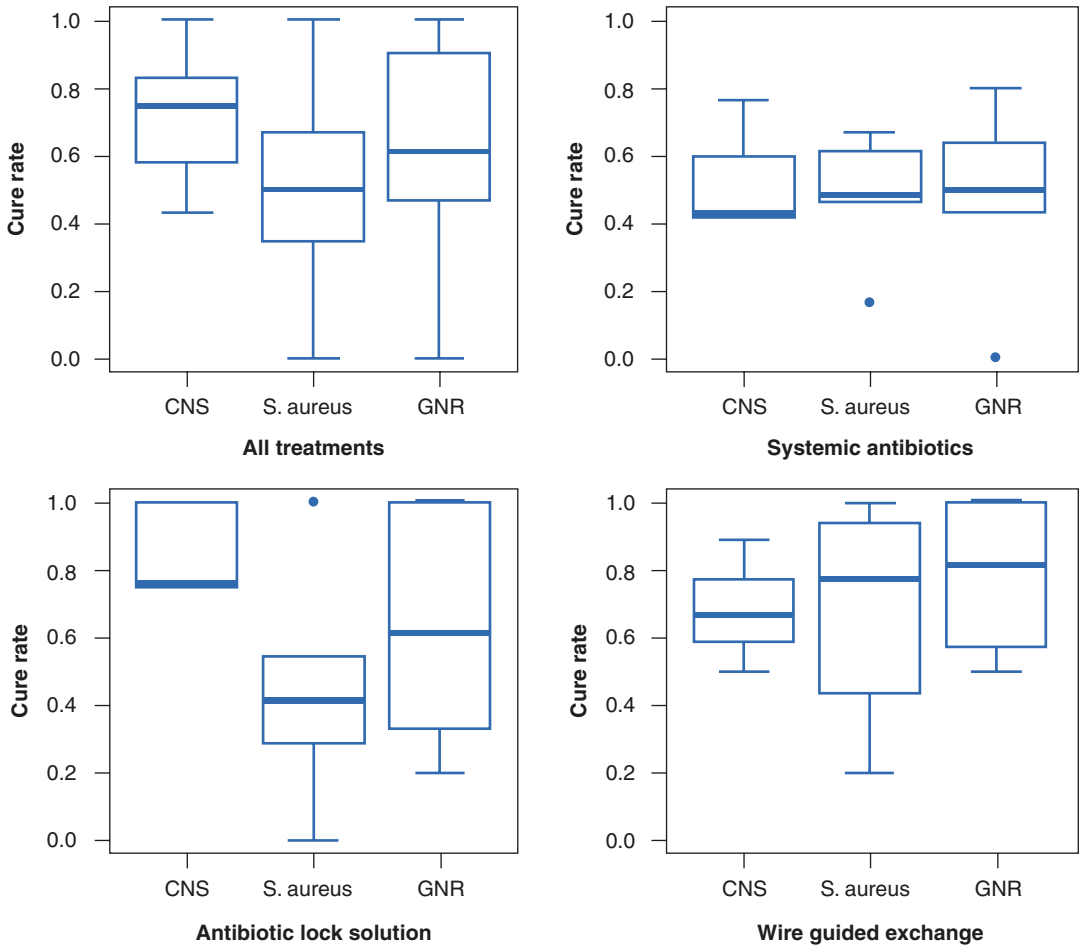


Fig. 24.4 Cure rates of CRBSI, stratified by infecting organism and treatment strategy. Cure rates for coagulase-negative *Staphylococcus* (CNS), gram-negative rods/bacteria (GNR), and *Staphylococcus aureus* (*S. aureus*) were compared overall and by each treatment strategy. The highest cure rate was for CRBSI caused by CNS, followed by GNR, and then *S. aureus*. Systemic antibiotics alone had the lowest cure rates for all infecting organisms. Antibiotic locks along with systemic antibiotics improved clearance rates for CNS and GNR, without changing *S. aureus* outcomes. Wire guided exchange resulted in better *S. aureus* cure rates. The odds ratio for clearance of CNS CRBSI versus GNR, 1.71 (95% CI, 0.99–2.97; $p = 0.06$); CNS versus *S. aureus*, 3.13 (95% CI, 1.73–5.67; $p < 0.001$); and GNR versus *S. aureus*, 1.83 (95% CI, 1.13–2.97; $p = 0.02$). (Modified from: Aslam et al. [105])

of *Staphylococcus* in the pediatric HD unit, but in select cases of recurrent or severe infection, such approaches may be considered.

Exit Site Care

Since the HD catheter exit site is the crucial interface between the external catheter limbs and hubs and the subcutaneous or tunneled portion of the catheter, attention to the skin integrity of the exit site and appropriate periodic antisepsis of the site to decrease skin colonization is thought critical in maintenance HD catheter care. Exit site skin antisepsis is best provided with >0.5% chlorhexidine with alcohol, with 70% alcohol or povidone-iodine as alternatives. Chlorhexidine's antimicrobial effect is rapid and can have some residual efficacy, whereas povidone-iodine must have longer skin contact and be allowed to dry.

In an observational study in children on HD that collected >20,000 HD catheter days of data,

the CRBSI rate in children receiving chlorhexidine antisepsis of the exit site was half the rate of those receiving povidone-iodine antisepsis, with an advantage to chlorhexidine use in reducing exit site infection and days of hospitalization for infection [120–122]. There is similar data to suggest that chlorhexidine skin antisepsis at the time of placement of the HD catheter is also superior to the use of povidone-iodine [120, 123, 124]. Sodium hypochlorite is not recommended in current guidelines since it is less efficacious than chlorhexidine, and there is more limited data as to its efficacy in the dialysis population in comparison to povidone-iodine or 70% alcohol as chlorhexidine alternatives.

In addition to periodic skin antisepsis, a topical antimicrobial ointment or a chlorhexidine impregnated patch dressing is generally placed at the exit site, based on several studies that have shown efficacy of such practice in reducing rates of exit site infection and CRBSI in HD [125–129]. Most guidelines currently recommend a triple antibiotic ointment containing bacitracin, gramicidin, or neomycin and polymyxin B or an ointment with povidone-iodine. The triple antibiotic ointment is thought to have efficacy against both gram-positive and gram-negative organisms and has been shown to have short-term and long-term efficacy in decreasing infections. One report showed CRBSI rates falling from 4.1 to1 episodes/1000 HD catheter days with routine triple antibiotic ointment use, with low bloodstream and exit site infection rates continuing through at least 6 years of ongoing use [130]. In this long-term cohort, the bacterial isolates from those with infections were similar to those seen before the intervention, suggesting that there was no evolving antimicrobial resistance or selection for certain types of infection with the triple antibiotic ointment [131].

Of note, though often recommended for peritoneal dialysis catheter exit site care, gentamicin ointment or cream is not recommended with HD catheters due to limited data studying its use and efficacy in this setting. Similarly, mupirocin is also often recommended for peritoneal dialysis catheter care but not endorsed with HD catheters related to concerns for mupirocin-resistant organisms, especially *Staphylococcus aureus*, developing with chronic exposure [116, 117].

There has been some interest in the use of medical-grade honey as a safe and inexpensive topical antimicrobial. Medical-grade honey has several antimicrobial characteristics including a low pH due to flavonoid and phenolic acid, a high osmolality due to low water content, and an ability to generate hydrogen peroxide as it becomes dilute [132–134]. In one study of 101 dialysis patients, medical-grade honey was found not inferior to mupirocin in preventing CRBSI and exit site infections, without apparent development of any antimicrobial resistance [135]. There is no significant data, however, comparing medical-grade honey use with currently recommended HD catheter exit site care choices such as triple antibiotic or povidone-iodine ointments or chlorhexidine impregnated patch dressings.

There are two reports on the efficacy of chlorhexidine impregnated patch dressings in decreasing dialysis-related infections specifically in children. In one study, the addition of a chlorhexidine impregnated patch to a skin antisepsis regimen using povidone-iodine decreased exit site infection rates from 1.1 to 0.2 episodes/1000 catheter days, though there was no effect on CRBSI rates or long-term HD catheter survival [125]. When chlorhexidine gluconate 2% and isopropyl alcohol 70% were substituted for povidone-iodine to provide skin antisepsis, along with continued use of the chlorhexidine impregnated patch at the exit site, the CRBSI rate fell significantly from 2.2 to 1 episode/1000 HD catheter days, with significantly lower days of hospitalization and a tendency for longer catheter survival.

Except when uncovered for direct exit site care, the HD catheter exit site is covered by a dressing. Traditionally, gauze had been used, but there has been a transition to a transparent semipermeable dressing in many centers. At the time of exit site care, either a chlorhexidine impregnated patch dressing or antimicrobial ointment and sterile gauze are covered by these transparent dressings. The HD catheter exit site should be directly visualized with every HD treatment. If there cannot be direct visualization of the actual

exit site through a transparent dressing or if any dressing becomes wet, soiled, or detached, then the dressing needs to be changed, with appropriate preceding exit site care [35, 36]. Even if an exit site can be visualized and looks normal, a dressing change with exit site care should occur at least once weekly.

There has been little formal direct comparison of gauze versus transparent outer dressings on infection rates. One study showed that CRBSI rates were lower with transparent dressings, but the patients with transparent dressings had chlorhexidine patches placed at the exit site, whereas the patients with gauze outer dressings had antibiotic ointment, so the relative effect of the difference in dressing versus the difference in direct exit site care could not be distinguished [128].

HD Catheter Hubs

When the HD catheter is accessed or disconnected, there are multiple opportunities for contamination of the hubs and entry of microorganisms into the catheter lumen. Various checklists have been devised as part of dialysis guidelines to try to standardize practice and reduce opportunities for infection, and auditing of catheter connection and disconnection plays a major part in many initiatives such as CDC's Making Dialysis Safer for Patents Coalition or the SCOPE collaborative.

Proper disinfection of the catheter hubs is critical as part of any catheter connection or disconnection. Appropriate antiseptics include >0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine. Scrubbing the hubs for an appropriate period of time and then allowing the antiseptic to dry enhance efficacy of this step. This disinfection of the hub needs to occur for any disconnection or reconnection that occurs prior to the conclusion of a dialysis session and not only at the start and stop of a session. When new caps are being placed back over the hubs, they need to be attached in an aseptic technique so that the inner portion of the cap that occludes the catheter is not contaminated.

Although it may be local practice to soak the capped hub for 3–5 minutes in antiseptic prior to removing the cap, this is not recommended by the CDC and has not been included in recent KDOQI recommendations as well. Similarly, in some centers tape may be placed over caps to help secure them and prevent accidental dislocation [23], but tape residue in the hub area will then require extra attention during disinfection since its ongoing presence serves as an additional nidus for potential bacterial contamination.

Changes with cap design or catheter connectors have also been proposed as strategies to reduce infection that originates at the hub. Needle-free connector systems that stay attached to the catheter hubs for up to a week and do not need to be removed to perform dialysis create a closed system that eliminates opening the hub with every dialysis session. Disinfecting caps containing 70% isopropyl alcohol can also be twisted onto these needleless connectors to either sanitize the connector before it is used or to sit in place as an additional anti-infectious barrier for at least a week. There is little data in pediatric HD patients to date, however, to show that these needle-free connectors result in significant changes in CRBSI rates.

More traditional caps have also been engineered that have a chlorhexidine embedded rod extending from the inside of the cap. When these caps are placed into position onto a hub after a dialysis session, this rod extends into the initial portion of the attached HD catheter limb, and chlorhexidine is slowly released, effectively eliminating contaminating microbes near the hub and in that portion of the catheter limb [136]. A randomized prospective trial of 2500 HD patients compared use of these caps to traditional caps and showed a significant reduction in CRBSI rates from 0.59 to 0.26 episodes/1000 HD catheter days [136]. Even with long-term use, it appears that the chlorhexidine that is released does not generate resistance to this antiseptic agent [120, 121].

In a randomized prospective trial of HD patients over 13 months comparing use of a needle-free connector/disinfecting cap system to use of a cap with a chlorhexidine rod, CRBSI

rates in the group using the cap with a chlorhexidine rod were significantly lower than rates in the group with the needleless connector/disinfecting cap (0.28 vs 0.75 episodes/1000 HD catheter days).

Innovative HD Catheter Design and Composition

There have also been considerations to change the composition or design of HD catheters to try to reduce catheter-related infections. Much of this effort has focused on preventing bacterial colonization and biofilm formation in catheters [137, 138]. Catheters impregnated with various antibiotics, antimicrobials, or anticoagulants have been designed, most of them for acute care HD catheters since the active agents are limited in potency, often eluting away by 7–10 days [139–145]. There is limited data to date as to the broad efficacy of this approach in the chronic dialysis setting, however, with even less data in children with end-stage kidney disease.

Catheters are also being designed with polymers or additives aimed at maintaining a smooth intraluminal surface over time [51]. Since microorganisms find it easier to attach to and then produce biofilm on roughened surfaces, bacterial colonization should be impeded in catheters with smooth intraluminal surfaces that resist developing irregularities [50, 51]. Again there is limited data currently as to the clinical efficacy of this approach, though it seems to better address the role of biofilm in catheter-associated infections.

Antimicrobial Locks as Preventative Strategy

Antimicrobial locks have also been used as a preventative strategy to protect the intraluminal catheter surface from microorganism colonization and biofilm formation, with some reports suggesting more than 50% reduction in CRBSI rates [146–148]. A concern about long-term antimicrobial locks is the development of resistant microorganisms, though this seems to have been more problematic when such locks were first being utilized and much higher antibiotic concentrations were used [147, 149]. The risk-benefit analysis of preventative locks in any dialysis setting must also take into account the current frequency of CRBSI in that population and the risks that ensue from CRBSI treatment, including the impact of repetitive exposure to systemic antibiotics [150].

In a pediatric study of 43 children and over 16,000 HD catheter days, a group of children considered high risk for CRBSI received prophylactic tobramycin-TPA catheter locks after each dialysis session for 6 months and then weekly for an additional 6 months. CRBSI rates dropped significantly in these high-risk children to nearly a third of baseline levels. There was a trend toward increased infections again when prophylaxis was decreased to weekly. Additionally, there was significant decrease in systemic antibiotic exposure and percentage of HD catheters lost to malfunction during the period of prophylaxis.

More extensive data exists in adult HD patients looking at both the efficacy and potential adverse consequences of prophylactic antibiotic locks. Many studies have demonstrated decreased rates of CRBSI using various antimicrobial-anticoagulant mixes [33, 151–153]. Table 24.2 lists combinations of antimicrobials and anticoagulants that have been reported effective with both treating infection and in HD catheter prophylaxis. Several studies have shown that antibiotic resistance can become problematic with prophylactic locks and contribute to significant drug-resistant infections in these HD patients [33, 154], though other studies have not shown a significant change in antibiotic resistance over time [151–153, 155].

Given the results of initiatives like the SCOPE collaborative that reduced HD catheter-associated infections in children by implementing specific bundles of clinical care, it remains to be seen whether antibiotic locks may prove an additional strategy to reduce infections further and whether sequelae like antibiotic resistance will be a relevant issue in the setting of even less frequent prior or ongoing systemic exposure to antibiotics.

Table 24.2 Antibiotic lock solutions

Antibiotic	Antibiotic concentration	Anticoagulant	Anticoagulant concentration	Reference
Vancomycin	5 mg/ml	Heparin	5000 units/ml	[156]
Vancomycin	2.5 mg/ml	Heparin	2500 units/ml	[79]
Vancomycin	5 mg/ml	TPA	1 mg/ml	[30]
Cefazolin	5 mg/ml	Heparin	5000 units/ml	[6]
Tobramycin	5 mg/ml	TPA	1 mg/ml	[30]
Tobramycin	5 mg/ml	Heparin	5000 units/ml	[156]
Gentamicin	5 mg/ml	Heparin	5000 units/ml	[147]
Gentamicin	4 mg/ml	Trisodium citrate	3.13%	[157]
Gentamicin	1 mg/ ml	Heparin	5000 units/ml	[153]
Gentamicin	0.32 mg/ml	Trisodium citrate	4%	[151]

Exit Site and Tunnel Infections

An *exit site infection* usually presents with erythema of the site, often accompanied by tenderness, discharge, and even swelling and induration of the subcutaneous catheter tunnel within 2 cm of the exit site. An isolated exit site infection infrequently presents with fever, and most can be diagnosed readily with inspection of the exit site. Chronic poor exit site care, a breach of the exit site dressing, issues with immobilization of the catheter at the exit site, and *Staphylococcus aureus* nasal carriage are all risk factors for HD catheter exit site infections. *Staphylococcus* species are the most likely microorganisms causing HD catheter exit site infections.

When exit site infections are suspected from external inspection, the immediate subcutaneous catheter tunnel should also be carefully examined for tenderness or induration and to make sure that no discharge can be readily expressed out the exit site. Any discharge should be cultured, and there should be a low threshold to consider blood cultures from the HD catheter if there is any concern for an associated CRBSI. Ultrasound examination of the area may also be indicated to further delineate tunnel involvement or help define the extent of infection.

Meticulous exit site care must follow any initial concern for or diagnosis of an exit site infection, with special attention to antisepsis of the skin and application of triple antibiotic ointment or a chlorhexidine patch dressing at the exit site. This care should be repeated at every dialysis session until there is no longer any acute concern. Additionally, antibiotics are usually prescribed, most often oral cefazolin as empiric therapy. Culture results of any discharge and clinical response can guide ongoing antibiotic therapy. In the setting of concern for CRBSI or a more systemic process, intravenous antibiotic therapy should be used.

The typical duration of antibiotic treatment for an uncomplicated HD exit site infection is 10–14 days, and symptoms are expected to resolve within the first week. Lack of resolution of symptoms or early recurrence after the completion of treatment should prompt re-evaluation. MRSA or gram-negative bacterial infection is the usual reason for suboptimal early response to typical measures. The more widespread adoption of agents such as >0.5% chlorhexidine with alcohol, 70% alcohol, or povidone-iodine for skin antisepsis near the exit site along with use of triple antibiotic ointment or a chlorhexidine patch should continue to help reduce the frequency with which exit site infections are faced in children on HD.

In comparison to an exit site infection, a tunnel infection is a more serious complication of HD catheter use. Tunnel infections are diagnosed by erythema, induration, or tenderness along the subcutaneous HD catheter tunnel distal to the exit site. On occasion, purulent discharge may be milked along the tunnel to the exit site. Tunnel infections may occur without a concomitant exit site infection, but their development is always a concern when a child with an HD catheter has an exit site infection. Tunnel infections are more dif-

ficult to clear than exit site infections given they are not as readily accessible for local care, and there is always concern about involvement of surrounding tissue or hematogenous spread, especially when there is concomitant fever. Accordingly, it is typical practice to treat a tunnel infection with intravenous antibiotics.

Prior to antibiotic administration, any discharge from the exit site or expressed from the tunnel should be cultured, and blood cultures should also be obtained from the HD catheter ports. If there is palpation of any collection along the tunnel, tunnel ultrasound should be obtained to look for abscess. Generally, most centers begin to treat tunnel infections with the same empiric antibiotics as CRBSI, with narrowing of antibiotic coverage determined by culture results. Given the concern for deeper tissues being at risk of infection, the treatment duration is typically 3 weeks. If the symptoms exacerbate, do not substantially improve during the first week, or recur early after the completion of treatment, the HD catheter should be removed and replaced with the creation of a new exit site and tunnel.

AVF and AVG Infections

An AVF is always the vascular access of choice for any patient on long-term HD. An AVF provides better dialysis efficacy and is much less likely to have issues with infection than a catheter. An AVG is considered in those in whom AVF cannot be created. Although infections may be seen more often in an AVG than an AVF, their frequency is still dramatically lower than rates seen with HD catheters, with overall incidence estimated at <0.1 episodes/1000 access days.

Risk factors for AVF-/AVG-associated bacteremia include suboptimal antisepsis of the skin prior to cannulation, nasal or skin carriage of *Staphylococcus aureus*, and failure to receive typical pre-surgical site antibiotic prophylaxis with access creation or revision. Others have described infections related to pseudoaneurysms and secondarily infected hematomas that arise from infiltration with needle placement. The buttonhole technique for cannulation has also been associated with access infections [158]. Buttonhole cannulation uses the same needle insertion sites and the same subcutaneous tract for every dialysis session. This technique was derived to allow easier cannulation with less pain and was also thought to be less likely to cause infiltration or aneurysms, with more rapid hemostasis after needle removal. The standard rope-ladder cannulation method does seem, however, to decrease the risk of local infections and bacteremia.

Infections of AVF/AVG most often present with erythema, pain, drainage, or induration, typically near sites of cannulation. In some cases, fever may be present, but this is more typical with more advanced infections or systemic spread. Any discharge or exudate should be cultured and blood cultures should also be obtained. Ultrasound of the access area may be helpful to diagnose any subcutaneous abscess or other changes suggesting deeper infection. Based on examination and review of any imaging studies, a clinical determination can be made as to whether the infection is more along the lines of a superficial cellulitis or whether it extends to deeper tissue and vasculature. With concern for more significant infections, there may be a need to discontinue using the access, and a temporary dialysis catheter may need to be placed.

As with exit site or tunnel infections, the most likely pathogen is *Staphylococcus* species or another gram-positive organism. Empiric therapy with both gram-positive and gram-negative coverages, akin to treatment for CRBSI, should be started with any concern for actual infection of the AVF or AVG, with ongoing therapy guided by culture results and clinical response. On occasion, surgical intervention will be necessary for drainage of an infected hematoma or abscess. The recommended duration of treatment is 6 weeks of systemic antibiotics [75]. Most infections can be cleared with antibiotics without loss of the access. If metastatic infections or septic emboli arise from the infected access, surgical excision of AVF/AVG needs to be considered. Similarly, there should be a low threshold to do echocardiography with persistent fevers or positive blood cultures or other sites of infection arising to rule out concomitant endocarditis.

Related to the need to use exogenous material in its creation, bacteremia and local infec-

tions are more common with an AVG than an AVF, as are metastatic or systemic manifestations or the need for surgical intervention. With partial or complete resection of the AVG and associated infected tissue and skin, temporary HD access may be needed while there is ongoing antibiotic therapy. With creation of a new access, healthy subcutaneous tissue and overlying skin need to be used. Recurrence of fever or other symptoms during treatment or shortly following its completion raises concerns for residual or metastatic infections such as osteomyelitis or endocarditis and generally benefits from consultation with an infectious disease specialist.

Preventive strategies to reduce AVF- and AVG-associated infections are part of common clinical care. Perioperative gram-positive antibiotic coverage during creation or surgical revisions of a permanent HD access is standard, as is provision of appropriate antibiotic prophylaxis with high-risk interventions that may have associated bacteremia such as dental procedures and gastrointestinal or genitourinary interventions. Use of appropriate antiseptics such as >0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine on the skin over the access reduces the risk of introduction of microorganisms into the access during cannulation. As with any skin antisepsis, cleaning the site for an appropriate amount of time and then allowing the site to dry optimize the benefits of such care.

In the setting of persistent fevers without an apparent source of infection, chronic elevation of inflammatory markers, or erythropoietin-resistant anemia, a prior thrombosed AVG that is still in place may need to be investigated as a source of ongoing clinically significant inflammation or even infection. Physical examination and ultrasound of the area may be helpful. There is also data to suggest that technetium-labeled leukocyte scans may be able to more precisely assess if there is ongoing infection in an old or unused AVG, with close correlation between positive findings on scan and eventual positive bacterial cultures following surgical excision [159]. This potential complication may be especially important for kidney transplant patients with clotted but not resected AVGs [160].

Transmissible Infections in the Pediatric Hemodialysis Unit

Given the nature of hemodialysis, there is a high risk for blood exposure for both hemodialysis patients and their healthcare providers. Of particular concern are blood-borne pathogens such as hepatitis and HIV. With the more widespread adoption of specific guidance regarding infection control in the hemodialysis unit, the number of such infections is quite small, especially considering the ever-increasing number of adult chronic hemodialysis patients. Given that children on hemodialysis make up such a tiny fraction of the entire hemodialysis population and are much less likely to spend long periods of time on hemodialysis prior to transplantation, the number of such pediatric infections is even smaller.

Transmission of hepatitis B infection was of particular concern when chronic hemodialysis first became widespread in the early 1970s, with incidence rates up to 30% being described related to poor infection control practices and the need for repeated blood transfusions in the era before erythropoietin availability [161]. With stricter infection control requirements, the advent of erythropoietin, and the development of the hepatitis B vaccine, dialysis-acquired incident hepatitis B infections have dropped to 0.05% in the United States [162], and most patients with hepatitis infections receiving dialysis now acquired their infection prior to their need for dialysis.

Routine childhood hepatitis B vaccination was begun in 1991 with that recommendation extending to adolescents in 1995 to limit the number of non-immune pediatric patients entering adulthood. As a result, almost all children now starting hemodialysis in the United States are already vaccinated against hepatitis B. Nonetheless, any child starting dialysis needs to be screened for hepatitis B infection (HBsAg, HBsAb, HBcAb) before or within 7 days of initiation. Until there is confirmation that the child does not have an active hepatitis B infection, the child needs to be kept isolated from other patients while on dialysis and needs to be dialyzed on a dedicated machine.

In the child who has never been immunized, a primary series of hepatitis B vaccine should be provided, with follow-up serologic testing to con-

firm subsequent immunity. In the immunized child, with initial serologic evidence of immunity, subsequent periodic serologic assessment while on HD is needed, since children with CKD and on dialysis lose serologic evidence of immunity at an increased rate compared to healthy children [163]. With loss of immunity, revaccination is recommended, with reassessment of serologies to confirm if there has been seroconversion once more.

Similar to hepatitis B, hepatitis C or HIV infection is less of a concern in children on dialysis as well. It is rare to find a young child with hepatitis C or HIV infection outside of perinatal transmission. The advent of antiretroviral therapy has substantially reduced the likelihood of perinatal HIV transmission. Since both of these viruses are primarily transmitted through IV drug abuse or sexual activity, these infections are more of a concern in adolescents, but again their frequency is very low. Children initiating hemodialysis should, nonetheless, be screened for both these infections.

Unlike hepatitis B, infection with hepatitis C or HIV does not require patient isolation, dedicated equipment, or any other special practice during hemodialysis. Typical infection control measures for provision of care and procurement and handling of laboratory samples, recommended sanitization and maintenance of dialysis equipment, as well as well-established blood bank practices to screen blood products for these infections should effectively prevent any iatrogenic disease transmission. Moreover, ongoing antiviral therapy for HIV and consideration of antiviral therapy for hepatitis C should also help reduce the very low transmission risk during dialysis even further. The use of antiviral prophylaxis after needle stick injury can also reduce concern for this route of acquired infection.

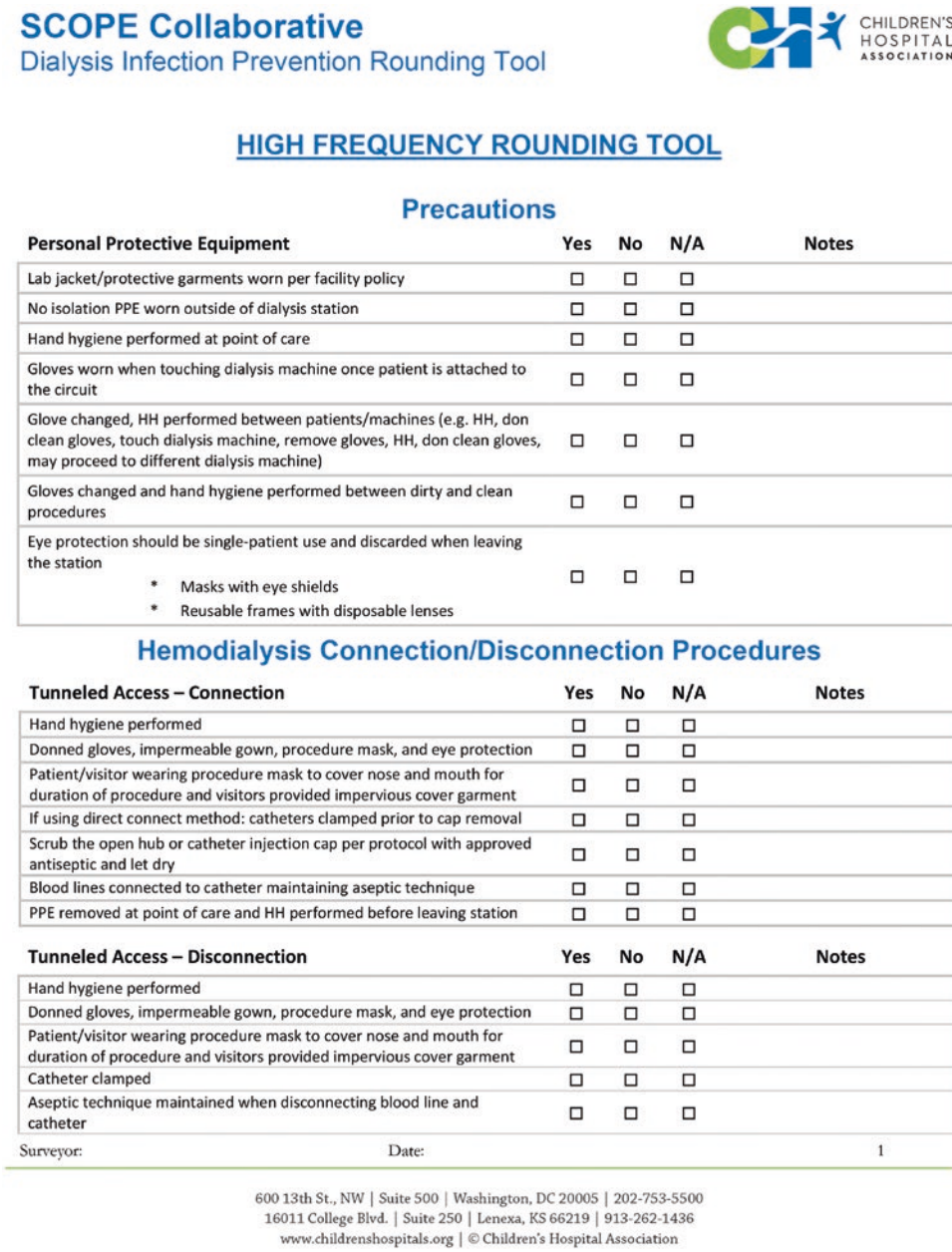
Infection Prevention and Surveillance

As alluded to elsewhere in this chapter, embedding strategies to prevent infection into day-to-day dialysis care can play an important role in reducing the number of dialysis-associated infections that occur. Strict adherence to practice guidelines for catheter connection and disconnection and for exit site and dressing care is often made difficult by time constraints or varying levels of patient cooperation. Moreover, it is important for there to be general awareness that guidelines may change or be revised as new evidence is gained from clinical experience, such as the switch to 0.5% chlorhexidine with alcohol solutions from 10% povidone-iodine solutions for catheter hub and exit site care [120, 121]. Concomitant with efforts to optimize the technical aspects of dialysis provision to reduce infection risk, there also needs to be ongoing attention to aspects of a general infection prevention strategy, such as the environment of care, screening for infection in patients and staff, and use of personal protective equipment.

One of the earliest reports of successful reduction of CRBSI by using standardized catheter care practices was by Eisenstein et al. in a pediatric dialysis unit [23]. Similar results were achieved in adults with implementation of the CDC Dialysis Bloodstream Infection Prevention Collaborative Interventions [35, 36], with reduction in infection shown to be sustainable over a prolonged period of time [164]. Recent data from the Children's Hospital Association's Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) collaborative has also shown how the implementation of standardized care practices can affect short-term and long-term dialysis-associated infection rates in children [165]. The SCOPE collaborative standardized HD catheter care via implementation of care bundles that were aligned with the preventive practices earlier recommended by the CDC [36, 37]. Ongoing adherence to these recommendations was tracked by active surveillance within each participating center. During the first 4 years of SCOPE, increasing rates of adherence to recommended bundle practices were demonstrated. During this same time, the adjusted CRBSI rate significantly decreased from 3.3/100 patient months in the 12 months prior to implementation of the care bundles to 0.8/100 patient months during the study period ($p < 0.001$) [166].

When implementing standardized practices and auditing for adherence over time, it is critical to have auditing tools that guide assessment of performance across the spectrum of care practices that need to be assessed. Additionally, including

more routine infection prevention surveillance into these auditing tools facilitates ongoing data collection. Identifying staff members responsible for the audits and sharing the audit results with dialysis staff and patients also help to inculcate a culture of safety and quality within the dialysis unit. In Figs. 24.5, 24.6, and 24.7, auditing tools from the SCOPE collaborative detail key factors



SCOPE Collaborative
Dialysis Infection Prevention Rounding Tool

CHILDREN'S HOSPITAL ASSOCIATION

HIGH FREQUENCY ROUNDING TOOL

Precautions

Personal Protective Equipment	Yes	No	N/A	Notes
Lab jacket/protective garments worn per facility policy	☐	☐	☐	
No isolation PPE worn outside of dialysis station	☐	☐	☐	
Hand hygiene performed at point of care	☐	☐	☐	
Gloves worn when touching dialysis machine once patient is attached to the circuit	☐	☐	☐	
Glove changed, HH performed between patients/machines (e.g. HH, don clean gloves, touch dialysis machine, remove gloves, HH, don clean gloves, may proceed to different dialysis machine)	☐	☐	☐	
Gloves changed and hand hygiene performed between dirty and clean procedures	☐	☐	☐	
Eye protection should be single-patient use and discarded when leaving the station * Masks with eye shields * Reusable frames with disposable lenses	☐	☐	☐	

Hemodialysis Connection/Disconnection Procedures

Tunneled Access – Connection	Yes	No	N/A	Notes
Hand hygiene performed	☐	☐	☐	
Donned gloves, impermeable gown, procedure mask, and eye protection	☐	☐	☐	
Patient/visitor wearing procedure mask to cover nose and mouth for duration of procedure and visitors provided impervious cover garment	☐	☐	☐	
If using direct connect method: catheters clamped prior to cap removal	☐	☐	☐	
Scrub the open hub or catheter injection cap per protocol with approved antiseptic and let dry	☐	☐	☐	
Blood lines connected to catheter maintaining aseptic technique	☐	☐	☐	
PPE removed at point of care and HH performed before leaving station	☐	☐	☐	

Tunneled Access – Disconnection	Yes	No	N/A	Notes
Hand hygiene performed	☐	☐	☐	
Donned gloves, impermeable gown, procedure mask, and eye protection	☐	☐	☐	
Patient/visitor wearing procedure mask to cover nose and mouth for duration of procedure and visitors provided impervious cover garment	☐	☐	☐	
Catheter clamped	☐	☐	☐	
Aseptic technique maintained when disconnecting blood line and catheter	☐	☐	☐	

Surveyor: Date: 1

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Fig. 24.5 Infection prevention high-frequency rounding tool. Various factors relating to the environment of care, personal protective equipment, dialysis connection and disconnection techniques, and exit site care that can play a role in infection risk. Successful mitigation of infection risk requires active surveillance for adherence to expected performance. This rounding tool covers parameters that should be assessed frequently. (Rounding tool shared with permission: Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative, Children's Hospital Association)

Scrub the open hub or catheter injection cap per protocol with approved antiseptic and let dry	☐	☐	☐	
New caps attached maintaining aseptic technique	☐	☐	☐	
PPE removed at point of care and HH performed before leaving station	☐	☐	☐	

Graft/Fistula Cannulation	**Yes**	**No**	**N/A**	**Notes**
Site cleaned with soap and water by either patient or staff member	☐	☐	☐	
Hand hygiene performed	☐	☐	☐	
Donned gloves, impermeable gown, procedure mask, and eye protection	☐	☐	☐	
Patient/visitor wearing procedure mask to cover nose and mouth for duration of procedure and visitors provided impervious cover garment	☐	☐	☐	
Apply skin antiseptic and allow to dry per protocol	☐	☐	☐	
No contact with fistula/graft site after antisepsis	☐	☐	☐	
Insert needles while maintaining aseptic technique and secure with sterile dressing	☐	☐	☐	
Maintain aseptic technique while connecting blood lines	☐	☐	☐	
PPE removed at point of care and HH performed before leaving station	☐	☐	☐	

Graft/Fistula Decannulation	**Yes**	**No**	**N/A**	**Notes**
Hand hygiene performed	☐	☐	☐	
Donned gloves, impermeable gown, procedure mask, and eye protection	☐	☐	☐	
Patient/visitor wearing procedure mask to cover nose and mouth for duration of procedure and visitors provided impervious cover garment	☐	☐	☐	
After rinse back step, remove gloves, perform hand hygiene, and don clean gloves before disconnecting blood lines	☐	☐	☐	
Aseptic technique maintained while disconnecting from blood lines	☐	☐	☐	
Needles removed aseptically and retraction device activated	☐	☐	☐	
Gloves removed and hand hygiene performed	☐	☐	☐	
Donned clean gloves (patient or staff) to compress site	☐	☐	☐	
Clean bandage applied to site	☐	☐	☐	
PPE removed at point of care and HH performed before leaving station	☐	☐	☐	

Dressing and Line Care

Dressing Change	**Yes**	**No**	**N/A**	**Notes**
Perform hand hygiene	☐	☐	☐	
Maintain aseptic technique throughout procedure	☐	☐	☐	
Patient/visitor wearing procedure mask to cover nose and mouth for duration of procedure	☐	☐	☐	
Gather supplies below and place on cleaned surface				
Supplies needed for sterile dressing change	☐	☐	☐	
Masks	☐	☐	☐	
Antibiotic ointment or antimicrobial impregnated disc/dressing per policy	☐	☐	☐	

Surveyor: Date: 2

CHILDREN'S HOSPITAL ASSOCIATION
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Fig. 24.5 (continued)

Close curtains or shut door to minimize air circulation and interruptions	☐	☐	☐	
Perform hand hygiene and don clean gloves and mask	☐	☐	☐	
Open dressing supplies and place on sterile barrier	☐	☐	☐	
Remove old dressing and dispose of appropriately	☐	☐	☐	
Remove gloves and perform hand hygiene	☐	☐	☐	
Don sterile gloves	☐	☐	☐	
Clean insertion site and allow to dry per product recommendations or policy	☐	☐	☐	
Apply antibiotic ointment to insertion site with sterile cotton tipped applicator and cover with sterile gauze **or** place antimicrobial impregnated disc per policy	☐	☐	☐	
Apply transparent or CHG securement dressing over insertion site and secure to protect against dislodgement (i.e. Primafix tape)	☐	☐	☐	
Remove gloves and perform hand hygiene	☐	☐	☐	

Line Care	**Yes**	**No**	**N/A**	**Notes**
Maintain line visibility throughout dialysis treatment	☐	☐	☐	

Environmental Considerations

Waste Disposal	**Yes**	**No**	**N/A**	**Notes**
Sharps containers are puncture-resistant, rigid, labeled, secured and not overfilled	☐	☐	☐	
Non-sharp biohazardous waste is placed in biohazard containers and stored in a secured dirty utility room and removed for disposal regularly to avoid overfilling of containers *(Note: Biohazardous waste would include but is not limited to blood tubing, dialyzer filter, grossly saturated linens/towels/gauze)*	☐	☐	☐	

Dialysis Station Disinfection	**Yes**	**No**	**N/A**	**Notes**
Dialysis station (chair and machine) cleaning does not start until patient has left the bay and is performed in a timely manner	☐	☐	☐	
Don gloves, impermeable gown, and eye protection if reasonable concern for splash of bleach present.	☐	☐	☐	
Wipe all surfaces with hospital-approved disinfectant per protocol	☐	☐	☐	
Surfaces remain visibly wet per disinfectant instructions	☐	☐	☐	
Patient Chair				
Make sure the chair is open all the way and clean all surfaces	☐	☐	☐	
Clean from top to bottom and reach all crevices	☐	☐	☐	
If crib present, lift mattress to clean all sides	☐	☐	☐	

Surveyor: Date: 3

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Fig. 24.5 (continued)

Hemodialysis machine			
Dialyzer filter and blood tubing discarded in leak-proof container	☐	☐	☐
Priming bucket empty and dry prior to disinfection (if applicable)	☐	☐	☐
Single use supplies discarded	☐	☐	☐
Remove gloves, perform hand hygiene, don clean gloves	☐	☐	☐
Clean from top to bottom	☐	☐	☐
All surfaces cleaned (including but not limited to Hansen connectors, insides of doors, fold down keyboard)	☐	☐	☐
If acid and bicarb are in reusable containers, exterior must be cleaned, and jugs lifted to clean the machine underneath	☐	☐	☐
Wall Box			
Wall boxes cleaned at end of day when in use, and PRN	☐	☐	☐
Wipes or supplies used to clean wall box are discarded and not used to clean other surfaces/items	☐	☐	☐
After cleaning, gloves removed and hand hygiene performed	☐	☐	☐
Reusable supplies cleaned per policy (e.g., BP cuff, clip board, chart)	☐	☐	☐
PPE removed at point of care and HH performed before leaving station	☐	☐	☐

Electronic Devices	**Yes**	**No**	**N/A**	**Notes**
Hand-held devices are disinfected between patients with correct product and according to policy/procedure				
Tablet Computers/E-readers	☐	☐	☐	
Bar Code Scanners	☐	☐	☐	
Thermometers	☐	☐	☐	
Blood Glucose Meter	☐	☐	☐	
Personal Communication Devices (if used during patient care)	☐	☐	☐	
Gaming Devices	☐	☐	☐	
Portable devices are disinfected between patients with correct product and according to policy/procedure:				
Computers-on-wheels	☐	☐	☐	
Pulse oximeters	☐	☐	☐	
CR Monitors	☐	☐	☐	
BP Cuffs	☐	☐	☐	

Surveyor: Date: 4

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Fig. 24.5 (continued)

Toys	Yes	No	N/A	Notes
Stored in separate area from other patient care supplies	☐	☐	☐	
Stored in designated space after patient use until cleaned	☐	☐	☐	
Shared toys are cleanable and disinfected between patient uses per policy/procedure	☐	☐	☐	
Cleaned by trained staff per guidelines in a non-hand washing sink with a hospital-approved disinfectant	☐	☐	☐	
Toy carts not taken into patient care stations	☐	☐	☐	

Surveyor: Date: 5

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Fig. 24.5 (continued)

to assess during such infection-centered rounds, with separate auditing tools for items that should be surveyed frequently compared to those requiring only intermittent or special consideration.

Conclusion

This risk of infection for the child on hemodialysis is most influenced by the child's dialysis access. Although children with permanent vascular access in the form of AVF or AVG are much less likely to have dialysis-related infections than children who receive HD via catheter, many children on HD rely on catheters. The ongoing development and adoption of practices specific to HD catheter use and care should help minimize infection risk, with special focus on improving rates of CRBSI (Fig. 24.8).

Key Take-Home Messages for This Chapter Include

Reports from both single pediatric centers and a multicenter collaborative of pediatric dialysis units show that implementation of guidelines that stress meticulous hand hygiene, chronic care of the catheter exit site, and aseptic connections to the HD catheter hubs decreases CRBSI in children.

Antisepsis of skin near the exit site and of the HD catheter hubs should use agents with demonstrated efficacy in the dialysis setting, notably >0.5% chlorhexidine with alcohol, 70% alcohol, or 10% povidone-iodine.

Triple antibiotic ointment or a chlorhexidine patch should be placed at the exit site and then covered with a transparent dressing or gauze; the exit site should be visualized with each dialysis treatment, and exit site care and a new dressing placed at least weekly.

Antibiotic locks are an effective prophylactic strategy and have also been shown to augment cure rates when used with systemic antibiotics for treatment of CRBSI.

With suspected CRBSI, blood cultures should be obtained from the catheter hubs/HD circuit prior to antibiotic treatment; broad-spectrum antibiotics such as vancomycin and ceftazidime are commonly used empirically while awaiting culture results.

CRBSI with microorganisms that are difficult to clear from vascular catheters such as *Pseudomonas*, *Staphylococcus aureus*, or fungus generally mandates catheter removal.

Persistently positive blood cultures or recurrent symptoms during antibiotic treatment also require HD catheter removal; wire-guided exchange can be safely utilized for most patients.

Antibiotics should be provided with CRBSI for at least 2–3 weeks after negative blood cultures are first obtained; complicated infections may require longer therapy.

Exit site and tunnel infections generally respond rapidly to initiation of antibiotics and usually are not associated with CRBSI.

AVF and AVG infections are rare; AVG infections are more likely to be complicated or require surgical intervention.

SCOPE Collaborative
Dialysis Infection Prevention Rounding Tool

CHILDREN'S HOSPITAL ASSOCIATION

INTERMITTENT ROUNDING TOOL

Environmental Considerations

Water Room	Yes	No	N/A	Notes
Water room floors clean and free of clutter	☐	☐	☐	
All open test strips labeled with open and discard date	☐	☐	☐	
No rust present on carts or shelves	☐	☐	☐	
Any signs are laminated and kept clean	☐	☐	☐	
Alcohol based hand sanitizer available	☐	☐	☐	
Separate sink available for hand hygiene, if applicable	☐	☐	☐	
All open chemicals are labeled with open and discard dates	☐	☐	☐	

Medication Storage and Preparation	Yes	No	N/A	Notes
Medication room is clean and secured	☐	☐	☐	
Medication refrigerator monitored for proper temperature	☐	☐	☐	
Different Heparin concentrations should be stored separately to avoid dosing errors	☐	☐	☐	
Designated area for medication preparation, not near treatment area	☐	☐	☐	
Injectable medication should be handled and transported from medication preparation area in a manner that minimizes contamination risk	☐	☐	☐	
Counter area around sink is not used for temporary or permanent storage of meds or supplies	☐	☐	☐	
Single dose medication vials discarded after one-time use. *(Note: single dose vials and bottles are recommended over multi-dose products)*	☐	☐	☐	
If multi-dose medication vials are needed, they are labeled with opening date and discard date *(NOTE: Good for 28 days after opening or by manufacturer's expiration date, whichever is sooner)*	☐	☐	☐	
Multi-dose vials are not stored in the immediate patient care areas	☐	☐	☐	
Vial tops scrubbed with sterile alcohol pads and let dry before entry	☐	☐	☐	
Vials are only entered once and always with a new needle	☐	☐	☐	
IV bags are designated for single patient	☐	☐	☐	
If vaccines stored on unit, they are in temperature monitored refrigerator in either a designated refrigerator or in clearly labeled, separate bins from other medications	☐	☐	☐	
No expired items	☐	☐	☐	

Surveyor: Date: 1

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Fig. 24.6 Infection prevention intermittent frequency rounding tool. Various factors relating to the environment of care that play a more limited role in infection risk, but nonetheless should be assessed at intervals. This rounding tool covers environmental parameters that should be assessed with intermittent frequency. (Rounding tool shared with permission: Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative, Children's Hospital Association)

Clean Supply Storage	Yes	No	N/A	Notes
Supply and equipment storage area is clean and free of dust or clutter	☐	☐	☐	
Supplies stored at least six inches off floor	☐	☐	☐	
Supply carts with solid bottoms	☐	☐	☐	
No corrugated cardboard or outside shipping boxes present	☐	☐	☐	
No expired items	☐	☐	☐	
Supplies are stored covered or in a positive pressure room	☐	☐	☐	
Supplies are not stored under sinks	☐	☐	☐	

Linen Storage	Yes	No	N/A	Notes
Linen is stored according to policy/procedure *(Note: For example, it is covered or in closed cabinets when stored)*	☐	☐	☐	
Storage location is clean and if stored on a cart, the lowest shelf is a solid bottom and at least six inches off the floor	☐	☐	☐	
Stored separate from other patient care supplies	☐	☐	☐	

Ice Machines	Yes	No	N/A	Notes
Trays are free of buildup and visibly clean	☐	☐	☐	
Preventative maintenance performed per manufacturer's recommendations and documented	☐	☐	☐	

Refrigerator/Freezer	Yes	No	N/A	Notes
If not electronically monitored- Refrigerator/freezer temperature logs complete for days clinic is open with no blank spaces or lines through spaces	☐	☐	☐	
Refrigerator/freezer free of spills/stains	☐	☐	☐	
Freezer with no frost build up	☐	☐	☐	
Cleaning logs complete (if applicable)	☐	☐	☐	

Waiting Area	Yes	No	N/A	Notes
Hand sanitizer, tissues, and waste receptacle available for use	☐	☐	☐	
Disinfectant wipes and gloves available to disinfect check-in kiosks/stations	☐	☐	☐	
IP signage visible in waiting area:				
Cover your cough	☐	☐	☐	
Flu shot posters	☐	☐	☐	
Hand hygiene information	☐	☐	☐	

Surveyor: Date: 2

CHILDREN'S HOSPITAL ASSOCIATION
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Fig. 24.6 (continued)

SCOPE Collaborative
Dialysis Infection Prevention Rounding Tool

CHILDREN'S HOSPITAL ASSOCIATION

SPECIAL CONSIDERATIONS ROUNDING TOOL

Screening and Precautions

Illness Screening	Yes	No	N/A	Notes
Patients, parents/caregivers, and visitors are screened daily for contagious illnesses upon arrival to clinic AND includes the following components:	☐	☐	☐	
Questions about exposure to illness	☐	☐	☐	
Fever or rash present	☐	☐	☐	
Cough/Upper Respiratory Infection	☐	☐	☐	

Isolation Considerations	Yes	No	N/A	Notes
Hepatitis Bstatus confirmed (prior to initiation of dialysis treatment, when feasible) and positive patients are properly isolated with dedicated machine and nurse/tech.	☐	☐	☐	
Hepatitis unknown status patients (e.g. those awaiting results) in isolation pending results.	☐	☐	☐	
Appropriate isolation signage is available and followed as indicated	☐	☐	☐	
Machine chemical disinfection after each treatment of Hepatitis B confirmed or unknown status	☐	☐	☐	
Bleach disinfection procedure performed before machine returned to general patient use.	☐	☐	☐	

Environmental Considerations

Privacy Curtain	Yes	No	N/A	Notes
Free of stains or tears	☐	☐	☐	
Avoiding touching with dirty gloves/hands	☐	☐	☐	
Hand hygiene performed immediately before and after touching the curtains	☐	☐	☐	
Changed on schedule per manufacturer's recommendations or institution policy/procedure	☐	☐	☐	

Surveyor: Date: 1

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Fig. 24.7 Infection prevention special considerations rounding tool. Various factors relating to illness screening for patients, staff, or visitors and certain environment of care parameters can impact infection risk in the dialysis unit and warrant special consideration for inclusion in dialysis unit surveillance. This rounding tool covers such special considerations. (Rounding tool shared with permission: Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative, Children's Hospital Association)

Patient and family education	• Share information early and often as to risk of long-term catheter use and benefits of AVF • Consider peritoneal dialysis as alternate dialysis modality • Discuss importance of transplant evaluation if candidate • Ongoing education on catheter care at home
Hemodialysis staff	• Track and trend infections with comparison to benchmarks • Audit handwashing • Audit exit site care • Audit catheter connection and disconnection • Ongoing staff education and competency testing
Exit site care	• Skin antisepsis with chlorhexidine-alcohol, povidone-iodine, or 70% alcohol during dressing changes • Use of povidone-iodine or polysporin triple antibiotic topical oinment during dressing changes OR use of chlorhexidine-impregnated dressing
Catheter care	• Catheter hub disinfection with chlorhexidine alcohol, povidone-iodine, or 70% alcohol with any connection/disconnection

Fig. 24.8 Strategies for prevention of hemodialysis catheter infections. Various factors relating to the patient and family, the hemodialysis staff, and the approach to chronic care of the catheter and exit site influence the likelihood of a catheter-related infection. Successful mitigation of infections generally requires attention to multiple factors across these domains. (Modified from: Fischer et al. [101])

Transmission of infection from dialysis equipment or between dialysis patients is uncommon when standard infection control practices are followed.

References

1. Shroff R, Calder F, Bakkaloglu S, Nagler EV, Stuart S, Stronach L, Schmitt CP, Heckert KH, Bourquelot P, Wagner AM, Paglialonga F, Mitra S, Stefanidis CJ on behalf of the European Society for Pediatric Nephrology Dialysis Working Group. Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group. Nephrol Dial Transplant. 2019;34:1–20.
2. Borzych-Duzalka D, Shroff R, Ariceta G, Yap YC, Paglialonga F, Xu H, Kang HG, Thumfart J, Aysun KB, Stefanidis CJ, Fila M, Sever L, Vondrak K, Szabo AJ, Szczepanska M, Ranchin B, Holtta T, Zaloszyc A, Bilge I, Warady BA, Schaefer F, Schmitt CP. Vascular access choice, complications, and outcomes in children on maintenance hemodialysis: findings from the International Pediatric Hemodialysis Network (IPHN) Registry. Am J Kidney Dis. 2019;74:193–202.
3. 2018 USRDS annual data report, volume 2: ESRD in the United States: Chapter 7: ESRD among children, adolescents and young adults. https://www.usrds.org/2018/view/v2_07.aspx.
4. Baracco R, Mattoo T, Jain A, Kapur G, Valentini RP. Reducing central venous catheters in chronic hemodialysis- a commitment to arteriovenous fistula creation in children. Pediatr Nephrol. 2014;29(10):2013–20.

5. Allon M. Dialysis catheter-related bacteremia: treatment and prophylaxis. Am J Kidney Dis. 2004;44:779–91.
6. Onder AM, Chandar J, Coakley S, Abitbol CL, Montane B, Zilleruelo G. Predictors and outcome of catheter-related bacteremia in children on chronic hemodialysis. Pediatr Nephrol. 2006;21:1452–8.
7. Paglialonga F, Esposito S, Edefonti A, Principi N. Catheter-related infections in children treated with hemodialysis. Pediatr Nephrol. 2004;19:1324–33.
8. Stefanidis C. Prevention of catheter-related bacteremia in children on hemodialysis: time for action. Pediatr Nephrol. 2009;24:2087–95.
9. Dryden MS, Samson A, Ludlam HA, et al. Infective complications associated with the use of the Quinton "Permcath" for long-term central vascular access in haemodialysis. J Hosp Infect. 1991;19:257–62.
10. Stevenson KB, Hannah EL, Lowder CA, et al. Epidemiology of hemodialysis vascular access infections from longitudinal infection surveillance data predicting the impact of NKF-DOQI clinical practice guidelines for vascular access. Am J Kidney Dis. 2002;39:549–64.
11. Shingarev R, Barker-Finkel J, Allon M. Natural history of tunneled dialysis catheters placed for hemodialysis initiation. J Vasc Interv Radiol. 2013;24:1289–95.
12. Schwab SJ, Beathard GA. The hemodialysis catheter conundrum: hate living with them, but can't live without them. Kidney Int. 1999;56:1–17.
13. Pastan S, Soucie M, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. Kidney Int. 2002;62:620–6.
14. Allon M, Depner TA, Radeva M, Bailey J, Beddhu S, Butterly D, Coyne DW, Gassman JJ, Kaufman AM, Kaysen GA, Lewis JA, Schwab SJ, for the HEMO Study Group. Impact of dialysis dose and membrane on infection-related hospitalization and death: results of the HEMO Study. J Am Soc Nephrol. 2003;14:1863–70.
15. Fadrowski JJ, Hwang W, Frankenfield DL, Fivush BA, Neu AM, Furth SL. Clinical course associated with vascular access type in a national cohort of adolescents who receive hemodialysis: findings from the clinical performance measures and US renal data system projects. Clin J Am Soc Nephrol. 2006;1:987–92.
16. Brem AS, Lambert C, Kitsen J, Somers M, Shemin DG. Chronic dialysis and access-related morbidities in children. Nephrol Dial Transplant. 2005;34:278–89.
17. Fadrowski JJ, Hwang W, Neu AM, Fivush BA, Furth SL. Patterns of use of vascular catheters for hemodialysis in children in the United States. Am J Kidney Dis. 2009;53:91–8.
18. Lofaro D, Vogelzang JL, van Stralen KJ, Jager KJ, Groothoff JW. Infection-related hospitalizations over 30 years of follow-up in patients starting renal replacement therapy at pediatric age. Pediatr Nephrol. 2016;31:315–23.
19. Hayes WN, Watson AR, Callaghan N, Wright E, Stefanidis CJ, European Pediatric Dialysis Working Group. Vascular access: choice and complications in European pediatric hemodialysis units. Pediatr Nephrol. 2012;27:999–1004.
20. Sheth R, Kale A, Brewer ED, Brandt ML, Nuchtern JG, Goldstein SL. Successful use of Tesio catheters in pediatric patients receiving chronic hemodialysis. Am J Kidney Dis. 2001;38:553–9.
21. Kovalski Y, Cleper R, Krause I, Davidovits M. Hemodialysis in children weighing less than 15 kg: a single-center experience. Pediatr Nephrol. 2007;22:2105–10.
22. Lee T, Barker J, Allon M. Tunneled catheters in hemodialysis patients: reasons and subsequent outcomes. Am J Kidney Dis. 2005;46:501–8.
23. Eisenstein I, Tarabeith M, Magen D, Pollack S, Kassis I, Ofer A, Engel A, Zelikovic I. Low infection rates and prolonged survival times of hemodialysis catheters in infants and children. Clin J Am Soc Nephrol. 2011;6:793–8.
24. Sharma A, Zilleruelo G, Abitbol CL, Montane B, Strauss J. Survival and complications of cuffed central venous catheters in children and young adults on chronic hemodialysis. Pediatr Nephrol. 1999;13:245–8.
25. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. Pediatr Nephrol. 1997;11:74–7.
26. Ramage IJ, Bailie A, Tyerman KS, McColl JH, Pollard SG, Fitzpatrick MM. Vascular access survival in children and young adults receiving long-term hemodialysis. Am J Kidney Dis. 2005;45:708–15.
27. Marsenic O, Rodean J, Richardson T, Swartz S, Claes D, Day JC, Warady B, Nue A, Scope Investigators. Tunneled hemodialysis catheter care practices and blood stream infection rate in children: results from the SCOPE collaborative. Pediatr Nephrol. 2020;35:135–43.
28. Chawla PG, Nevins TE. Management of hemodialysis catheter-related bacteremia- a 10-year experience. Pediatr Nephrol. 2000;14:198–202.
29. Araya CE, Fennell RS, Neilberger RE, Dharnidharka VR. Hemodialysis catheter-related bacteremia in children: increasing antibiotic resistance and changing bacteriological profile. Am J Kidney Dis. 2007;50:119–23.
30. Onder AM, Chandar J, Simon N, Saint-Vil M, Francoeur D, Nwobi O, Abitbol CL, Zilleruelo G. Treatment of catheter-related bacteremia with tissue plasminogen activator antibiotic locks. Pediatr Nephrol. 2008;28:457–64.
31. Von Baum H, Schehl J, Geiss HK, Schaefer F. Prevalence of vancomycin-resistant enterococci among children with end-stage renal failure. Mid-European Pediatric Peritoneal Dialysis Study Group. Clin Infect Dis. 1999;29:912–6.
32. Berns JS. Infection with antimicrobial-resistant microorganism in dialysis patients. Semin Dial. 2003;16:30–7.

33. Landry DL, Sweet SJ, Gobeille SL, et al. Long-term gentamicin lock catheter prophylaxis is associated with gentamicin-resistant Gram –positive bacteremia in chronic hemodialysis. Clin J Am Soc Nephrol. 2010;5:1799–804.
34. O'Grady NP, Alexander M, Burn LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S. Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. 2011. http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guielines-2011.pdf. Accessed om 12/26/2018.
35. Patel PR, Yi SH, Booth S, Bren V, Downham G, Hess S, Kelley K, Lincoln M, Morrissette K, Lindberg C, Jernigan JA, Kallen AJ. Bloodstream infection rates in outpatient hemodialysis facilities participating in a collaborative prevention effort: a quality improvement report. 2013. Am J Kidney Dis. 2013;62:322–30.
36. Centers for Disease Control and Prevention. Dialysis safety: infection prevention tools. Available at: https://www.cdc.gov/dialysis/prevention-tools/core-interventions.html. Accessed at 12/27/2019.
37. Patel PR, Brinsley-Rainisch K. The making dialysis safer for patients coalition: a new partnership to prevent hemodialysis-related infections. Clin J Am Soc Nephrol. 2018;13:175–81.
38. NTDS: promoting infection prevention in dialysis facilities 2017 annual report. Available at: http://www.asn-online.org/ntds.
39. Hoshal VL Jr, Ause RG, Hoskins PA. Fibrin sleeve formation on indwelling subclavian central venous catheter. Arch Surg. 1971;102:253–8.
40. Tapia G, Yee J. Biofilm: its relevance in kidney disease. Adv Chronic Kidney Dis. 2006;13:215–24.
41. Passerini L, Lam K, Costerton JW, King EG. Biofilms on indwelling vascular catheters. Crit Care Med. 1992;20:665–73.
42. Costerton JW, Steward PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284:1318–22.
43. Donlan RM. Biofilm formation: a clinically relevant microbiological process. Clin Infect Dis. 2001;33:1387–92.
44. Dasgupta MK. Biofilms and infection in dialysis patients. Semin Dial. 2002;15:338–46.
45. Raad I, Costerton JW, Sabharwal U, Sacilowski M, Anaisse E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis. 1993;168:400–7.
46. Fux CA, Costerton JW, Stewart PS, et al. Survival strategies of infectious biofilms. Trends Microbiol. 2005;13:34–40.
47. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet. 2001;358:135–8.
48. Jones SM, Ravani P, Hemmelgam BR, Muruve D, MacRae JM. Morphometric and biological characterization of biofilm in tunneled hemodialysis catheters. Am J Kidney Dis. 2011;57:449–55.
49. Ramanathan V, Riosa S, Al-Sharif AH, Mansouri MD, Tranchina A, Kayyal T, Abreo A, Aslam S, Nassar G, Darouiche RO. Characteristics of biofilm on tunneled cuffed hemodialysis catheters in the presence and absence of clinical infection. Am J Kidney Dis. 2012;60:976–82.
50. Kanaa M, Wright MJ, Sandoe JA. Examination of tunneled hemodialysis catheters using scanning electron microscopy. Clin Microbiol Infect. 2010;16:780–6.
51. Verbeke F, Haug U, Dhondt A, Beck W, Schnell A, Dietrich R, Deppisch R, Vanholder R. The role of polymer surface degradation and barium sulphate release in the pathogenesis of catheter-related infection. Nephrol Dial Transplant. 2010;25:1207–13.
52. Shanks RMQ, Sargent JL, Martinez RM, et al. Catheter lock solutions influence staphylococcal biofilm formation on abiotic surfaces. Nephrol Dial Transplant. 2006;21:2247–55.
53. Bosma JW, Siegert GE, Peerbooms PG, et al. Reduction of biofilm formation with trisodium citrate in haemodialysis catheters: a randomized controlled trial. Nephrol Dial Transplant. 2010;25:1213–7.
54. Cheesbrough JS, Finch RG, Burden RP. A prospective study of the mechanisms of infection associated with hemodialysis catheters. J Infect Dis. 1986;154:579–84.
55. Almirall J, Gonzalez J, Rello J, et al. Infection of hemodialysis catheters: incidence and mechanisms. Am J Nephrol. 1989;9:454–7.
56. Powe NR, Jaar B, Furth SL. Septicemia in dialysis patients: incidence, risk factors and prognosis. Kidney Int. 1999;55:1081–90.
57. Kaplowitz LG, Comstock JA, Landwehr DM. A prospective study of infections in hemodialysis patients: patient hygiene and other risk factors for infection. Infect Control Hosp Epidemiol. 1988;9:534–41.
58. Hoen B, Kessler M, Hestin D, Mayeux D. Risk factors for bacterial infections in chronic hemodialysis adult patients: a multicenter prospective survey. Nephrol Dial Transplant. 1995;10:377–81.
59. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. J Am Soc Nephrol. 1998;9:869–76.
60. Jean G, Charra B, Chazot C, Vanel T, Terrat JC, Hurot JM, Laurent G. Risk factor analysis for long-term tunneled dialysis catheter-related bacteremias. Nephron. 2002;91:399–405.
61. Mokrzycki MH, Schroppel B, Von Gersdorff G, Rush H, Zdunek MP, Feingold R. Tunneled –cuffed catheter associated infections in hemodialysis patients who are seropositive for the human immunodeficiency virus. J Am Soc Nephrol. 2000;11:2122–7.
62. Mokrzycki MH, Zhang M, Cohen H, Golestaneh L, Laut JM, Rosenberg SO. Tunnelled haemodialysis catheter bacteremia: risk factors for bacteremia

recurrence, infectious complications and mortality. Nephrol Dial Transplant. 2006;21:1024–31.
63. Jaber BL. Bacterial infections in hemodialysis patients: pathogenesis and prevention. Kidney Int. 2005;67:2508–19.
64. Onder AM, Chandar J, Saint-Vil M, Lopez-Mitnik G, Abitbol CL, Zilleruelo G. Catheter survival and comparison of catheter exchange methods in children on hemodialysis. Pediatr Nephrol. 2007;22:1355–61.
65. Sirken G, Raja R, Rizkala AR. Identification of infectious risk factors in maintenance hemodialysis patients: the role of intravenous iron. J Am Soc Nephrol. 2004;15:627A.
66. Brewster UC, Coca SG, Reilly RF, Perazella MA. Effect of intravenous iron on hemodialysis catheter microbial colonization and blood borne infection. Nephrology (Carlton). 2005;10:124–8.
67. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ, Van Landuyt HW. Iron overload in haemodialysis patients increases the risk of bacteremia: a prospective study. Nephrol Dial Transplant. 1990;5:130–4.
68. Tielemans CL, Lenclud CM, Wens R, Collart FE, Dratwa M. Critical role of iron overload in the increased susceptibility of haemodialysis patients to bacterial infections: beneficial effects of desferrioxamine. Nephrol Dial Transplant. 1989;4:883–7.
69. Teehan GS, Bahdouch D, Ruthazer R, et al. Iron storage indices: novel predictors of bacteremia in hemodialysis patients initiating intravenous iron therapy. Clin Infect Dis. 2004;38:1090–5.
70. Lumsden AB, MacDonald MJ, Allen RC, Dodson TF. Hemodialysis access in the pediatric population. Am J Surg. 1994;168:197–201.
71. Tanriover B, Carlton D, Saddekni S, Hamrick K, Oser R, Westfall A, Allon M. Bacteremia associated with tunneled dialysis catheters: comparison of two treatment strategies. Kidney Int. 2000;57:2151–5.
72. Onder AM, Chandar J, Billings AA, Simon N, Diaz R, Francoeur D, Abitbol CL, Zilleruelo G. Comparison of early versus late use of antibiotic locks in the treatment of catheter-related bacteremia. Clin J Am Soc Nephrol. 2008;3:1048–56.
73. Allon M. Treatment guidelines for dialysis catheter-related bacteremia: an update. Am J Kidney Dis. 2009;54:13–7.
74. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49:1–45.
75. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for vascular access 2006. Am J Kidney Dis. 2006;48(Suppl 1):S176–S322.
76. Haimi-Cohen Y, Vellozi EM, Rubin LG. Concentration of Staphylococcus epidermidis in simulated pediatric blood cultures correlates with time to positive results with the automated, continuously monitored BACTEC blood culture system. J Clin Microbiol. 2002;40:898–901.
77. Pelletier FQ, Joarder M, Poutanen SM, Lok CE. Evaluating approaches for the diagnosis of hemodialysis catheter-related bloodstream infections. Clin J Am Soc Nephrol. 2016;11:847–54.
78. Lumsden AB, MacDonald MJ, Isiklar H, Martin LG, Kikeri D, Harker LA, Allen RC. Central venous stenosis in the hemodialysis patient: incidence and efficacy of endovascular treatment. Cardiovasc Surg. 1997;5:504–9.
79. Krishnasami Z, Carlton D, Bimbo L, Taylor ME, Balkovetz DF, Barker J, Allon M. Management of hemodialysis catheter-related bacteremia with an adjunctive lock solution. Kidney Int. 2002;61:1136–42.
80. Onder AM, Billings AA, Chandar J, Nield L, Francoeur D, Simon N, Abitbol CL, Zilleruelo G. Antibiotic lock solutions allow less systemic antibiotic exposure and less catheter malfunction without adversely affecting antimicrobial resistance patterns. Hemodial Int. 2013;17:75–85.
81. Farrington CA, Allon M. Management of the hemodialysis patient with catheter-related bloodstream infection. Clin J Am Soc Nephrol. 2019;14:611–3.
82. Shaffer D. Catheter-related sepsis complicating long-term, tunneled central venous dialysis catheters: management by guide-wire exchange. Am J Kidney Dis. 1995;25:593–6.
83. Robinson D, Suhocki P, Schwab SJ. Treatment of infected tunneled venous access hemodialysis catheter with guidewire exchange. Kidney Int. 1998;53:1792–4.
84. Beathard GA. Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. J Am Soc Nephrol. 1999;10:1045–9.
85. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev. 2000;13:686–707.
86. Fishbane S, Cunha BA, Mittal SK, Ruggian J, Shea K, Schoch PE. Vancomycin-resistant enterococci in hemodialysis patients is related to intravenous vancomycin use. Infect Control Hosp Epidemiol. 1999;7:461–2.
87. Kim SH, Kim KH, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. Outcome of vancomycin treatment in patients with methicillin-susceptible Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2008;52:192–7.
88. Sowinski KM, Magner SJ, Lucksiri A, Scott MK, Hamburger RJ, Mueller BA. Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis and recommended dosing. Clin J Am Soc Nephrol. 2008;3:355–61.
89. Sychev D, Maya ID, Allon M. Clinical outcomes of dialysis catheter-related candidemia in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4:1102–5.
90. Lewis SS, Sexton DJ. Metastatic complications of blood stream infections in hemodialysis patients. Semin Dial. 2013;26:47–53.

91. Philipneri M, Al-Aly Z, Amin K, et al. Routine replacement of tunneled cuffed hemodialysis catheters eliminates para-spinal/vertebral infections in patients with catheter associated bacteremia. Am J Nephrol. 2003;23:202–7.
92. Marr KA, Sexton D, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med. 1997;127:275–80.
93. Kovalik E, Albers F, Raymond J, Conlon P. A clustering of cases of spinal epidural abscess in hemodialysis patients: risks of salvaging access catheters in cases of infection. J Am Soc Nephrol. 1996;7:2264–7.
94. Bastani B, Minton J, Islam S. Insufficient penetration of systemic vancomycin into the PermCath lumen. Nephrol Dial Transplant. 2000;15:1035–7.
95. Obrador GT, Levenson DJ. Spinal epidural abscess in hemodialysis patients: report of three cases and review of the literature. Am J Kidney Dis. 1996;27:75–83.
96. Bailey E, Berry N, Cheesbrough JS. Antimicrobial lock therapy for catheter-related bacteremia among patients on maintenance haemodialysis. J Antimicrob Chemother. 2002;50:615–7.
97. Vardhan A, Davies J, Daryanani I, Crowe A, McClelland P. Treatment of haemodialysis catheter-related infections. Nephrol Dial Transplant. 2002;17:1149–50.
98. Ghani MK, Boccalandro F, Denktas AE, et al. Right atrial thrombus formation associated with central venous catheters utilization in hemodialysis patients. Intensive Care Med. 2003;29:1829–32.
99. Aslam S. Effect of antibacterials on biofilms. Am J Infect Control. 2008;36:e09–11.
100. Nielsen J, Ladefoged SD, Kolmos HJ. Dialysis catheter-related septicaemia- focus on Staphylococcus aureus septicemia. Nephrol Dial Transplant. 1998;13:2847–55.
101. Fisher M, Golestaneh L, Allon M, Abreo K, Mokrzycki MH. Prevention of bloodstream infections in patients undergoing hemodialysis. Clin J Am Soc Nephrol. 2020;15:132–151; pushlished online 12/2019.
102. Raad I, Rosenblatt J, Reitzel R, Jiang Y, Dvorak T, Hachem R. Chelator-based catheter lock solutions in eradicating organisms in biofilm. Antimicrob Agents Chemother. 2013;57:586–8.
103. Capdevila JA, Segarra A, Planes AM, Ramirez-Arellano M, Pahissa A, Pierra L, Martinez-Vazquez JM. Successful treatment of haemodialysis catheter-related sepsis without catheter removal. Nephrol Dial Transplant. 1993;8:231–4.
104. Johnson DC, Johnson FL, Goldman S. Preliminary results treating persistent central venous catheter infections with the antibiotic lock technique in pediatric patients. Pediatr Infect Dis J. 1994;13:930–1.
105. Aslam S, Vaida F, Ritter M, Mehta RL. Systematic review and meta-analysis on management of hemodialysis catheter-related bacteremia. J Am Soc Nephrol. 2014;25:2927–41.
106. Onder AM, Billings AA, Chandar J, Francoeur D, Simon N, Abitbol CL, Zilleruelo G. PREFABL: predictors of failure of antibiotic locks for the treatment of catheter-related bacteremia. Nephrol Dial Transplant. 2010;25:3686–93.
107. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, Bander J, Kepros J, Goeschel C. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006;355:2725–32.
108. Johnson LB, Jose J, Yousif F, Pawlak J. Prevalence of colonization with community-associated methicillin-resistant Staphylococcus aureus among end-stage renal disease patients and healthcare workers. Infect Control Hosp Epidemiol. 2009;30:4–8.
109. Bloom BS, Fendrick AM, Chernew ME, Patel P. Clinical and economic effects of mupirocin calcium on preventing Staphylococcus aureus infection in hemodialysis patients: a decision analysis. Am J Kidney Dis. 1996;27:687–94.
110. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339:520–32.
111. Langer JM, Cohen RM, Berns JS, Chittams J, Cooper ET, Trerotola SO. Staphylococcus-infected tunneled dialysis catheters: is over-the-wire exchange an appropriate management option? Cardiovasc Intervent Radiol. 2011;34:1230–5.
112. Yu VL, Goetz A, Wagener M, Smith PB, Rihs JD, Hanchett J, Zuravleff JJ. Staphylococcus aureus nasal carriage and infection in patients on hemodialysis: efficacy of antibiotic prophylaxis. N Engl J Med. 1986;315:91–6.
113. Boelaert JR, De Smedt RA, De Baere YA, Godard CA, Matthys EG, Schurgers ML, Daneels RF, Gordts BZ, Van Landuyt HW. The influence of calcium mupirocin nasal ointment on the incidence of Staphylococcus aureus infections in hemodialysis patients. Nephrol Dial Transplant. 1989;4:278–81.
114. Kluytmans JA, Manders MJ, van Bommel E, Verbrugh H. Elimination of nasal carriage of Staphylococcus aureus in hemodialysis patients. Infect Control Hosp Epidemiol. 1996;17:793–7.
115. Grothe C, Taminato M, Belasco A, Sesso R, Barbosa D. Screening and treatment of Staphylococcus aureus in patients undergoing hemodialysis: a systemic review and meta-analysis. BC Nephrol. 2014;15:202–10.
116. Teo BW, Low SJX, Ding Y, Koh TH, Hsu LY. High prevalence of mupirocin-resistant staphylococci in a dialysis unit where mupirocin and chlorhexidine are routinely used for prevention of catheter-related infections. J Med Microbiol. 2011;60:865–7.
117. Annigeri R, Conly J, Vas S, Dedier H, Prakashan KP, Bargman JM, Jassal V, Oreopoulos D. Emergence of mupirocin-resistant Staphylococcus aureus in chronic peritoneal dialysis patients using mupirocin

prophylaxis to prevent exit-site infection. Perit Dial Int. 2001;21:554–9.
118. Cookson BD. Mupirocin resistance in staphylococci. J Antimicrob Chemother. 1990;25:497–501.
119. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant Staphylococcus aureus after widespread use of nasal mupirocin ointment. Infect Control Hosp Epidemiol. 1996;17:811–3.
120. Onder AM, Chandar J, Billings AA, Diaz R, Francoeur D, Abitbol CL, Zilleruelo G. Chlorhexidine-based antiseptic solutions effectively reduce catheter-related bacteremia. Pediatr Nephrol. 2009;24:1741–7.
121. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med. 2002;136:792–801.
122. Mimoz O, Villeminey S, Ragot S, Dahyot-Fizelier C, Laksiri L, Petitpas F, Debaene B. Chlorhexidine-based antiseptic solution versus alcohol –based povidone- iodine for central venous catheter care. Arch Intern Med. 2007;167:2066–72.
123. Valles J, Fernandez I, Alcaraz D, Chacon E, Cazorla A, Canals M, Mariscal D, Fontanals D, Moron A. Prospective randomized trial of 3 antiseptic solutions for prevention for catheter colonization in an intensive care unit for adult patients. Infect Control Hosp Epidemiol. 2008;29:847–53.
124. Darouiche RO, Wall MJ Jr, Itani KMF, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH. Chlorhexidine- alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med. 2010;362:18–26.
125. Onder AM, Chandar J, Coakley S, Francoeur D, Abitbol CL, Zilleruelo G. Controlling the exit site infections: does it decrease the incidence of catheter-related bacteremia in children on chronic hemodialysis? Hemodial Int. 2009;13:11–8.
126. Safdar N, O'Horo JC, Ghufran A, Bearden A, Didier ME, Chateau D, Maki DG. Chlorhexidine –impregnated dressing for prevention of catheter-related blood stream infection: a meta-analysis. Crit Care Med. 2014;42:1703–13.
127. Timsit JF, Mimoz O, Mourvillier B, Souweine B, Garrouste-Orgeas M, Alfandari S, Plantefeve G, Brncard R, Troche G, Gauzit R, Antona M. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. Am J Respir Crit Care Med. 2012;186:1272–8.
128. Apata IW, Hanfelt J, Bailey JL, Niyyar VD. Chlorhexidine-impregnated transparent dressings decrease catheter-related infections in hemodialysis patients: a quality improvement project. J Vasc Access. 2017;18:103–8.
129. Centers for Disease Control and Prevention. Updated recommendations on the use of chlorhexidine-impregnated dressings for prevention of intravascular catheter-related infections. Available at: https://www.cdc.gov/infectioncontrol/guidelines/bsi/c-i-dressings/appendix/index.html. Accessed on 03/07/2019.
130. Lok CE, Stanley KE, Hux JE, Richardson R, Tobe SW, Conly J. Hemodialysis infection prevention with polysporin ointment. J Am Soc Nephrol. 2003;14:169–79.
131. Battistella M, Bhola C, Lok CE. Long-term follow-up of the hemodialysis infection prevention with Polysporin ointment (HIPPO) study: a quality improvement report. Am J Kidney Dis. 2011;57:432–41.
132. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed. 2017;7:901–8.
133. Kwakman PHS, Van den Akker JP, Guclu A, Aslami H, Binnekade JM, de Boer L, Boszhard L, Paulus F, Middelhoek P, te Velde AA, Vandenbroucke-Grauls CMJE, Schultz MJ, Zaat SAJ. Medical-grade honey kills antibiotic-resistant bacteria in vitro and eradicates skin colonization. Clin Infect Dis. 2008;46:1677–82.
134. Kwakman PHS, de Boer L, Ruyter-Spira CP, Creemers-Molenaar T, Helsper JPFG, Vandenbroucke-Grauls CMJE, Zaat SAJ, te Velde AA. Medical-grade honey enriched with antimicrobial peptides has enhanced activity against antibiotic-resistant pathogens. Eur J Clin Microbiol Infect Dis. 2011;30:251–7.
135. Johnson DW, van Eps C, Mudge DW, Wiggins KJ, Armstrong K, Hawley CM, Campbell SB, Isbel NM, Nimmo GR, Gibbs H. Randomized, controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter-associated infections I hemodialysis patients. J Am Soc Nephrol. 2005;16:1456–62.
136. Hymes JL, Mooney A, Zandt CV, Lynch L, Ziebol R, Killion D. Dialysis catheter-related blood stream infections: a cluster-randomized trial of the ClearGuard HD antimicrobial barrier cap. Am J Kidney Dis. 2017;69:220–7.
137. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. Ann Intern Med. 1997;127:257–66.
138. Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. JAMA. 1999;281:261–7.
139. Darouiche RO, Berger DH, Khardori N, Robertson CS, Wall MJ, Metzler MH, Shah S, Mansouri MD, Cerra-Stewart C, Versalovic J, Reardon MJ, Raad

II. Comparison of antimicrobial impregnation with tunneling of long-term central venous catheters. Ann Surg. 2005;242:193–200.
140. Trerotola SO, Johnson MS, Shah H, Kraus MA, McKusky MA, Ambrosius WT, Harris VJ, Snidow JJ. Tunneled hemodialysis catheters: use of a silver-coated catheter for prevention of infection – a randomized study. Radiology. 1998;207:491–6.
141. Chatzinikolaou I, Finkel K, Hanna H, Boktour M, Foringer J, Ho T, Raad II. Antibiotic-coated hemodialysis catheters for the prevention of vascular catheter-related infections: a prospective, randomized study. Am J Med. 2003;115:352–7.
142. Rupp ME, Lisco SJ, Lipsett PA, Perl TM, Keatimg K, Civetta JM, Mermel LA, Lee D, Dellinger EP, Donahoe M, Giles D, Pfaller MA, Maki DG, Sherertz R. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections: a randomized, controlled trial. Ann Intern Med. 2005;143:570–80.
143. Schindler R, Heemann U, Haug U, Stoelck B, Karatas A, Pohle C, Deppisch R, Beck W, Hollenbeck M. Bismuth coating of non-tunneled haemodialysis catheters reduces bacterial colonization: a randomized controlled trial. Nephrol Dial Transplant. 2010;25:2651–6.
144. Jain G, Allon M, Saddekni S, Barker JF, Maya ID. Does heparin coating improve patency or reduce infection of tunneled dialysis catheters? Clin J Am Soc Nephrol. 2009;4:1787–90.
145. Mojibian H, Spector M, Ni N, Eliseo D, Pollak J, Tal M. Initial clinical experience with a new heparin-coated chronic hemodialysis catheter. Hemodial Int. 2009;13:329–34.
146. Bleyer AJ. Use of antimicrobial catheter lock solutions to prevent catheter-related bacteremia. Clin J Am Soc Nephrol. 2007;2:1073–8.
147. McIntyre CW, Hulme LJ, Taal M, Fluck RJ. Locking of tunneled hemodialysis catheters with gentamicin and heparin. Kidney Int. 2004;66:801–5.
148. Betjes MGH, Agteren MV. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. Nephrol Dial Transplant. 2004;19:1546–51.
149. Dogra GK, Herson H, Hutchison B, Irish AB, Heath CH, Golledge C, Luxton G, Moody H. Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. J Am Soc Nephrol. 2002;13:2133–9.
150. Vanholder R, Canaud B, Fluck R, Jadoul M, Labriola L, Marti-Monros A, Tordoir J, Van Biesen W. Diagnosis, prevention and treatment of haemodialysis catheter-related blood stream infections (CRBSI): a position statement of European Renal Best Practice (ERBP). Nephrol Dial Transplant. 2010;3:234–46.
151. Moore CL, Besarab A, Ajluni M, Soi V, Peterson EL, Johnson LE, Zervos MJ, Adams E, Yee J. Comparative effectiveness of two catheter locking solutions to reduce catheter related bloodstream infection in hemodialysis patients. Clin J Am Soc Nephrol. 2014;9:1232–9.
152. Moran J, Sun S, Khababa I, Pedan A, Doss S, Schiller B. A randomized trial comparing gentamicin/citrate and heparin locks for central venous catheters in maintenance hemodialysis patients. Am J Kidney Dis. 2012;59:102–7.
153. Abbas SA, Haloob IA, Taylor SL, Curry EM, King BB, Van der Merwe WM, Marshall MR. Effect of antimicrobial locks for tunneled hemodialysis catheters on blood stream infection and bacterial resistance: a quality improvement report. Am J Kidney Dis. 2009;53:492–502.
154. Venditto M, du Montcel ST, Robert J, Trystam D, Dighiero J, Hue D, Bessette C, Deray G, Mercadal L. Effect of catheter-lock solutions on catheter-related infection and inflammatory syndrome in hemodialysis patients: heparin versus citrate 46% versus heparin/gentamicin. Blood Purif. 2010;29:268–73.
155. Fernandez-Gallego J, Martin M, Gitierrez E, Cobelo C, Frias P, Jironda C, Hidalgo P, Jimenez T. Prophylaxis with gentamicin locking of chronic tunneled central venous catheters does not cause bacterial resistance. Nefrologia. 2011;31:308–12.
156. Onder AM, Chandar J, Simon N, Diaz R, Nwobi O, Abitbol CL, Zilleruelo G. Comparison of tissue plasminogen activator-antibiotic locks with heparin-antibiotic locks in children with catheter-related bacteremia. Nephrol Dial Transplant. 2008;23:2604–10.
157. Nori US, Manoharan A, Yee J, Besarab A. Comparison of low-dose gentamicin with minocycline as catheter lock solutions in the prevention of catheter-related bacteremia. Am J Kidney Dis. 2006;48:596–605.
158. Wong B, Muneer M, Wiebe N, Storie D, Shurraw S, Pannu N, et al. Buttonhole versus rope-ladder cannulation of arteriovenous fistulas for hemodialysis: a systemic review. Am J Kidney Dis. 2014;64:918–36.
159. Ayus JC, Sheikh-Hamad D. Silent infection in clotted hemodialysis access grafts. J Am Soc Nephrol. 1998;9:1314–9.
160. Nassar GM, Ayus JC. Infectious complications of old nonfunctioning arteriovenous grafts in renal transplant recipients: a case series. Am J Kidney Dis. 2002;40:832–5.
161. Snydman DR, Bregman D, Bryan J. Hemodialysis-associated hepatitis in the United States, 1974. J Infect Dis. 1977;135:687–91.
162. Tokars JI, Miller ER, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 1997. Semin Dial. 2000;13:75–85.

163. Sheth R, Peskin MF, Du XI. The duration of hepatitis B vaccine immunity in pediatric dialysis patients. Pediatr Nephrol. 2014;29:2029–37.
164. Yi SH, Kallen AJ, Hess S, Bren VR, Lincoln ME, Downham G, Kelley K, Booth SL, Weirich H, Shugart A, Lines C, Melville A, Jernigan JA, Kleinbaum DG, Patel PR. Sustained infection reduction in outpatient hemodialysis centers participating in a collaborative bloodstream infection prevention effort. Infect Control Hosp Epidemiol. 2016;37:863–6.
165. Neu AM, Miller MR, Stuart J, Lawlor J, Richardson T, Martz K, Rosenberg C, Newland J, McAfee N, Begin B, Warady BA, Collaborative Participants SCOPE. Design of the standardizing care to improve outcomes in pediatric end stage renal disease collaborative. Pediatr Nephrol. 2014;29:1477–84.
166. Marsenic O, Rodean J, Richardson T, Swartz S, Claes D, Day JC, Warady BA, Neu AM, on behalf of the SCOPE Investigators. Tunneled hemodialysis catheter care practices and blood stream infection rate in children: results from the SCOPE collaborative. Pediatr Nephrol. 2020;35:135–43.

Non-infectious Complications of Hemodialysis in Children

25

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Introduction

Hemodialysis (HD) is a life-sustaining therapy utilized in the management of both acute kidney injury and end-stage renal disease (ESRD). Advances in dialysis technology in the last 5 decades have vastly improved the safety and efficacy of HD. However, acute and technical problems may occur during initiation of dialysis or during chronic treatments. Conventional HD imperfectly replaces renal function and may be associated with chronic long-term consequences. While not all inclusive, this chapter reviews some of the acute and chronic complications associated with HD.

Acute Complications

Dialysis Disequilibrium Syndrome (DDS)

Dialysis disequilibrium syndrome (DDS) is a well-recognized complication of acute and chronic hemodialysis [1]. DDS is an acute neurological syndrome attributed to cerebral edema and increased intracranial pressure. The spectrum of presentation ranges from mild symptoms such as headache, restlessness, nausea, vomiting, muscle cramps, and blurred vision through to seizures, central pontine myelinolysis, and coma [2]. Death has been reported in both adults and children [3–5]. It is more common in acutely uremic patients initiating dialysis, but it can occur in any dialysis session associated with rapid lowering of urea. DDS is more common in children [6]. Intraocular hypertension associated with eye pain and altered visual acuity may be another manifestation of DDS [7]. Table 25.1 outlines risk factors for the development of DDS.

DDS is associated with EEG abnormalities, and evidence of cerebral edema on neuroimaging with CT or MRI. Increased intracranial pressure (ICP) has been documented during ICP monitor-

Table 25.1 Risk factors for dialysis disequilibrium

Patient-related factors	Dialysis-related factors
Children	First dialysis treatment
Very high pre-dialysis urea	High urea removal rate per unit time
Hyponatremia/hypernatremia	Low sodium dialysate
Chronic kidney disease	
Neurological disease:	
Head trauma	
Stroke	
Seizure disorder	
Severe hypertension	
Severe acidosis	
Liver disease	
Poorly controlled diabetes	

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ing [8, 9]. While the pathogenesis remains incompletely understood, two main hypotheses have been invoked, namely, the "reverse urea" effect and "idiogenic osmoles."

Reverse Urea Effect During hemodialysis, urea removal occurs more rapidly from the blood than from the brain cells, creating a reverse osmotic gradient favoring water movement into the brain, causing cerebral edema. Limited patient studies from the 1960s showed that pre-dialysis, there were lower urea levels in the CSF than plasma, with a baseline CSF to plasma urea gradient of 0.9. Post-dialysis this gradient reversed, with a CSF to plasma urea gradient of 1.99, creating an osmolar gradient favoring water movement into the brain cells, which normalized by 24 hours. This gradient was greater in more uremic patients, creating a greater risk for cerebral edema [10]. Subsequent experiments in uremic rats have demonstrated a decrease in the astrocyte urea transporter UT-B1 and an increase in astrocyte aquaporins AQP4 and AQP9. This combination could account for slower urea clearance from astrocytes when the plasma urea is rapidly lowered, with increased water influx in response to the osmolar gradient [11]. Whether these changes occur in the brain of uremic humans, and the factors driving these changes are unknown. Additionally, newer imaging studies suggest the resulting cerebral edema in DDS is interstitial rather than intracellular.

Idiogenic Osmoles The second hypothesis is the presence of the so-called idiogenic osmoles contributing to hypertonicity of the cerebral cells. It is hypothesized that the increased plasma osmolality associated with uremia results in the generation of organic osmoles in the brain to prevent cellular dehydration. This theory postulates that rapid dialysis lowers the plasma osmolality without removing these idiogenic osmoles, creating an osmolar gradient favoring water movement into the brain, while slower dialysis allows for removal of these osmoles, resulting in a smaller osmolar gradient. However, the nature of these putative osmoles has not been elucidated, and the reverse urea effect is generally accepted as the mechanism for dialysis disequilibrium.

Treatment of DDS The primary treatment of DDS is **prevention**. Two factors seem to be important in the generation of DDS, namely, the severity of the initial urea accumulation and the rate of urea removal. There are two approaches to the prevention of DDS in severely uremic patients on conventional HD. The first is to use a dialyzer with a surface area proportional to the patients' body surface area, and calculate the time required to achieve a urea reduction ratio of 30–40% at a standard clearance, usually less than 1 hour. The second is to use a smaller surface area dialyzer, and lower urea clearance, with a blood flow of 2 ml/kg/min, over a 2-hour dialysis, to achieve the same proportionate urea clearance of approximately 40% [6]. Given that urea reduction is not the sole purpose of dialysis, a gentle treatment over a 2-hour period also facilitates ultrafiltration, correction of acidosis, and phosphate removal. Convective therapy in the form of hemofiltration can also be used to achieve solute and water removal without creating large osmolar differences. Slow continuous modalities such as veno-venous hemofiltration (CVVH) or hemodialysis (CVVHD) are alternatives to prevent rapid lowering of urea [9]. However, DDS can still occur, especially if there are concomitant risk factors such as hypernatremia [8, 12].

Addition of an osmotic agent is another strategy to avoid DDS. The two common osmotic agents are sodium [13] and mannitol. Modern dialysis machines can be programmed to provide sodium ramping, where the initial sodium is raised 5–10 mmol/L above the patients' sodium to offset the initial osmolar drop due to urea removal, with gradual return to slightly below the baseline sodium in a linear or step fashion. Reverse sodium ramping, raising the sodium from an initial value of 135–137 up to 142–148 over the course of the dialysis, is physiologically sound to offset the osmolar drop caused by urea removal. However, the higher plasma sodium may lead to increased thirst and interdialytic weight gain. Mannitol in a dose of 1 gram/kg (maximum 30 grams) infused over the first 30–60 minutes of the treatment has also been shown to be effective in preventing DDS.

DDS can occur in chronic HD patients who present with chronically or acutely elevated urea levels. Strategies to prevent DDS in this situation include dietary counselling to lower protein intake, more frequent dialysis sessions, routine use of mannitol or sodium ramping, especially after the long interdialytic period, or hemodiafiltration. Frequently symptomatic patients may benefit from a switch to nocturnal dialysis or peritoneal dialysis.

If DDS occurs, therapy is directed at lowering the intracranial pressure. Mannitol 1 gram/kg or 3% sodium chloride may be used to increase plasma osmolality.

Table 25.2 outlines the measures to prevent DDS in acute and chronic dialysis patients.

Differential Diagnosis The symptoms of DDS are non-specific and there are no confirmatory tests, so it is largely a diagnosis of exclusion. Thus, other etiologies for the patients' symptoms should be considered. These include hyponatremia, excessive ultrafiltration, seizure disorder, intracranial bleeding or subdural hematoma, malignant hypertension, hypoglycemia, hypoxia, cerebrovascular accident, and air embolism [6]. Involvement of the brain by the underlying disease may also be considered in certain acute conditions such as hemolytic uremic syndrome or vasculitic disorders. Other uncommon etiologies include chronic aluminum toxicity (dialysis dementia) and thiamine deficiency (Wernicke's encephalopathy) [14]. Although aluminum-containing phosphate binders are no longer routinely used, patients may have inadvertent exposure to aluminum in over the counter antacids. Dialysis patients are at risk for water-soluble vitamin deficiency and should be supplemented with B&C multivitamins.

Table 25.2 Prevention of dialysis disequilibrium syndrome

Acute	Chronic
Short initial dialysis session (~1–2 hours)	Protein restriction
Smaller dialyzer surface area	Increased frequency of dialysis
Low urea clearance (2 ml/min)	Short daily
Slower dialysate flow (2:1 dialysate/blood flow)	Nocturnal
Sodium ramping or high dialysate sodium	Mannitol
Mannitol 1 gm/kg (max 30 gm)	Sodium ramping
Hemofiltration	Hemodiafiltration
Continuous renal replacement therapy – CVVH or CVVHD	Switch to peritoneal dialysis
Prophylactic phenytoin	

MRI may be helpful, with subcortical white matter lesions in the parietal and occipital lobes [15], but an appearance similar to posterior reversible leukoencephalopathy syndrome (PRES) has also been described in DDS [16, 17].

Acute Hemodynamic Changes

Acute hemodynamic instability is a natural consequence of disordered cardiovascular physiology during hemodialysis (HD) and is the most common complication of treatment, contributing to patient morbidity and mortality. Most commonly the rapid removal of excess fluid compromises cardiovascular hemodynamics, reducing cardiac output and mean arterial pressure (MAP). On the other hand, excessive ultrafiltration leads to activation of the renin-angiotensin system, resulting in angiotensin II-mediated vasoconstriction and intradialytic hypertension. This section reviews the pathophysiology, risk factors, prevention, and treatment of intradialytic hypotension and paradoxical hypertension.

Intradialytic Hypotension

Definition and Pathophysiology Numerous definitions are used to define intradialytic hypotension (IDH). European Best Practice Guidelines and KDOQI guidelines define it as a decrease in systolic BP $\geq$ 20 mmHg or a decrease in MAP $\geq$ 10 mmHg associated with clinical events and the need for nursing interventions [18, 19]. IDH symptoms include abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting, and anxiety. Nevertheless, IDH is variably defined in clinical investigations and the recorded prevalence varies from 6% to 50% of dialytic sessions, depending on the used cut-off values and inclusion of clinical symp-

toms [20–22]. Data on the prevalence of pediatric IDH are scarce and range between 20 and 30% [23]. Notably, there is no recognized definition of intradialytic hypotension in children. Most commonly, it is defined as a decrease of intradialytic SBP below the 5th percentile for age and gender [24].

The pathophysiology of IDH is complex and multifactorial. During dialysis, mobilization of fluid from the interstitial to the intravascular space, vasoconstriction of capacitance vessels, and increase in vascular tone, heart rate, and contractility preserve circulatory adequacy and prevent hypotension [24]. The ability to mobilize blood from the splanchnic venous pool is vital for preserving the central blood volume. Venous tone is affected by vasoactive hormones, sympathetic nervous system, and upstream filling pressures. During arteriolar constriction, the distending pressure to the vein is reduced and blood is extruded centrally toward the heart to maintain cardiac refilling. Vasoconstriction is mediated by an increase in sympathetic activity. In dialysis patients, this response can be inadequate due to an increased production of vasodilators or impaired sympathetic response to hypovolemia. It is hypothesized that during a sudden intradialytic hypotension episode, ischemia prevails resulting in increased consumption of adenosine triphosphate (ATP) and generation of adenosine, which is an endogenous vasodilator. It is also postulated that conditions associated with reduced cardiac refilling pressures such as left ventricular hypertrophy and/or diastolic dysfunction stimulate cardiac stretch receptors and thus maladaptively trigger a variant of the Bezold-Jarisch reflex resulting in hypotension [24, 25]. Importantly, there is increasing evidence that IDH leads to subclinical myocardial injury. In children and adults, reversible myocardial dysfunction (myocardial stunning) has been demonstrated by serial echocardiography during conventional HD sessions [26]. Stunning within myocardial segments correlates with intradialytic blood pressure changes and ultrafiltration volume and with reductions in myocardial blood flow [27, 28]. Thus, the hemodynamic stress of fluid removal by HD predisposes to clinically significant myocardial ischemia, even in children with presumably patent coronary arteries, most likely indicating an insufficient microvascular response [29, 30].

Risk Factors There are many patient-related and dialysis-related risk factors for IDH. Among the former ones, large *interdialytic weight gain, low body weight, food consumption* during HD sessions, and taking *antihypertensives* on HD days are important predictors of IDH. In a recent study in adults, the occurrence of dialysis hypotension was independently strongly associated with higher ultrafiltration volume and low body weight [20]. Food consumption during dialysis promotes hypotension by diverting blood to the splanchnic bed. Among dialysis-related risk factors, *sodium dialysate concentration* is crucial. Dialysate sodium activity is approximately equal to 97% of the measured sodium concentration, but varies with changes in dialysate temperature, pH, and the presence of additional ions, so we can achieve isotonic dialysis by correcting the blood sodium measured by a Donnan factor of 0.967. Hyponatremic dialysis promotes osmotic fluid shift from the extracellular to the intracellular space, causing IDH, while hypernatremic dialysis transfers sodium to the patient, causing interstitial edema, increasing thirst, and interdialytic weight gain, which also predisposes to IHD [24]. As *hypocalcemia* depresses myocardial activity, low dialysate Ca concentrations (1.25 mmol/l), despite being favored by nephrologists, may contribute to hypotensive episodes [31]. Also, the use of acetate-based buffer (nowadays mostly replaced by bicarbonate) leads to vasodilatation and LV depression, increasing the risk of IDH [32]. In younger patients, the volume of blood that is required to fill the extracorporeal circuit can be a significant proportion of the effective circulating volume with resultant hypovolemia. Blood and dialyzer membrane *inflammatory reactions* can result in early decompensation, with evidence suggesting cellulosic membranes to be greater offenders in activating complement and a number of cytokine systems than synthetic membranes. Finally, the choice of *anticoagulant* can be important. Regional citrate

is likely to cause hypotension due to its plasma calcium chelating effect.

Prevention and Treatment Management of IDH includes prevention and acute treatment of hypotensive episodes. Preventive interventions encompass preventing volume overload by limiting interdialytic weight gain and salt intake, accurate dry weight assessment, withholding antihypertensive medications on dialysis days, and avoiding food consumption during dialysis. Modifications of the dialysis prescription include acetate buffer replacement, increasing dialysate calcium concentration (unless contraindicated due to hypercalcemia), blood volume monitoring (BVM) during UF, individualized dialysis prescription with sodium and ultrafiltration (UF) profiling, lowering of dialysate temperature to 36–36.5 °C, and a switch to online HDF or HF. Also, extra dialysis sessions, prolonged/nocturnal dialysis, or short daily dialysis could be done for volume overload. Pharmacological treatments include intravenous mannitol, midodrine, and carnitine administration.

Identifying a simple measurable index of volume overload remains challenging. Pre-dialysis blood pressure is not a good marker of volume control, whereas bioimpedance spectroscopy is not accurate enough in pediatric dialysis [33, 34]. Despite this, bioimpedance, when used regularly and the results trended, can be a useful tool in clinical practice to better estimate dry weight. Lung ultrasound is a promising technique, but its use is still limited [35, 36].

The European Pediatric Hemodialysis Guidelines recommend UF rates of 1.5 ± 0.5% of body weight per hour and a maximum UF volume of 5% of the patients dry weight per 3–4 h hemodialysis session, without UF or sodium ramping and/or cooling dialysate [37]. In most cases, such ultrafiltration rates are well tolerated by patients. Nevertheless, ultrafiltration tolerance is individual, and *blood volume monitoring (BVM)* is currently the most widely used technique for guiding UF, as most of the newer dialysis machines have built-in BVM devices. BMV can be conducted through RBV (relative blood volume) or hematocrit (Hct) monitoring. In the former, the RBV is set to 100% at dialysis start, and all changes are registered according to the initial value. Once the RBV decreases below the critical relative blood volume (RBV_{crit}), the control system adjusts ultrafiltration by decreasing its rate and/or increasing the dialysate sodium. The RBV_{crit} is defined as the RBV below which the frequency of IDH increases, so it varies between patients and has to be established by the physician. In the latter, the blood volume is monitored through devices that measure hemoglobin or hematocrit concentration. Similarly, when the hematocrit rises, meaning that BV has decreased, the system automatically decreases UF and/or increases the dialysate sodium. A recent prospective, observational study of 15 children on chronic HD confirmed the efficacy of BVM using a hematocrit monitoring system in reducing the frequency of intradialytic morbid events (nausea, vomiting, cramps) and hypotension [38]. In another retrospective study by Merouani et al., although there was no difference between BVM monitored and unmonitored patients, the UF was higher in the BVM group, without affecting hypotensive episodes [39]. According to the recent recommendation of the Pediatric CRRT working group, the blood volume change should not exceed 3–5% per hour (up to 8% in first hour) with a maximal 16% blood volume change at the end of a 4-hour session [40]. The BVM concept is not perfect as it assumes a constant circulating blood volume and/or hematocrit, depending only on fluid removal. Hence, limitations of this method are due to other factors influencing blood volume, such as oncotic pressure, vascular refilling (due to capillary vasoconstriction), and UF rate [41–43].

Recently, numerous studies suggest that *refill capacity* can be used as a more reliable marker of volume overload than simple BVM assessment, as it characterizes the dynamics of both ultrafiltration and vascular refill from the interstitium [44–46]. Paglialonga et al. proposed an index of pre-HD volume overload, calculated as the ratio between the ultrafiltration rate indexed for body weight during the first HD hour and the percent of blood volume change at the first hour of the

treatment. This concept is based on an assumption that in patients with a normal plasma oncotic pressure, the refill capacity is proportional to volume overload. A first hour refill index greater than 2 was associated with high left ventricular mass and a higher number of antihypertensive drugs suggesting fluid overload [44].

As fluid overload is inseparably linked to salt overload, adequate fluid and salt homeostasis is essential to prevent high interdialytic weight gain, which is a risk factor for IDH. Once IDH develops during dialysis, treatment by sodium administration increases thirst, creating a vicious cycle, which further promotes fluid overload. Hence, the preventive strategies should include dialysis prolongation and/ or *sodium ramping***.** Sodium ramping with a higher dialysate sodium at dialysis start allows a diffusive sodium influx to counterbalance the rapid decline in plasma osmolality due to clearance of urea and other small molecular weight solutes, thus promoting plasma refilling. As the osmolar gradient decreases toward the end of the HD session, the low sodium concentration promotes the diffusive clearance of the accumulated sodium load. Sodium ramping can be linear, or stepwise. In the linear approach, sodium steadily declines throughout the session, while in a stepwise profile the initial sodium concentration remains constant until 30 min prior to the end of HD, when the sodium is decreased to the final concentration. Available clinical data show that stepwise profiling is more effective in terms of reducing IDH symptoms than other alternatives [46, 47]. However, it results in net sodium gain and may be associated with increased thirst and intradialytic weight gain. *UF profiling* with a high UF rate at the beginning of the session, followed by progressive reduction, may also be beneficial [44].

Online hemodiafiltration (HDF) is considered the most efficient technique in terms of both increasing clearances of small and middle molecular weight solutes and providing intradialytic hemodynamic stability. In a prospective, randomized, multicenter trial comparing convective and diffusive treatment modalities in 380 patients followed for 24 months, the incidence of IDH was much lower in the former group [48]. In patients enrolled in the 3H (HDF, Heart, and Height) Study, the interdialytic weight gains were significantly lower in HDF as compared to HD patients, resulting in lower UF rates. A low ultrafiltration rate facilitates vascular refilling, reducing the propensity for hypotensive episodes, which allows better patient tolerance with fewer headaches, dizziness, or cramps. Indeed, in the Quality of Life Questionnaire, the symptoms related to fluid status including headaches, dizziness, and cramps were reported less commonly in HDF children as compared to the HD group [49].

Interestingly, Donauer et al. identified *blood cooling* as the main blood pressure-stabilizing factor in online HDF in adults [50]. Pediatric data on cooling dialysate are limited. While cooling dialysate below 36.5 °C in adults increases hemodynamic stability, its usefulness in children might be limited by patient comfort and well-being. In a pediatric study, cooling dialysate to 35 °C showed improved heart rate, UF tolerance, and reduced frequency of IHD episodes [40].

Pediatric experience with *pharmacological treatment* of IDH is limited. In one study including six children prone to severe IDH, with 399 dialysis sessions analyzed, intradialytic mannitol infusion (1 g/kg/week) or oral midodrine (2.5–7.5 mg) was effective in increasing UF volume and reducing hypotensive episodes [51]. Other interventions to prevent IDH including sequential dialysis, quotidian dialysis, biofeedback, or UF rate adjustment based on body surface area will not be described in detail, due to limited evidence of usefulness in children.

Acutely, IDH requires immediate action to reduce the severity of symptoms and prevent a further drop in blood pressure. The acute management includes temporary suspension of ultrafiltration, placing the patient in Trendelenburg position and administration of isotonic saline (5–10 ml/kg bolus) or discontinuation of HD in cases resistant to a conservative approach. The most recent recommendations on pediatric intradialytic hypotension from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup reviews the IDH preventive strategies and grades them according to evidence-based medicine criteria [40]. Table 25.3 outlines

Table 25.3 Prevention and treatment of intradialytic hypotension

Prevention	Recommendation strength and evidence level
General strategy	
Avoid excess interdialytic weight gain Minimize salt intake Accurate dry weight assessment Withhold antihypertensive medications on dialysis days Avoid food intake during dialysis sessions	
Dialysis-related intervention	
BVM-driven UF algorithms	1C
Cooled dialysate	2C
Sodium ramping	3C
Pharmacological intervention: mannitol, midodrine, carnitine	3D
UF profiling	4D
Bioelectric impedance	4D
Sequential dialysis	3D
Biofeedback	3D
Hemodiafiltration	2C
Hemofiltration	4D
Quotidian hemodialysis	4D
Treatment	
Suspension of UF Saline bolus 5–10 ml/kg Trendelenburg patient positioning Cessation of dialysis for treatment of resistant hypotension	

the strategies for prevention and treatment of IHD, with grading of the recommendation strength and evidence.

Intradialytic Hypertension

Definition and Pathophysiology Intradialytic or paradoxical hypertension (IH) is defined as an increase in mean arterial pressure (MAP) of more than 15 mmHg or systolic BP of 10 mmHg during or immediately after dialysis, which is resistant to fluid removal. Estimates of the incidence in adults range from 5% to 15% with no pediatric-specific numbers currently available [52]. IH may be asymptomatic or associated with headache, blurred vision, seizures, or chest pain. Sustained hypertension is often due to failure to achieve an appropriate dry weight [53]. However, many patients manifest IH despite proper dry weight assessment. The proposed pathophysiological mechanism includes activation of the renin-angiotensin axis due to excessive ultrafiltration during HD. Additionally, patients with IH have been shown to have smaller changes in osmolality from pre- to post-dialysis compared to other HD patients, which contributes to increased vascular resistance. Chronic endothelial cell dysfunction has also been shown in patients prone to IH, and an imbalance between endothelin-1 and other endothelial cell–derived vasoregulators is responsible for increased vascular resistance. Finally, a number of antihypertensive drugs are removed by dialysis, and their removal over the course of a dialysis session may contribute to IH [52].

Risk Factors Extracellular volume overload is a consistent finding among patients with IH. Patients with low BMI, low interdialytic weight gain, and those with short dialysis sessions often present with chronic volume overload, which promotes IH. Other risk factors include older age and the presence of comorbidity such as heart, lung, or cerebrovascular disease. It was also demonstrated that IH patients have low pre-dialysis creatinine, serum albumin, phosphorus, and normalized protein nitrogen appearance (nPNA), which further characterizes the IH patients as individuals with little dietary protein and fluid intake [54].

Prevention and Treatment Preventive management includes establishing correct dry weight, preservation of residual renal function, fluid and salt restriction, and where feasible, augmentation of urine output with loop diuretics. Decreasing dialysate sodium concentration reduces interdialytic thirst and volume overload, which prevents IH. Increased frequency of dialysis or intensified regimens may be required to ascertain the correct dry weight. Nocturnal and frequent dialysis is associated with better BP control with fewer antihypertensives in children [55, 56]. If hypertension persists despite preventing fluid and salt

overload, an angiotensin receptor blocker (ARB) should be introduced in order to block sympathetic activity.

Blood and Circuit Component Reactions

Patients may experience a multitude of symptoms during or shortly after a dialysis session, some of which may be related to exposure of blood to the foreign material of the extracorporeal circuit. Reactions that are more common with new, non-reused dialyzers are referred to as "first-use" reactions. In 1998, utilizing a previously reported grading system [57], Daugirdas and Ing proposed a classification system for these first-use reactions [58] as outlined in Table 25.4. Reactions were classified as type A, hypersensitivity reactions with anaphylactic features, and type B, reactions with non-specific symptoms such as back and chest pain. A definite anaphylactic reaction was defined as 3 major or 2 major and 1 minor criteria, while a probable reaction was defined as 2 major, 1 major and 2 minor, or 3 minor criteria. Severity was Grade 1 (mild) if the reaction was non-life threatening, no medications were required, and the dialysis treatment was completed. Grade 2 (severe) reactions required medications and/or premature termination of the dialysis session. Grade 3 (fatal) reactions resulted in death of the patient.

Table 25.4 Classification of dialyzer reactions

Type A (Anaphylaxis)		Type B (Non-specific)
Major criteria	Minor criteria	symptoms
Onset within 20 min Shortness of breath Hot/burning sensation at access or throughout the body Angioedema	Occurs in subsequent dialysis sessions with the same dialysis circuit Hives and/or itching Runny nose, watery eyes Abdominal cramping	Chest pain Back pain Nausea Vomiting Dyspnea Fever General malaise

The exact incidence of dialyzer reactions is impossible to ascertain in the absence of systematic reporting, but it is likely lower now than in the early days of dialysis with the widespread use of biocompatible membranes and newer sterilization methods. Older literature suggests an incidence of 3–5 per 100,000 dialysis sessions for non-fatal type A reactions and 3–5 per 100 dialysis sessions for type B reactions [57, 58].

Allergic Reactions

Anaphylactic reactions are severe, potentially fatal reactions usually mediated by antigen-antibody complex formation. They typically occur early in the dialysis session, within minutes of dialyzed blood being returned to the patient, and are characterized by shortness of breath, wheezing, urticaria, headache, and hypotension, and may progress to hypoxia, cardiovascular collapse, and death. Allergy to medications infused during the treatment is temporally related to their administration. Non-specific symptoms are far more common than anaphylaxis and may relate to allergy or other aspects of the HD treatment.

Patients may have an adverse reaction to any component of the extracorporeal circuit as outlined below, although membrane reactions are far less common in the era of widespread use of biocompatible membranes. The dialyzer itself consists of a membrane, the dialyzer housing, the potting compound into which the hollow fibers are embedded, the manufacturers sterilizing agent, and residual reuse chemicals in centers that practice reuse. Additionally, the circuit includes the tubing and manufacturers' sterilizing agent, and medications infused during the treatment, most commonly heparin, erythrocyte-stimulating agents, and iron [59, 60] Potential causes of type A reactions are discussed below.

Ethylene Oxide Ethylene oxide (ETO) is a bactericidal gas used as a sterilizing agent in some dialyzers and tubing sets. Sensitivity to ETO was first recognized in the 1970s, with anaphylaxis mediated by IgE anti-ETO antibodies [61–64]. Symptoms range from full-blown anaphylactic reactions within minutes of dialysis initiation, to

grumbling non-specific symptoms such as fever, malaise, and myalgias. Avoidance of tubing and dialyzers sterilized with ETO is the best preventive strategy. When not feasible, dialyzers should be well flushed to remove the sterilizing agent. The polyurethane potting compound in hollow fiber dialyzers is a reservoir for ETO, so circuits which sit stagnant after the initial priming should be re-primed before use [65]. ETO may also be found in fistula needles and continuous renal replacement circuits. Alternate methods of dialyzer sterilization such as steam, gamma irradiation, and e-beam are not associated with allergic reactions and have therefore largely replaced ETO sterilization in recent years.

Membrane Reactions The biocompatibility of a dialyzer relates to its propensity to activate the complement, coagulation, and kallikrein systems and to cause sequestration of leucocytes [66]. The development of synthetic biocompatible membranes has been one of the major advances in dialysis technology.

Polysulfone membranes: Polysulfone is one of the most widely used membrane materials. While polysulfone is a synthetic biocompatible membrane, anaphylactic reactions have been reported [67, 68], and all polysulfone membranes are not created equally. Polyvinylpyrrolidone (PVP), a known allergen, may be used to hydrophilize some polysulfone membranes to prevent platelet and plasma protein aggregation on the membrane. Reaction to PVP or the polysulfone-PVP complex may result in anaphylaxis, and eosinophilia and elevated IgE levels have been demonstrated in patients with recurrent anaphylactic reactions to polysulfone. Eosinophilia is relatively common in hemodialysis patients, in keeping with subclinical allergy to a component of the circuit [69]. Eosinophilia improved in one series of patients switched from a polysulfone to a polyflux membrane [70].

AN69 membranes: The association between anaphylactic reactions, ACE inhibitor use, and dialysis with an AN69 membrane was first recognized in the 1990s [71, 72]. Affected patients had elevated levels of bradykinin (BK) leading to the hypothesis that BK was generated by the negatively charged membrane, with degradation blocked by the ACE inhibitor [73]. Subsequent in vitro studies and clinical experience have shown that this "bradykinin release reaction" is a pH-dependent phenomenon occurring in acidotic patients or those requiring a circuit blood prime, even when not receiving ACE inhibitors. This reaction can be reduced or avoided by alkaline rinsing of the blood and dialysate compartments or by increasing the patients' or circuit pH prior to blood-membrane interaction [74, 75]. The propensity to develop this reaction appears to be a complex interaction between increased BK production, decreased degradation of BK due to the ACE inhibitor, and a genetic predisposition to reduced plasma levels of aminopeptidase activity [76]. Given the potential severity of this reaction and the widespread availability of alternate biocompatible dialyzers, common sense dictates that AN69 membranes should be avoided in patients on ACE inhibitors.

Heparin Inexpensive, effective, readily available, and with predictable kinetics, unfractionated heparin is the most common anticoagulant used during HD worldwide. Unlike low-molecular-weight heparins, it can be reversed with protamine if excessive anticoagulation occurs. Hypersensitivity reactions to heparin are rare but have been described [77], and may also be a manifestation of heparin-induced thrombocytopenia (HIT) [78]. First described in a pediatric dialysis unit, heparin contaminated with oversulfated chondroitin sulfate was the source of a widespread outbreak of reactions in multiple dialysis units, with symptoms occurring within minutes of initiation of dialysis [79], mediated by complement activation.

Endotoxin Creation of dialysate involves rigorous treatment of municipal water to remove bacteria and chemical contaminants, with standards dictated by the Association for Advancement of Medical Instrumentation (AAMI) in North America and other groups around the world. Maximum allowable bacterial and endotoxin concentrations are <100 colony forming units (CFU)/ml and <0.25 endotoxin unit (EU)/ml,

respectively [80]. Standards for ultrapure water, a prerequisite for hemodiafiltration, are <0.1 CFU/ml bacteria and <0.03 EU/ml endotoxin. Ultrapure water is achieved by additional filtration of dialysate through filters, which retain endotoxin and bacteria just prior to use.

Endotoxins or lipopolysaccharides are large molecules found in the outer layer of gram-negative bacteria, which may thrive in water and alkaline dialysate. They are capable of inducing inflammation in humans. Regular testing of dialysate purity and maintenance of the water purification system is essential to prevent blood stream infections and pyrogenic reactions caused by cytokine-inducing endotoxins. Diffusion or back-filtration of endotoxin or other bacterial pyrogens from the dialysate may be associated with fever, chills, rigors, or general malaise. Bacterial endotoxins are less able to cross polysulfone and polyamide membranes due to adsorption onto the membrane [81].

Reuse "First-use" reactions, adverse events occurring during dialysis with a new dialyzer, were relatively common in the early days of dialysis, and are largely attributable to ETO, bio-incompatible cellulosic dialyzers, or the concomitant use of AN69 membranes and ACE inhibitors. Dialyzer reuse as a cost-saving measure and a means of reducing these "first-use" reactions was widely practiced in adult units in the 1980s and 1990s, though few, if any pediatric centers practiced dialyzer reuse. With the availability of less expensive biocompatible membranes and non-ETO sterilization, dialyzer reuse has fallen out of favor [82]. Reactions of variable severity related to dialyzer reprocessing include exposure to residual sterilizing agents, especially formaldehyde and bleach [83]; blood stream infections due to suboptimal concentrations of germicide; and pyrogenic reactions (fever, chills, and hypotension) due to bacteria or endotoxin.

Other Contaminants Contamination of dialyzers with perfluorohydrocarbon has resulted in deaths, while outdated, degraded cellulose dialyzers have been associated with scleritis, iritis, acute loss of vision and hearing, and death [83, 84].

Thrombocytopenia A transient drop in platelet count in the first 1–2 hours of dialysis, with recovery by the end of dialysis, is a well-recognized phenomenon [85]. Biocompatible synthetic membranes are associated with a 7–9% reduction in platelet count, unlike the more robust reduction in platelet number and function seen with the older bioincompatible cellulosic and cuprophane membranes. Thrombocytopenia (TCP) nowadays is more likely due to medications, immune-mediated disorders, hematological diseases, or sepsis. However, dialyzer membrane configuration and sterilization technique may result in TCP. Widespread TCP with small dialyzers with polymethylmethylacrylate (PMMA) membranes was seen in pediatric patients in the early 1990s leading to discontinuation of their use.

Electron Beam (E-Beam) Sterilization and Polysulfone membranes E-beam sterilized polysulfone dialyzers were reported to cause a 7% incidence of TCP, as defined by an absolute platelet count $<100 \times 10^3/\mu L$ and/or a 15% decrease in platelet count post dialysis [86]. Switching to a non-e-beam sterilized polysulfone dialyzer resulted in significant improvement in TCP in the affected patients. However, sterilization technique alone may not be the culprit, as TCP is reported to improve when switching from one e-beam sterilized polysulfone dialyzer to another from another manufacturer, implicating the specific polysulfone membrane configuration as a contributing factor [87]. The mechanism of TCP has not been elucidated.

Heparin-Induced Thrombocytopenia Heparin-induced TCP (HIT) is an immune mediated syndrome, which typically presents 5–14 days after exposure to heparin. It is associated with the presence of HIT antibodies. Manifestations include TCP, venous thrombotic events, and clotting of vascular access. Skin necrosis at heparin injection sites and venous gangrene may also

occur. More recently, an acute systemic reaction has been reported, occurring 5–30 minutes after intravenous injection of unfractionated heparin, which may be mistaken for a dialyzer reaction [78]. The two clinical presentations are an acute inflammatory reaction with fever and chills, or a cardiorespiratory event with hypotension, tachycardia, tachypnea, and shortness of breath, similar to a pulmonary embolism. Symptoms are postulated to result from release of interleukin 6 and von Willebrand factor due to endothelial injury. As the TCP may be transient, a CBC should be done following any presumed hypersensitivity reaction.

HIT is caused by the development of a heparin-platelet factor 4 (PF4) complex, which binds to platelets causing their activation. The pretest probability of HIT can be estimated using the "4T's" algorithm, which includes the presence of TCP, timing of the fall in platelet count, thrombosis, and the presence of other possible causes, along with confirmatory testing. Unfortunately, functional tests of platelet activation are specific and sensitive but not readily available. Immunologic assays detecting antibodies to the heparin-PF4 complex are sensitive but not specific. A high clinical suspicion for HIT should result in cessation of heparin, including heparin for CVL locking or low-molecular-weight heparins. An alternate anticoagulant such as danaparoid, hirudin, or argatroban should be employed until the diagnosis is confirmed or refuted.

Treatment of Anaphylaxis During HD The response to an anaphylactic reaction on hemodialysis is two pronged: support of the patient followed by a systematic attempt to identify the possible offending agent [60]. The initial response consists of *immediate cessation of dialysis without re-transfusion* of the circuit blood to prevent further exposure to potential allergens. The circuit should be saved for later examination as the differential diagnosis of a serious adverse event on HD also includes hemolysis, sepsis or pyrogenic reaction, and air embolism. Bloodwork should be obtained for complete blood count and white cell differential, routine electrolytes and renal function (Na, K, Cl, TCO2, urea, creatinine, Ca, PO4), blood culture, IgE levels, and C3. Bloodwork may assist with determination of the etiology and will help determine the need for urgent re-initiation of dialysis once the patient is stabilized.

Table 25.5 Approach to a serious allergic reaction on HD

Immediate response	Supportive care	Subsequent response
Cessation of dialysis *without re-transfusion* of the circuit	Oxygen: high flow >95% O_2 via rebreather mask titrated to O_2 saturation	Inspection of the circuit for potential etiologies of the reaction
Bloodwork: CBC, differential Electrolytes, renal function Blood culture IgE C3	Diphenhydramine 1 mg/kg IV (max 50 mg) Hydrocortisone 5 mg/kg IV IM Epinephrine: 1:1000 (1 mg/ml) 0.01 ml/kg (max 0.5 mg) Salbutamol: 1 ml (5 mg) in 3 ml saline via inhalation	Systematic elimination of potential allergens
	Saline bolus 10 ml/kg if hypotensive	

Supportive care is outlined in Table 25.5. Medication choice is determined by the patients' clinical status and response to management [88].

In the era of bicarbonate dialysate, biocompatible dialyzers, and non-ETO sterilization methods, allergic reactions are far less common, but may still occur. Clustering of multiple affected individuals suffering adverse reactions or TCP in a dialysis unit should prompt a systematic investigation of the root cause, including contaminated water source, new dialyzers, or a manufacturing issue resulting in corruption of one component of the dialysis circuit.

Air Embolism and Microbubbles

Air Embolism Air embolism (AE) is a rare but potentially fatal complication of HD. Exact estimates of frequency are not available, but are likely lower in the modern era due to advances in

machine safety features. No pediatric-specific data exist. Air can be introduced into the circulation both during a dialysis session and in the interdialytic period. AE can also occur during both insertion and removal of dialysis lines. The latter may be due to the presence of a fibrin sheath and highlights the need for proper Trendelenburg positioning during CVL removal, and firm pressure and the use of an occlusive pressure dressing for 24 hours following line removal [89–91].

To create an AE requires a source of air, a mechanism of entry into the body (CVL or AV fistula or graft) and a pressure differential between the vasculature and the atmospheric pressure, the latter easily achieved during inspiration. Air in the systemic venous circulation causes venous AE, while air in the pulmonary veins or systemic arterial circulation causes arterial AE.

The clinical consequences of AE depend on the volume and location of air and the patient's position at the time of air entry [91]. In the supine position, venous air enters the right heart. Large emboli may cause obstruction of the right ventricular outflow tract (RVOT) resulting in hypotension and circulatory collapse. 3-5 ml/kg or 300-500 ml of air delivered at a rate of 100 ml/sec is the estimated lethal dose in adults. In supine patients, or with smaller amounts of air, air enters the pulmonary circulation creating a cascade of pulmonary hypertension, pulmonary vasoconstriction, lowered systemic vascular resistance, increased cardiac output, and pulmonary edema with resultant hypoxia.

In the upright position, air entering the right heart may ascend into the cerebral vessels. The presentation is neurological, with altered level of consciousness, seizures, focal neurological deficits, signs of cerebral edema, and/or coma.

In the presence of right to left shunts or with large volume air emboli, which overwhelm the lungs' absorptive capacity, paradoxical embolization into the arterial circulation occurs. Coronary and cerebral arterial circulations are most commonly affected, but paradoxical emboli can affect any organ system, resulting in ischemic dysfunction.

Table 25.6 outlines the pathophysiology and clinical sequalae of the three major types of AE.

Table 25.6 Patterns of air embolism

Type of air embolism	Position at time of embolism	Pathophysiology	Clinical presentation
Large venous embolism	Supine	Right ventricular outflow tract obstruction	Hypotension, circulatory collapse Machinery murmur
Small venous embolism	Supine	Pulmonary artery hypertension and vasoconstriction Reduced systemic vascular resistance Increased cardiac output	Pulmonary edema Hypoxia
Retrograde	Upright	Retrograde ascension of air into cerebral vessels	Altered level of consciousness Seizures Cerebral edema Focal deficits Patient may hear a rushing noise in the head
Paradoxical	n/a	Right to left shunts Pulmonary AV malformations Large emboli exceeding pulmonary absorption Coronary and cerebral arteries most common target	*Cardiac*: Angina/Myocardial infarct Arrhythmias Hypotension *CNS:* Altered level of consciousness Seizures Cerebral edema Focal deficits

Table 25.7 Sources of air embolism in dialysis patients

	Intradialytic	Interdialytic
Venous – access related	Connection and disconnection of CVL at start and completion of dialysis Line disconnection from CVL during treatment AV fistula – dislodged arterial needle	CVL insertion and removal Accidental CVL disconnection CVL misadventure (cap disconnection, line severance)
Venous – circuit related	Loose connectors Defects in tubing Infusions into the circuit Empty or tilted venous drip chamber	
Arterial	Patent foramen ovale Paradoxical venous embolism	

Treatment of Air Embolism Modern dialysis machines have multiple safety features, including air detectors to prevent AE [92–94]. They are designed to detect air infusion >0.1 ml/kg body weight for bolus infusion, or 0.03 ml/kg/minute for continuous infusion, but do not detect microbubbles. Table 25.7 outlines the sources of AE both during and between dialysis sessions. Prevention of air emboli is key, requires an understanding of the potential sources of air in a dialysis circuit, and emphasizes the need for constant vigilance during treatment. Although many dialysis patients prefer to withdraw under a blanket for their treatment, all components of the extracorporeal circuit, particularly the access and connections, should be completely visible to the dialysis nurse, and regular checks of the circuit integrity should be the standard of nursing care. The use of needle-less connectors such as the Tego™ lessens the risk of AE due to line manipulation during connection to and disconnection from the dialysis circuit, or from accidental line disconnection during HD itself. They are an added safety feature, especially in children who may be active during dialysis.

Prompt recognition and management of an air embolism may lessen the impact to the patient. Treatment is both supportive and diagnostic. An attempt should be made to locate the source of air entry to prevent further AE, and dialysis should be terminated immediately. In patients with central venous lines, an attempt can be made to withdraw air from the right side of the heart. Placing the patient in the Durrant's position of left lateral decubitus is suggested to prevent further air entry into the pulmonary circulation. Trendelenburg position has been previously recommended for retrograde or paradoxical cerebral emboli, but more recent literature suggests a flat, supine position to prevent worsening of cerebral edema. The Trendelenburg position may also result in lower limb venous obstruction and ischemic symptoms.

Supportive care includes administration of high concentration oxygen, fluid resuscitation, and inotropes when required. Imaging with CT or ECHO as dictated by the clinical scenario may be helpful, but negative studies do not exclude the diagnosis. Hyperbaric oxygen therapy has been used successfully to treat symptomatic HD-associated venous and arterial AE [95–97].

Microbubbles Microbubbles are generally invisible to the naked eye, although bubble formation may be visualized in the dialyzer "header" or venous drip chamber [98]. They are too small to trigger the air detector on the dialysis machine [93, 99–101]. Newer imaging techniques confirm that microbubbles occur routinely during HD treatments, and originate within the extracorporeal circuit. Sources include residual air in the dialysis circuit following dialyzer and line priming, air leaks at circuit connectors, and de novo bubbles created by turbulence at the access site or venous drip chamber, especially when there is a mismatch between access and prescribed blood flow [102–104]. Pre-filled dialyzers are associated with lower microbubble formation than dry dialyzers [105].

Removal of microbubbles in the venous drip chamber is influenced by bubble size and blood flow, with higher flows contributing to infusion of larger bubbles into the patient. Dissolution of microbubbles in vivo is influenced by size and

configuration, with a range of 1 second for microbubbles to 70 days or longer for larger cylindrical bubbles. In the body, microbubbles travel through the circulation until they are dissolved, or lodge in the microvasculature, where they may initiate tissue injury through mechanical damage, initiation of an inflammatory response, or activation of complement and clotting cascades [92, 102, 106].

The hemodialysis situation is unique in that patients are exposed to microbubble infusion repeatedly for an extended time. Repeated microbubble exposure may contribute to the development of pulmonary hypertension, which occurs in 30–40% of HD patients [107, 108]. Venous emboli are not generally considered a risk to the brain. However, approximately 30% of the population have right-to-left shunts through a patent foramen ovale (PFO), microbubbles may reach the arterial circulation via passage through the lungs, and pulmonary hypertension also contributes to right-to-left shunting. Thus, microbubbles may contribute to the brain dysfunction or other organ dysfunction seen in patients on chronic HD [108–110]. However, at least one study failed to show microbubbles in the middle cerebral artery in patients with a PFO [111]. These differences may relate to different dialysis circuits, microbubble monitoring equipment, or duration of monitoring.

Mechanisms to prevent microbubble formation include lower blood flow rates and maintenance of higher fluid levels in the bubble trap [105, 112]. Development of microbubble filters, which do not impede blood flow or expose the patient to harmful chemicals, is ongoing and desirable [113]. The primary treatment for microbubble embolization is prevention [92, 106]. Hyperbaric oxygen has been shown to improve neurological outcome in some patients, but has not been systematically studied. Heparin, routinely given during HD, may contribute to the prevention of microbubble disease by inhibiting activation of the clotting cascade. The use of surfactants or fluorocarbon compounds to hasten bubble dissolution is not yet ready for clinical use.

Miscellaneous Complications

Advancements in dialysis machine safety monitoring parameters, and stringent dialyzer manufacturing and water purification standards have reduced the incidence of many complications. However, they are most successful when used with careful ongoing evaluation of the patient and circuit with every treatment, and root analysis cause of adverse events such as those described below.

Blood Leaks The absolute maintenance of two separate compartments for blood and dialysate is essential for the safety and efficacy of HD. Blood leaks occur when there is a disruption in the integrity of the dialyzer hollow fibers, allowing passage of blood into the dialysate. Stringent manufacturing standards, including tests for fiber integrity, have reduced the incidence of blood leaks. However, fiber disruption can occur as a result of manufacturing defects, "misadventure" during shipping, storage or handling, during dialyzer processing for reuse, or when the dialyzer is subjected to transmembrane pressures (TMP) at or exceeding the manufacturers' maximum TMP, which is 600 mmHg for most dialyzers. Damaged dialyzers will usually be detected by failure of the initial pressure testing during priming, but this will not pick up fiber rupture that occurs after the start of dialysis.

All hemodialysis machines have a mandatory blood leak detector (BLD), which will sound an alarm and automatically stop the blood pump. The BLD is an optical sensor designed to pick up blood leaks of 0.35 ml/min or greater. False positives may be caused by air bubbles or dirty optical sensors. False triggering of the BLD can also occur with hemolysis during dialysis with high flux dialyzers [114]. Free hemoglobin has a molecular weight of 64.5 kiloDaltons and can trigger the BLD if sufficient free Hb crosses the membrane into the dialysate. More recently, hydroxocobalamin, used to treat suspected or confirmed cyanide toxicity, has been reported to interfere with hemodialysis by triggering the BLD [115–117]. Hydroxocobalamin stains bodily fluids a red/orange color, which may be

Table 25.8 Blood leak detector alarms

True blood leaks	False-positive blood leak	Diagnosis of blood leak in dialysate
Fiber rupture	Free hemoglobin (hemolysis)	Blood leak detector alarm
Manufacturing defect	Hydroxocobalamin	Red dialysate
Mishandling	Air bubbles	Positive dialysate dipstick for blood
Dialyzer reprocessing	Dirty blood leak detector	Free hemoglobin in dialysate
High TMP		

detected by BLD using photosensors with a dual LED array, as opposed to those with a single optical emitter [115].

Suspected blood leaks should be confirmed by inspection of the dialysate for red staining, and if the dialysate is clear, testing for hemoglobin in the dialysate via dipstick or measurement of free Hb in the lab (Table 25.8). Dialysate Hb dipsticks will pick up a Hb concentration of 15 mg/L, which corresponds to a blood leak of 0.1 ml/min [114].

Management of a confirmed blood leak includes immediate cessation of dialysis, testing to exclude hemolysis, and restarting dialysis with a freshly primed circuit if indicated. The dialysis circuit should be retained for inspection to determine the cause of the leak.

Hemolysis Hemolysis is an uncommon, but potentially life-threatening complication of HD. The spectrum of presentation of acute hemolysis ranges from non-specific general malaise, with nausea, weakness, abdominal or back pain, acute hypertension and sometimes gross hematuria, to arrhythmias and sudden cardiac arrest [118, 119]. By contrast, chronic, low-grade hemolysis may present with erythropoiesis-stimulating agent (ESA)-resistant chronic anemia. The presentation may relate both to the etiology of the hemolysis and to the hemolysis itself. (Table 25.9).

Diagnosis Clinically, hemolysis is diagnosed by an acute fall in plasma hemoglobin, pink plasma, elevated free plasma hemoglobin, elevated LDH, and low haptoglobin. Plasma bilirubin may be elevated, and in dialysis patients, hyperkalemia may occur. The dialysis circuit may look brighter red and less opaque, the so-called "port wine" appearance.

Table 25.9 Causes of hemolysis during hemodialysis

Mechanical	Dialysate or dialyzer related	Underlying disease
Kinking of blood lines	High dialysate temperatures	Hemolytic anemia
Manufacturing defects in tubing	Low dialysate Na	Atypical hemolytic uremic syndrome
Mismatch between access and blood flow	Contaminants – copper, zinc, chloramine, nitrates, endotoxin, formaldehyde	RBC disorders including sickle cell, spherocytosis
Malpositioned fistula needles	Dialyzer reuse – formaldehyde	Malignant hypertension
Blood pump trauma		Mechanical heart valves

Significant hemolysis may go undetected by the dialysis machines' safety features, highlighting the need for careful observation of the patient and machine parameters during every treatment. A sustained >25 mmHg drop in arterial and venous pressures has been noted during hemolysis due to post-pump tubing kinks [120]. Hemolysis may also be detected by the blood leak detector when high flux dialyzers are used [114]. However, many factors influence the passage of free hemoglobin into the dialysate compartment, and this is not a reliable method for diagnosing hemolysis. Finally, blood volume monitoring may provide a clue to hemolysis, with affected patients showing a falling hematocrit, and a rising blood volume due to release of water from lysed cells. However, if the change in hematocrit is small, the CritLine™ may not be sufficiently sensitive to detect it [121].

Etiology The etiology of hemolysis may be classified as mechanical, dialysate, or dialyzer related, or due to an underlying disease process (Table 25.9).

Mechanical Hemolysis may occur due to a manufacturing defect in dialysis tubing causing narrowing of the lumen. A multistate outbreak of hemolysis in 1998, including fatalities, was linked to a manufacturing defect in dialysis tubing [122, 123]. Kinking of the blood lines, particularly as they come out of the dialyzer, has also been reported and underscores the need for visualization of the entire extracorporeal circuit during treatments [124–126], especially when introducing new machines or circuits.

Mechanical trauma to red blood cells within the extracorporeal circuit can occur with excessively negative pre-pump arterial pressures [127], in the pump tubing segment, with incorrectly placed fistula needles [128], or if there is a mismatch between the dialysis access and the desired blood flow [129]. The latter can be alleviated by the use of larger gauge access [130, 131].

Dialysate Related Both fatal hemolysis and non-fatal hemolysis have been described following inadvertent overheating of the dialysate to 50 °C or higher. Experimental studies suggest that human erythrocytes will tolerate temperatures of up to 47 °C without morphological change, that between 47 and 51 °C there is an increasing incidence of morphological change and risk of delayed hemolysis, and that above 51 °C, hemolysis is instantaneous and massive. Patients who have been exposed to overheated dialysate should thus be monitored for delayed hemolysis [132].

Dialysis against a hypotonic solution, with osmolality below approximately 250 mOsm/L, will also cause hemolysis. Hemolysis has also been reported in adults inadvertently dialyzed against distilled water as a result of improper reconstitution of Normocarb™ during continuous hemodialysis [133].

Contaminants such as copper [134], formaldehyde [135, 136], zinc and chloramines [137] in dialysate, and formaldehyde incompletely removed from the dialyzer during reuse are also reported causes of hemolysis.

Management of Hemolysis If hemolysis is diagnosed or suspected, the treatment should be terminated immediately without re-transfusion of the circuit. Bloodwork should be obtained for diagnosis and to determine the sequalae including severe anemia and hyperkalemia. Hyperkalemia must be managed medically if present, and a decision made regarding re-initiation of dialysis after analysis of, and correction of, potential causes. Supportive care may include blood transfusion. The dialysis circuit should be saved for inspection for mechanical causes of hemolysis such as manufacturing defects in the tubing if the cause is not readily apparent. The occurrence of hemolysis in multiple patients in a dialysis unit should prompt a thorough investigation into the etiology. The review article by Tharmaraj and Kerr contains an excellent algorithm for the diagnosis, management, investigation, and root cause analysis of hemolysis occurring during HD [118].

Chronic Hemodialysis Complications

Sleep Disorders

Though not specific to HD, sleep disorders merit discussion. Up to 60–80% of adults with CKD are reported to have a sleep disorder, which may contribute to hypertension and blood pressure variability [138], increased mortality, reduced quality of life [139], and depression [140]. The spectrum of sleep disorders includes insomnia, sleep-disordered breathing (SDB), restless leg syndrome (RLS), periodic limb movements (PLM), poor sleep quality, insufficient sleep time, and daytime somnolence. Sleep apnea can be central or obstructive. Central sleep apnea describes the cessation of respiratory effort and air flow for at least 20 seconds, or shorter if associated with desaturation, arousal, or awakening. Obstructive sleep apnea (OSA) is defined as the cessation of air flow in the presence of respiratory effort for at least 2 breaths. In children, it is

most commonly related to adeno-tonsillar hypertrophy. Peripheral edema and uremia are known risk factors for OSA.

Sleep disorders in children are associated with behavioral problems, poor school performance, and reduced health-related quality of life. The majority of studies of sleep disorders in children with CKD have been based on questionnaires. The first study published in 2005 reported an 86% incidence of sleep disorders characterized by a 46% incidence of sleep-disordered breathing, 29% RLS/PLM, and 60% incidence of excessive daytime sleepiness [141]. SDB based on questionnaire data was also associated with a reduced health-related quality of life score in children and adolescents with CKD [142].

Only three studies to date have utilized the gold standard of polysomnography (PSG) to examine sleep disorders in children with CKD. The first was a case-controlled PSG study on 25 children on HD. This confirmed markedly affected sleep quality in children on HD, with excessive daytime sleepiness, nocturnal awakening, difficult morning arousal, and increased limb pains compared to controls [143]. There was disordered sleep architecture with less slow wave sleep, and more sleep-disordered breathing and PLM in the HD patients. The second found a 37% incidence of SDB in a group of children with CKD 3-5, including obstructive sleep apnea, central sleep apnea, and hypoventilation [144]. There was discordance between the validated sleep questionnaire and the PSG, highlighting the limitations of diagnosing SDB in children based on questionnaires alone. The third was a study of eight children on automated peritoneal dialysis [145]. A sleep disorder was diagnosed in five of the eight children (62.5%) with four children (50%) having OSA and one having increased limb movements. Sleep architecture was abnormal with decreased sleep efficiency and sleep latency and a marked increase in awake time. Again, the sleep questionnaire was discordant with the PSG data, in this case underestimating the frequency of disordered sleep. Daytime sleepiness, headaches, irritability, or decreased attention may be unrecognized by parents as sequalae of a sleep disorder.

Restless leg syndrome is a neurological disorder. The 2014 consensus criteria require patients to meet five clinical criteria, namely, an urge to move the legs often associated with an uncomfortable sensation, worsening of the need to move the legs during periods of inactivity, partial or complete improvement of symptoms associated with leg movement, worse symptoms at night, and the absence of an alternate disease entity to explain the symptoms [146]. In one cohort of children with varying degrees of CKD, RLS was found in 35% based on questionnaire [147]. A larger case control study of children 8–18 years with CKD, dialysis, and transplant, utilizing a questionnaire designed to eliminate mimics of RLS, found a 15% incidence of RLS in CKD compared to 6% in the controls [148]. RLS was associated with subjectively poor sleep quality and the need for sleep-inducing medications. A detailed discussion of the treatment of RLS is beyond the scope of this chapter, but may include implementation of improved sleep hygiene habits, iron supplementation if anemic, or the use of clonidine, clonazepam, or dopaminergic medications for severely affected patients.

The adult literature suggests that objective improvement in sleep disorders may be seen with intensified dialysis (nocturnal HD or automated peritoneal dialysis) [149, 150], but no such data exist for pediatric patients. SDB has been shown to improve or resolve post-transplant in both adults [149, 151] and children [144, 152, 153].

The systematic review of the published literature on sleep disorders in CKD by Stabouli et al. included only the HD study utilizing PSG [154]. While this review confirmed the increased incidence of sleep disturbances in children with CKD and the impact on health-related quality of life, the data are based primarily on questionnaires which likely overestimate the incidence of SDB. Accurate

assessment of the incidence, type, and impact of sleep disorders will require systematic examination of large numbers of children with varying degrees of CKD by PSG.

Dialysis-Related Amyloidosis

Manifestation of the Disease Amyloidosis refers to the extracellular tissue deposition of fibrils composed of low-molecular-weight subunits of a variety of proteins. These deposits may result in a wide range of clinical manifestations depending upon their type, location, and the amount of deposition. Dialysis-related amyloidosis (DRA) is a serious complication of long-term dialysis therapy and is characterized by the deposition of amyloid fibrils, principally composed of β2 microglobulin (β2M), in the osteoarticular structures and viscera. The frequently involved articulations are arm joints, such as scapulohumeral and the carpal bones, and the cervical neck [155]. Gastrointestinal involvement is rare and generally occurs with pseudo-obstruction syndrome due to gastric or colonic dilatation [156].

Most of the β2M is eliminated through glomerular filtration and subsequent reabsorption and catabolism by the proximal tubules. As a consequence, the serum levels of β2M are inversely related to the glomerular filtration rate; therefore, in end-stage renal disease patients, β2M levels increase up to 60-fold. The incidence of DRA is not known; however, some past studies have suggested an incidence of >95% in patients in the USA who have been on dialysis for >15 years, while European experiences have suggested that DRA can be seen in as many as 20% of patients after 2–4 years of HD and in 100% of patients after 13 years of HD. However, the overall incidence and prevalence of β2 microglobulin (β2M)-related disease is not clear and there are no data in children [157]. In recent times, with the wide spread use of high-flux dialyzers and a move to longer or more frequent dialysis regimens and HDF, the incidence of DRA is thought to be declining.

Risk Factors The most important risk factors of DRA include long dialysis vintage, older age at HD onset, absence of RRF, and use of low-flux and bio-incompatible dialysis membranes [157–159].

Management Successful renal transplantation is the best treatment to prevent and manage DRA. If it is not feasible, β2 microglobulin clearance is higher with long daily or nocturnal dialysis, or HDF as compared to short-daily or conventional thrice-weekly HD [160–163]. High-volume, post-dilution hemodiafiltration (HDF) provides clearances of β2M, which are approximately twice those obtained with high-flux HD, and a reduction of β2M plasma concentration to 25–32% of pre-HD levels is obtained [164–166]. Synthetic high-flux membranes allow β2M removal not only by convection (highest for polysulfone) but also by adsorption to the membrane (highest for AN69, a negatively charged membrane) [167]. However, despite substantial clearance, there is still considerable retention of β2M with thrice-weekly high-flux HD [160, 168]. This underlines the importance of dialysis time, as shown in patients undergoing nocturnal long daily HD (48 hours/week) in whom weekly β2M mass removal is increased by 78% compared with thrice-weekly high-flux HD [162]. Thus, the major determinants of removal of β2M in HD are dialyzer clearance, duration and frequency of the sessions, and UF volume.

Conclusion

Advances in dialysis technology over the last half century have improved the safety, efficacy, and tolerability of HD. However, many patients continue to experience symptoms during and after their treatments with the most troubling identified by adult HD patients undergoing in-center dialysis as insomnia, fatigue, and muscle cramping [169]. Elucidating the cause of and ameliorating these symptoms, and the prevention of adverse short-term and long-term consequences of HD, remain a priority in the care of all patients on HD.

References

1. Kennedy AC, Linton AL, Eaton JC. Urea levels in cerebrospinal fluid after haemodialysis. Lancet. 1962;1(7226):410–1.
2. Patel N, Dalal P, Panesar M. Dialysis disequilibrium syndrome: a narrative review. Semin Dial. 2008;21(5):493–8.
3. Bagshaw SM, Peets AD, Hameed M, Boiteau PJ, Laupland KB, Doig CJ. Dialysis disequilibrium syndrome: brain death following hemodialysis for metabolic acidosis and acute renal failure--a case report. BMC Nephrol. 2004;5:9.
4. Yee M, Jern Y, Seng C. Dialysis disequilibrium syndrome: a preventable fatal acute complication. Med J Malaysia. 2016;71(2):91–2.
5. Harris CP, Townsend JJ. Dialysis disequilibrium syndrome. West J Med. 1989;151(1):52–5.
6. Zepeda-Orozco D, Quigley R. Dialysis disequilibrium syndrome. Pediatr Nephrol. 2012;27(12):2205–11.
7. William JH, Gilbert AL, Rosas SE. Keeping an eye on dialysis: the association of hemodialysis with intraocular hypertension. Clin Nephrol. 2015;84(5):307–10.
8. Lund A, Damholt MB, Strange DG, Kelsen J, Moller-Sorensen H, Moller K. Increased intracranial pressure during hemodialysis in a patient with anoxic brain injury. Case Rep Crit Care. 2017;2017:5378928.
9. Esnault P, Lacroix G, Cungi PJ, D'Aranda E, Cotte J, Goutorbe P. Dialysis disequilibrium syndrome in neurointensive care unit: the benefit of intracranial pressure monitoring. Crit Care. 2012;16(6):472.
10. Rosen SM, O'Connor K, Shaldon S. Haemodialysis disequilibrium. Br Med J. 1964;2(5410):672–5.
11. Trinh-Trang-Tan MM, Cartron JP, Bankir L. Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain. Nephrol Dial Transplant. 2005;20(9):1984–8.
12. Tuchman S, Khademian ZP, Mistry K. Dialysis disequilibrium syndrome occurring during continuous renal replacement therapy. Clin Kidney J. 2013;6(5):526–9.
13. Port FK, Johnson WJ, Klass DW. Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Kidney Int. 1973;3(5):327–33.
14. Bansal VK, Bansal S. Nervous system disorders in dialysis patients. Handb Clin Neurol. 2014;119:395–404.
15. Chang CH, Hsu KT, Lee CH, Lee YC, Chiou TT, Chuang CH, et al. Leukoencephalopathy associated with dialysis disequilibrium syndrome. Ren Fail. 2007;29(5):631–4.
16. Sengupta P, Biswas S. Dialysis disequilibrium leading to posterior reversible encephalopathy syndrome in chronic renal failure. CEN Case Rep. 2016;5(2):154–7.
17. Sheth KN, Wu GF, Messé SR, Wolf RL, Kasner SE. Dialysis disequilibrium: another reversible posterior leukoencephalopathy syndrome? Clin Neurol Neurosurg. 2003;105(4):249–52.
18. Kooman J, Basci A, Pizzarelli F, Canaud B, Haage P, Fouque D, et al. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant. 2007;22(Suppl 2):ii22–44.
19. Workgroup KD. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(4 Suppl 3):S1–153.
20. Kuipers J, Oosterhuis JK, Krijnen WP, Dasselaar JJ, Gaillard CA, Westerhuis R, et al. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions--a three-months, prospective study of 3818 haemodialysis sessions. BMC Nephrol. 2016;17:21.
21. Sands JJ, Usvyat LA, Sullivan T, Segal JH, Zabetakis P, Kotanko P, et al. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. Hemodial Int. 2014;18(2):415–22.
22. Tisler A, Akocsi K, Harshegyi I, Varga G, Ferenczi S, Grosz M, et al. Comparison of dialysis and clinical characteristics of patients with frequent and occasional hemodialysis-associated hypotension. Kidney Blood Press Res. 2002;26:97–102.
23. Hothi DK, Harvey E, Goia CM, Geary D. Blood-volume monitoring in paediatric haemodialysis. Pediatr Nephrol. 2008;23(5):813–20.
24. Hothi D. An investigation into the mechanisms, consequences and moderators of intradialytic hypotension in paediatric haemodialysis. London: University College London; 2009.
25. Reeves P, McCausland F. Mechanisms, clinical implications, and treatment of intradialytic hypotension. Clin J Am Soc Nephrol. 2018;13(8):1297–303.
26. Chesterton L, McIntyre C. The assessment of baroreflex sensitivity in patients with chronic kidney disease: implications for vasomotor instability. Curr Opin Nephrol Hypertens. 2005;1(4):586–91.
27. Hothi DK, Rees L, Marek J, Burton J, McIntyre CW. Pediatric myocardial stunning underscores the cardiac toxicity of conventional hemodialysis treatments. Clin J Am Soc Nephrol. 2009;4(4):790–7.
28. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009;4(12):1925–31.
29. McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol. 2008;3(1):19–26.
30. Charytan DM, Skali H, Shah NR, Veeranna V, Cheezum MK, Taqueti VR, et al. Coronary flow reserve is predictive of the risk of cardiovascular

death regardless of chronic kidney disease stage. Kidney Int. 2018;93(2):501–9.
31. Fellner S, Lang R, Neumann A, Spencer K, Bushinsky D, Borow K. Physiological mechanisms for calcium-induced changes in systemic arterial pressure in stable dialysis patients. Hypertension. 1989;13:213–8.
32. Tessitore N, Santoro A, Panzetta GO, Wizemann V, Perez-Garcia R, Martinez Ara J, et al. Acetate-free biofiltration reduces intradialytic hypotension: a European multicenter randomized controlled trial. Blood Purif. 2012;34(3–4):354–63.
33. Zaloszyc A, Schaefer B, Schaefer F, Krid S, Salomon R, Niaudet P, et al. Hydration measurement by bioimpedance spectroscopy and blood pressure management in children on hemodialysis. Pediatr Nephrol. 2013;28(11):2169–77.
34. Milani GP, Groothoff JW, Vianello FA, Fossali EF, Paglialonga F, Edefonti A, et al. Bioimpedance and fluid status in children and adolescents treated with dialysis. Am J Kidney Dis. 2017;69(3):428–35.
35. Allinovi M, Saleem MA, Burgess O, Armstrong C, Hayes W. Finding covert fluid: methods for detecting volume overload in children on dialysis. Pediatr Nephrol. 2016;31(12):2327–35.
36. Allinovi M, Saleem M, Romagnani P, Nazerian P, Hayes W. Lung ultrasound: a novel technique for detecting fluid overload in children on dialysis. Nephrol Dial Transplant. 2017;32(3):541–7.
37. Fischbach M, Edefonti A, Schroder C, Watson A. European Pediatric Dialysis Working G. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.
38. Fadel FI, Makar SH, Eskander AE, Aon AH. Decreasing intra-dialytic morbid events and assessment of dry weight in children on chronic hemodialysis using non-invasive changes in hematocrit. Saudi J Kidney Dis Transpl. 2014;25(5):1030–7.
39. Merouani A, Kechaou W, Litalien C, Ducruet T, Jouvet P. Impact of blood volume monitoring on fluid removal during intermittent hemodialysis of critically ill children with acute kidney injury. Nephrol Dial Transplant. 2011;26(10):3315–9.
40. Raina R, Lam S, Raheja H, Krishnappa V, Hothi D, Davenport A, et al. Pediatric intradialytic hypotension: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup. Pediatr Nephrol. 2019;34(5):925–41.
41. Dheu C, Terzic J, Menouer S, Fischbach M. Importance of the curve shape for interpretation of blood volume monitor changes during haemodiafiltration. Pediatr Nephrol. 2009;24(7):1419–23.
42. Candan C, Sever L, Civilibal M, Caliskan S, Arisoy N. Blood volume monitoring to adjust dry weight in hypertensive pediatric hemodialysis patients. Pediatr Nephrol. 2009;24(3):581–7.
43. Patel HP, Goldstein SL, Mahan JD, Smith B, Fried CB, Currier H, et al. A standard, noninvasive monitoring of hematocrit algorithm improves blood pressure control in pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(2):252–7.
44. Paglialonga F, Consolo S, Edefonti A, Montini G. The first hour refill index: a promising marker of volume overload in children and young adults on chronic hemodialysis. Pediatr Nephrol. 2018;33(7):1209–14.
45. Kron S, Schneditz D, Leimbach T, Aign S, Kron J. Vascular refilling is not reduced in dialysis sessions with morbid events. Blood Purif. 2017;43(4):309–14.
46. Hothi DK, Harvey E, Goia CM, Geary DF. Evaluating methods for improving ultrafiltration in pediatric hemodialysis. Pediatr Nephrol. 2008;23(4):631–8.
47. Dunne N. A meta-analysis of sodium profiling techniques and the impact on intradialytic hypotension. Hemodial Int. 2017;21(3):312–22.
48. Locatelli F, Altieri P, Andrulli S, Sau G, Bolasco P, Pedrini LA, et al. Phosphate levels in patients treated with low-flux haemodialysis, pre-dilution haemofiltration and haemodiafiltration: post hoc analysis of a multicentre, randomized and controlled trial. Nephrol Dial Transplant. 2014;29(6):1239–46.
49. Shroff R, Smith C, Ranchin B, Bayazit AK, Stefanidis CJ, Askiti V, et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, heart and height study. J Am Soc Nephrol. 2019;30(4):678–91.
50. Donauer J. Reduction of hypotensive side effects during online-haemodiafiltration and low temperature haemodialysis. Nephrol Dial Transplant. 2003;18(8):1616–22.
51. Hothi DK, Harvey E, Goia CM, Geary D. The value of sequential dialysis, mannitol and midodrine in managing children prone to dialysis failure. Pediatr Nephrol. 2009;24(8):1587–91.
52. Chen J, Gul A, Sarnak M. Management of intradialytic hypertension: the ongoing challenge. Semin Dial. 2006;19(2):141–5.
53. Cirit M, Akcicek F, Terzioglu E, Soydas C, Ok E, Ozbasli C, et al. Paradoxical rise in blood pressure during ultrafiltration in dialysis patients. Nephrol Dial Transplant. 1995;10:1417–20.
54. Park J, Rhee CM, Sim JJ, Kim YL, Ricks J, Streja E, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. Kidney Int. 2013;84(4):795–802.
55. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147(3):383–7.
56. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14(3):297–303.
57. Villarroel F, Ciarkowski AA. A survey on hypersensitivity reactions in hemodialysis. Artif Organs. 1985;9(3):231–8.
58. Daugirdas JT, Ing TS. First-use reactions during hemodialysis: a definition of subtypes. Kidney Int. 1988;33(Suppl 24):S37–43.

59. Salem M, Ivanovich PT, Ing TS, Daugirdas JT. Adverse effects of dialyzers manifesting during the dialysis session. Nephrol Dial Transplant. 1994;9(Suppl 2):127–37.
60. Ebo DG, Bosmans JL, Couttenye MM, Stevens WJ. Haemodialysis-associated anaphylactic and anaphylactoid reactions. Allergy. 2006;61(2):211–20.
61. Lemke HD. Mediation of hypersensitivity reactions during hemodialysis by IgE antibodies against ethylene oxide. Artif Organs. 1987;11(2):104–10.
62. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. Br Med J (Clin Res Ed). 1986;292(6530):1221–2.
63. Caruana RJ, Hamilton RW, Pearson FC. Dialyzer hypersensitivity syndrome: possible role of allergy to ethylene oxide. Report of 4 cases and review of one literature. Am J Nephrol. 1985;5(4):271–4.
64. Pearson F, Bruszer G, Lee W, Sagona M, Sargent H, Woods E, et al. Ethylene oxide sensitivity in hemodialysis patients. Artif Organs. 1987;11(2):100–3.
65. Ansorge W, Pelger M, Dietrich W, Baurmeister U. Ethylene oxide in dialyzer rinsing fluid: effect of rinsing technique, dialyzer storage time, and potting compound. Artif Organs. 1987;11(2):118–22.
66. Kokubo K, Kurihara Y, Kobayashi K, Tsukao H, Kobayashi H. Evaluation of the biocompatibility of dialysis membranes. Blood Purif. 2015;40(4):293–7.
67. Bacelar Marques ID, Pinheiro KF, de Freitas do Carmo LP, Costa MC, Abensur H. Anaphylactic reaction induced by a polysulfone/polyvinylpyrrolidone membrane in the 10th session of hemodialysis with the same dialyzer. Hemodial Int. 2011;15(3):399–403.
68. Sayeed K, Murdakes C, Spec A, Gashti C. Anaphylactic shock at the beginning of hemodialysis. Semin Dial. 2016;29(1):81–4.
69. Hildebrand S, Corbett R, Duncan N, Ashby D. Increased prevalence of eosinophilia in a hemodialysis population: longitudinal and case control studies. Hemodial Int. 2016;20:414.
70. Li Z, Ma L, Zhao S. Effect of polyflux membranes on the improvement of hemodialysis-associated eosinophilia: a case series. Ren Fail. 2016;38(1):65–9.
71. Tielemans C, Madhoun P, Lenaers M, Schandene L, Goldman M, Vanherweghem JL. Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. Kidney Int. 1990;38(5):982–4.
72. Parnes EL, Shapiro WB. Anaphylactoid reactions in hemodialysis patients treated with the AN69 dialyzer. Kidney Int. 1991;40(6):1148–52.
73. Verresen L, Fink E, Lemke HD, Vanrenterghem Y. Bradykinin is a mediator of anaphylactoid reactions during hemodialysis with AN69 membranes. Kidney Int. 1994;45(5):1497–503.
74. Coppo R, Amore A, Cirina P, Scelfo B, Giacchino F, Comune L, et al. Bradykinin and nitric oxide generation by dialysis membranes can be blunted by alkaline rinsing solutions. Kidney Int. 2000;58(2):881–8.
75. Brophy PD, Mottes TA, Kudelka TL, McBryde KD, Gardner JJ, Maxvold NJ, et al. AN-69 membrane reactions are pH-dependent and preventable. Am J Kidney Dis. 2001;38(1):173–8.
76. Molinaro G, Duan QL, Chagnon M, Moreau ME, Simon P, Clavel P, et al. Kinin-dependent hypersensitivity reactions in hemodialysis: metabolic and genetic factors. Kidney Int. 2006;70(10):1823–31.
77. Berkun Y, Haviv YS, Schwartz LB, Shalit M. Heparin-induced recurrent anaphylaxis. Clin Exp Allergy. 2004;34(12):1916–8.
78. Syed S, Reilly RF. Heparin-induced thrombocytopenia: a renal perspective. Nat Rev Nephrol. 2009;5(9):501–11.
79. Blossom DB, Kallen AJ, Patel PR, Elward A, Robinson L, Gao G, et al. Outbreak of adverse reactions associated with contaminated heparin. N Engl J Med. 2008;359(25):2674–84.
80. Upadhyay A, Jaber BL. We use impure water to make dialysate for hemodialysis. Semin Dial. 2016;29(4):297–9.
81. Ward RA. Ultrapure dialysate. Semin Dial. 2004;17(6):489–97.
82. Upadhyay A, Sosa MA, Jaber BL. Single-use versus reusable dialyzers: the known unknowns. Clin J Am Soc Nephrol. 2007;2(5):1079–86.
83. Twardowski ZJ. Dialyzer reuse - part II: advantages and disadvantages. Semin Dial. 2006;19(3):41–53.
84. Canaud B, Aljama P, Tielemans C, Gasparovic V, Gutierrez A, Locatelli F. Pathochemical toxicity of perfluorocarbon-5070, a liquid test performance fluid previously used in dialyzer manufacturing, confirmed in animal experiment. J Am Soc Nephrol. 2005;16(6):1819–23.
85. Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. Kidney Int. 2012;82(2):147–57.
86. Kiaii M, Djurdjev O, Farah M, Levin A, Jung B, MacRae J. Use of electron-beam sterilized hemodialysis membranes and risk of thrombocytopenia. JAMA. 2011;306(15):1679–87.
87. De Prada L, Lee J, Gillespie A, Benjamin J. Thrombocytopenia associated with one type of polysulfone hemodialysis membrane: a report of 5 cases. Am J Kidney Dis. 2013;61(1):131–3.
88. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergy and clinical immunology. Allergy. 2007;62(8):857–71.
89. Capozzoli G, Schenk C, Vezzali N. Cerebral air embolism after central dialysis line removal: the role of the fibrin sheath as portal (mechanism) of air entry. J Vasc Access. 2012;13(4):516–9.
90. Sahutoglu T, Sakaci T, Hasbal NB, Kara E, Ahbap E, Sevinc M, et al. Air embolism following removal of hemodialysis catheter. Hemodial Int. 2017;21(1):29–34.

91. Wong SS, Kwaan HC, Ing TS. Venous air embolism related to the use of central catheters revisited: with emphasis on dialysis catheters. Clin Kidney J. 2017;10(6):797–803.
92. Stegmayr B. Air contamination during hemodialysis should be minimized. Hemodial Int. 2017;21(2):168–72.
93. Stegmayr B, Forsberg U, Jonsson P, Stegmayr C. The sensor in the venous chamber does not prevent passage of air bubbles during hemodialysis. Artif Organs. 2007;31(2):162–6.
94. Ward M, Shadforth M, Hill A, Kerr D. Air embolism during haemodialysis. Br Med J. 1971;3(5766):74–8.
95. Baskin S, Wozniak R. Hyperbaric oxygenation in the treatment of hemodialysis-associated air embolism. N Engl J Med. 1975;293(4):184–5.
96. Dunbar E, Fox R, Watson B, Akrill P. Successful late treatment of venous air embolism with hyperbaric oxygen. Postgrad Med J. 1990;66(776):469–70.
97. Lau L, London K. Cortical blindness and altered mental status following routine hemodialysis, a case of iatrogenic cerebral air embolism. Case Rep Emerg Med. 2018;2018:9496818.
98. Jonsson P, Lindmark L, Axelsson J, Karlsson L, Lundberg L, Stegmayr B. Formation of blood foam in the air trap during hemodialysis due to insufficient automatic priming of dialyzers. Artif Organs. 2018;42(5):533–9.
99. Jonsson P, Karlsson L, Forsberg U, Gref M, Stegmayr C, Stegmayr B. Air bubbles pass the security system of the dialysis device without alarming. Artif Organs. 2007;31(2):132–9.
100. Keshavarzi G, Barber TJ, Yeoh G, Simmons A, Reizes JA. Two-dimensional computational analysis of microbubbles in hemodialysis. Artif Organs. 2013;37(8):E139–44.
101. Keshavarzi G, Simmons A, Yeoh G, Barber T. Effectiveness of microbubble removal in an airtrap with a free surface interface. J Biomech. 2015;48(7):1237–40.
102. Barak M, Nakhoul F, Katz Y. Pathophysiology and clinical implications of microbubbles during hemodialysis. Semin Dial. 2008;21(3):232–8.
103. Polaschegg H. Hemodialysis machine air detectors need not detect microbubbles. Artif Organs. 2007;31(12):911–2.
104. Wagner S, Rode C, Wojke R, Canaud B. Observation of microbubbles during standard dialysis treatments. Clin Kidney J. 2015;8(4):400–4.
105. Forsberg U, Jonsson P, Stegmayr C, Jonsson F, Nilsson B, Nilsson Ekdahl K, et al. A high blood level in the venous chamber and a wet-stored dialyzer help to reduce exposure for microemboli during hemodialysis. Hemodial Int. 2013;17(4):612–7.
106. Stegmayr BG. Sources of mortality on dialysis with an emphasis on microemboli. Semin Dial. 2016;29(6):442–6.
107. Kosmadakis G, Aguilera D, Carceles O, Da Costa Correia E, Boletis I. Pulmonary hypertension in dialysis patients. Ren Fail. 2013;35(4):514–20.
108. Stegmayr B, Brannstrom T, Forsberg U, Jonson P, Stegmayr C, Hultdin J. Microbubbles of air may occur in the organs of hemodialysis patients. ASAIO J. 2012;58(2):177–9.
109. Madero M, Sarnak MJ. Does hemodialysis hurt the brain? Semin Dial. 2011;24(3):266–8.
110. Forsberg U, Jonsson P, Stegmayr C, Stegmayr B. Microemboli, developed during haemodialysis, pass the lung barrier and may cause ischaemic lesions in organs such as the brain. Nephrol Dial Transplant. 2010;25(8):2691–5.
111. George S, Holt S, Hildick-Smith D. Patent foramen ovale, dialysis and microembolization. Nephrology. 2012;17(6):569–74.
112. Forsberg U, Jonsson P, Stegmayr C, Stegmayr B. A high blood level in the air trap reduces microemboli during hemodialysis. Artif Organs. 2012;36(6):525–9.
113. Palanchon P, Birmele B, Tranquart F. Acoustical bubble trapper applied to hemodialysis. Ultrasound Med Biol. 2008;34(4):681–4.
114. Lindley E, Finney D, Jones P, Lewington A, O'Reagan A, Webb G. Unexpected triggering of the dialysate blood leak detector by haemolysis. Acta Clin Belg. 2015;70(3):226–9.
115. Avila J, Prasad D, Weisberg L, Kasama R. Pseudo-blood leak? A hemodialysis mystery. J Clin Nephrol. 2013;79(4):323–5.
116. Lim K, Heher E, Steele D, Fenves A, Tucker J, Thadhani R, et al. Hemodialysis failure secondary to hydroxyocobalamin exposure. Proc (Bayl Univ Med Cent). 2017;30(2):167–8.
117. Gizaw A, Kidd JM. All that leaks is not blood. Kidney Int. 2015;88(3):645.
118. Tharmaraj D, Kerr PG. Haemolysis in haemodialysis. Nephrology. 2017;22(11):838–47.
119. Kirsch AH, Pollheimer MJ, Troppan K, Horina JH, Rosenkranz AR, Eller K. The case | acute kidney injury and hemolysis in a 58-year-old woman. Kidney Int. 2017;91(4):993–4.
120. Malinauskas R. Decreased hemodialysis circuit pressures indicating postpump tubing kinks: a retrospective investigation of hemolysis in five patients. Hemodial Int. 2008;12(3):383–93.
121. Paluszkiewicz A, Kellner J, Elshehabi M, Schneditz D. Effect of hemolysis and free hemoglobin on optical hematocrit measurements in the extracorporeal circulation. ASAIO J. 2008;54(2):181–4.
122. (CDC) CfDCaP. Multistate outbreak of hemolysis in hemodialysis patients - Nebraska and Maryland. MMWR Morb Mortal Wkly Rep. 1998;47(23):483–4.
123. Duffy R, Tomashek K, Spangenberg M, Spry L, Dwyer D, Safranek TJ, et al. Multistate outbreak of hemolysis in hemodialysis patients traced to faulty blood tubing sets. Kidney Int. 2000;57(4):1668–74.
124. Abtahi M, Uzan M, Souid M. Hemolysis-induced acute pancreatitis secondary to kinked hemodialysis blood lines. Hemodial Int. 2007;11(1):38–41.

125. Gault M, Duffett S, Purchase L, Murphy J. Hemodialysis intravascular hemolysis and kinked blood lines. Nephron. 1992;62(3):267–71.
126. Sweet S, McCarthy S, Steingart R, Callahan T. Hemolytic reactions mechanically induced by kinked hemodialysis lines. Am J Kidney Dis. 1996;27(2):262–6.
127. Shibata E, Nagai K, Takeuchi R, Noda Y, Makino T, Chikata Y, et al. Re-evaluation of pre-pump arterial pressure to avoid inadequate dialysis and hemolysis: importance of prepump arterial pressure monitoring in hemodialysis patients. Artif Organs. 2015;39(7):627–34.
128. Yoon J, Thapa S, Chow R, Jaar B. Hemolysis as a rare but potentially life-threatening complication of hemodialysis: a case report. BMC Res Notes. 2014;7:475.
129. Polaschegg HD. Red blood cell damage from extracorporeal circulation in hemodialysis. Semin Dial. 2009;22(5):524–31.
130. Techert F, Techert S, Woo L, Beck W, Lebsanft H, Wizemann V. High blood flow rates with adjustment of needle diameter do not increase hemolysis during hemodialysis treatment. J Vasc Access. 2007;8(4):252–7.
131. Mehta HK, Deabreu D, McDougall JG, Goldstein MB. Correction of discrepancy between prescribed and actual blood flow rates in chronic hemodialysis patients with use of larger gauge needles. Am J Kidney Dis. 2002;39(6):1231–5.
132. Berkes S, Kahn S, Chazan J, Garella S. Prolonged hemolysis from overheated dialysate. Ann Intern Med. 1975;83(3):363.
133. Pendergrast JM, Hladunewich MA, Richardson RM. Hemolysis due to inadvertent hemodialysis against distilled water: perils of bedside dialysate preparation. Crit Care Med. 2006;34(10):2666–73.
134. Matter B, Pederson J, Psimenos G, Lindeman R. Lethal copper intoxication in hemodialysis. Trans Am Soc Artif Intern Organs. 1969;15:309–15.
135. Orringer E, Mattern W. Formaldehyde-induced hemolysis during chronic hemodialysis. N Engl J Med. 1976;294(26):1416–20.
136. Punn K, Yeung C, Chen T. Acute intravascular hemolysis due to accidental formalin intoxication during hemodialysis. Clin Nephrol. 1984;21(3):188–90.
137. de Oliveira RM, de los Santos CA, Antonello I, d'Avila D. Warning: an anemia outbreak due to chloramine exposure in a clean hemodialysis unit--an issue to be revisited. Ren Fail. 2009;31(1):81–3.
138. Pengo MF, Ioratti D, Bisogni V, Ravarotto V, Rossi B, Bonfante L, et al. In patients with chronic kidney disease short term blood pressure variability is associated with the presence and severity of sleep disorders. Kidney Blood Press Res. 2017;42(5):804–15.
139. Scherer JS, Combs SA, Brennan F. Sleep disorders, restless legs syndrome, and uremic pruritus: diagnosis and treatment of common symptoms in dialysis patients. Am J Kidney Dis. 2017;69(1):117–28.
140. Gerogianni G, Kouzoupis A, Grapsa E. A holistic approach to factors affecting depression in haemodialysis patients. Int Urol Nephrol. 2018;50(8):1467–76.
141. Davis ID, Baron J, O'Riordan MA, Rosen CL. Sleep disturbances in pediatric dialysis patients. Pediatr Nephrol. 2005;20(1):69–75.
142. Davis ID, Greenbaum LA, Gipson D, Wu LL, Sinha R, Matsuda-Abedini M, et al. Prevalence of sleep disturbances in children and adolescents with chronic kidney disease. Pediatr Nephrol. 2012;27(3):451–9.
143. El-Refaey A, Elsayed R, Sarhan A, Bakr A, Hammad A, Elmougy A, et al. Sleep quality assessment using polysomnography in children on regular hemodialysis. Saudi J Kidney Dis Transpl. 2013;24(4):714–8.
144. Amin R, Sharma N, Al-Mokali K, Sayal P, Al-Saleh S, Narang I, et al. Sleep-disordered breathing in children with chronic kidney disease. Pediatr Nephrol. 2015;30(12):2135–43.
145. Gomes C, Oliveira L, Ferreira R, Simao C. Sleep disturbance in pediatric patients on automated peritoneal dialysis. Sleep Med. 2017;32:87–91.
146. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014;15(8):860–73.
147. Applebee GA, Guillot AP, Schuman CC, Teddy S, Attarian HP. Restless legs syndrome in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2009;24(3):545–8.
148. Riar SK, Leu RM, Turner-Green TC, Rye DB, Kendrick-Allwood SR, McCracken C, et al. Restless legs syndrome in children with chronic kidney disease. Pediatr Nephrol. 2013;28(5):773–95.
149. Kennedy C, Ryan SA, Kane T, Costello RW, Conlon PJ. The impact of change of renal replacement therapy modality on sleep quality in patients with end-stage renal disease: a systematic review and meta-analysis. J Nephrol. 2018;31(1):61–70.
150. Li L, Tang X, Kim S, Zhang Y, Li Y, Fu P. Effect of nocturnal hemodialysis on sleep parameters in patients with end-stage renal disease: a systematic review and meta-analysis. PLoS One. 2018;13(9):e0203710.
151. Brekke FB, Waldum-Grevbo B, von der Lippe N, Os I. The effect of renal transplantation on quality of sleep in former dialysis patients. Transpl Int. 2017;30(1):49–56.
152. Ball E, Kara T, McNamara D, Edwards EA. Resolution of sleep-disordered breathing in a dialysis-dependent child post-renal transplantation. Pediatr Nephrol. 2010;25(1):173–7.
153. Sharma N, Harvey E, Amin R. Sleep-disordered breathing in 2 pediatric patients on peritoneal dialysis. Perit Dial Int. 2016;36(1):109–12.
154. Stabouli S, Papadimitriou E, Printza N, Dotis J, Papachristou F. Sleep disorders in pediatric

chronic kidney disease patients. Pediatr Nephrol. 2016;31(8):1221–9.
155. Fenves A, Emmett M, White M, Greenway G, Michaels D. Carpal tunnel syndrome with cystic bone lesions secondary to amyloidosis in chronic hemodialysis patients. Am J Kidney Dis. 1986;7(2):130–4.
156. Dulgheru EC, Balos LL, Baer AN. Gastrointestinal complications of beta2-microglobulin amyloidosis: a case report and review of the literature. Arthritis Rheum. 2005;53(1):142–5.
157. Jadoul M, Garbar C, Noël H, Sennesael J, Vanholder R, Bernaert P, et al. Histological prevalence of β2-microglobulin amyloidosis in hemodialysis: a prospective post-mortem study. Kidney Int. 1997;51(6):1928–32.
158. van Ypersele de Strihou C, Jadoul M, Malghem J, Maldague B, Jamart J. Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int. 1991;39(5):1012–9.
159. McCarthy J, Williams A, Johnson W. Serum beta 2-microglobulin concentration in dialysis patients: importance of intrinsic renal function. J Lab Clin Med. 1994;123(4):495–505.
160. Dember L, Jaber B. Dialysis-related amyloidosis: late finding or hidden epidemic? Semin Dial. 2006;19(2):105–9.
161. Robindranath K, Strippoli G, Daly C, Roderick P, Wallace S, MacLeod A. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease (Review). Cochrane Database Syst Rev. 2006;4:1–93.
162. Raj D, Ouwendyk M, Francoeur R, Pierratos A. b2-microglobulin kinetics in nocturnal haemodialysis. Nephrol Dial Transplant. 2000;15:58–64.
163. Schiffl H, D'Agostini B, Held E. Removal of beta 2-microglobulin by hemodialysis and hemofiltration: a four year follow up. Biomater Artif Cell Immobil Biotechnol. 1992;20(5):1223–32.
164. Lornoy W, Becaus I, Billiouw J, Sierens L, van Malderen P, D'Haenens P. On-line haemodiafiltration. Remarkable removel of b2-microglobulin. Long-term clinical observations. Nephrol Dial Transplant. 2000;15(1):49–54.
165. van Ypersele de Strihou C. b2-Microglobulin amyloidosis: effect of ESRF treatment modality and dialysis membrane type. Nephrol Dial Transplant. 1996;11(2):147–9.
166. Ward RA, Greene T, Hartmann B, Samtleben W. Resistance to intercompartmental mass transfer limits beta2-microglobulin removal by post-dilution hemodiafiltration. Kidney Int. 2006;69(8):1431–7.
167. van Ypersele de Strihou C, Floege J, Jadoul M, Koch K. Amyloidosis and its relationship to different dialysers. Nephrol Dial Transplant. 1994;9(Suppl 2):156–61.
168. Drueke TB, Massy ZA. Beta2-microglobulin. Semin Dial. 2009;22(4):378–80.
169. Flythe JE, Hilliard T, Castillo G, Ikeler K, Orazi J, Abdel-Rahman E, et al. Symptom prioritization among adults receiving in-center hemodialysis: a mixed methods study. Clin J Am Soc Nephrol. 2018;13(5):735–45.

Part V

Management of Secondary Complications of Chronic Dialysis

26

Nutritional Assessment and Prescription for Children Receiving Maintenance Dialysis

Christina L. Nelms, Nonnie Polderman, and Rosanne J. Woloschuk

Introduction and Overview

Among the many priorities for the child receiving maintenance dialysis, attaining an optimal nutritional status is paramount and forms the foundation for a number of positive patient outcomes ranging from clinical status and biochemical control to quality of life and psychological well-being.

Adequate nutritional intake, especially in the early years of life, optimizes long-term growth [1]. Neurocognitive development and final adult height outcomes, which are established in the early years of life, are negatively impacted by poor nutritional intake in a child nearing or reaching end-stage kidney disease (ESKD) [2]. Historically, the focus of nutrition intervention has been to improve upon inadequate nutrition; however, the rising incidence of obesity is refocusing nutrition goals toward providing adequate, but not excessive, nutrition in order to reduce long-term obesity-related health concerns [3, 4].

Nutritional management, in concert with other medical management such as pharmacology, fluid balance, and dialysis prescription plays a key role in the achievement of electrolyte and biochemical control [5]. Each child on dialysis is unique, and each nutrition care plan must be individualized accordingly. Management of unique formula prescriptions and determination of best delivery route increase management complexity [6]. The multidisciplinary team caring for infants, children, and adolescents on dialysis must include a skilled clinical nutrition expert, such as a pediatric renal dietitian, who specializes in both pediatric and dialysis-specific nutrition management [7].

Nutrition Overview for Hemodialysis

A classic "sodium-, potassium-, and phosphorus-controlled diet" is the usual nutrition prescription for the pediatric hemodialysis (HD) patient. The typical thrice-weekly HD regimen does not provide adequate reduction of solutes to allow for complete diet liberalization. Post-dialysis treatment side effects impair appetite. While children with greater urine output enjoy more liberal fluid allowances, most children require some degree of fluid restriction. The use of HD in infants is rare, but in these patients, strict fluid management is imperative given the small size of the young child and concern for blood volume shifts during treatment [5, 8, 9].

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Less than 2% of all North American dialysis patients receive home hemodialysis [10] with the numbers of pediatric recipients unknown. One advantage of home HD is flexibility in providing intensified dialysis regimens in the form of shorter sessions of daily dialysis or nocturnal dialysis [11]. Patients undergoing nocturnal dialysis typically achieve excellent solute removal; supplementation of phosphorus, calcium, and vitamin D may be required. Although fluid and diet restrictions may be discontinued, electrolytes must be closely monitored to avoid suboptimal levels [12–14]. Patients receiving frequent daily dialysis do not enjoy the same dietary freedoms as those on nocturnal hemodialysis, but do report improved mental affect and quality of life, liberalized fluid allowances, and improved appetites [11, 15].

Nutrition Overview for Peritoneal Dialysis

Peritoneal dialysis (PD) is the most common modality of dialysis in pediatric patients worldwide [7]. The use of PD therapy requires in-depth assessment of factors related to PD to individualize the nutrition prescription. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) pediatric nutrition care guidelines [5] identify higher protein needs for PD patients compared to HD patients because of protein losses associated with PD (Tables 26.1 and 26.2). Ad lib eaters including children on PD typically consume adequate protein, but children receiving formula may require additional protein [16, 17].

The transport capacity of the peritoneum also impacts dietary needs (Table 26.1). High transporters have higher protein needs and greater peritoneal losses of other nutrients and will occasionally need potassium supplementation [18, 19]. Children who are low transporters have fewer nutrient losses, but potentially suffer from greater uremic affects resulting from relatively low solute removal, which can have a negative impact on appetite and gastrointestinal symptoms. Glucose absorption from the dextrose-containing dialysate is greater in high transporters and may alter the recommended nutrition prescription and biochemical status [5, 7]. For the young child with an underlying renal tubular disorder who is managed on PD, increased sodium supplementation and tighter potassium control may be required to offset an increased loss of sodium in the dialysis effluent and urine and associated potassium retention [5].

Growth

Suboptimal growth is a complication of CKD unique to children. Growth failure or "short stature" occurs at all stages of reduced kidney function, worsening with the progressive decline in kidney function [20, 21]. For each standard deviation score (SDS) decline in growth velocity, there is a reported 12–14% increase in mortality. Short stature is also associated with increased hospitalizations and infections, suggesting that linear growth is not just a cosmetic issue [21, 22]. Patients who receive a kidney transplant and who have very short stature have, on average, reduced allograft survival [20]. Lastly, final adult height impacts the education level and employment outcomes and thus overall quality of life [22, 23].

Early reports on growth from the North American Pediatric Renal Trials and Collaborative Studies (NAPTRCS) found that in the years leading up to 2004, 37% of pre-dialysis children fell below a height standard deviation score (HtSDS) of −1.88. While improvements to linear growth are being realized, recent reports from the Chronic Kidney Disease in Children (CKiD) study (2014) suggest that growth retardation remains prevalent with 12% of children with moderate CKD exhibiting a HtSDS of ≤ -1.88. Data suggests that for each drop in estimated glomerular filtration rate (eGFR) of 10 ml/min/1.73 m2, height is expected to drop by 0.14 SDS [24]. A child at or below the 3rd%ile, which is equivalent to a HtSDS of −1.88, or with a height velocity of −2 SDS, warrants further evaluation of factors which may be contributing to the poor growth and may ulti-

Table 26.1 Nutrition Guidelines by dialysis modality

	Conventional HD	Intensified HD (short daily, nocturnal, or increased duration)	PD (low transport status)	PD (high transport status)
Energy	Same as healthy children Consider comorbid conditions and alter needs			
Protein	Goal for age + 0.1 g/kg	Minimum goal for age + 0.1 g/kg May need increase above standard HD recommendations	Goal for age + 0.2–0.3 g/kg	Goal for age + 0.2–0.3 g/kg
Carbohydrate and fat	Use AMDR as guide Incorporate complex carbohydrates and healthy fats Adjust for dyslipidemia			
			Limit simple sugars	
Fluid total fluid intake (TFI)	Match TFI to urine output plus insensible losses	Match TFI to urine output plus insensible losses, more liberal with increased dialysis	TFI depends on urine output plus insensible losses plus fluid removal by ultrafiltration (varies with % dextrose concentration)	
Potassium	Restrict to control serum level	Restrict to control serum level May be more liberal than conventional HD	Restrict in most patients	Liberalize intake to control serum level Supplementation may be required
Sodium	Limit in most patients		Limit unless supplementing to replace losses due to polyuria	
Vitamins	Supplementation of water-soluble vitamins based on intake adequacy Supplement fat-soluble vitamins ONLY if evidence of deficiency or increased need			
Minerals	Avoid heavy metals and highly protein-bound minerals Assess trace minerals individually			
		May have increased losses of trace minerals	Elevated magnesium more likely	May have increased losses of trace minerals
Additional considerations	Tighter dietary and fluid management typical; acidosis can be treated through HD	Nocturnal dialysis may allow for more liberal dietary intake than shorter daily dialysis	"Low-average" transporters will have similar issues to low transporters but to a lesser extent	"High-average" transporters will have similar issues to high transporters but to a lesser extent

References [5, 7–19]

Table 26.2 Recommended protein intake by age in children receiving maintenance dialysis

Age	DRI for age (g/k/d)	Hemodialysis (g/k/d)[a]	Peritoneal dialysis (g/k/d)[b]
0–6 m	1.5	1.6	1.8
7–12 m	1.2	1.3	1.5
1–3 y	1.05	1.15	1.3
4–13 y	0.95	1.05	1.1
14–18 y	0.85	0.95	1.0

Adapted from the KDOQI Pediatric Nutrition Guidelines [5], http://www.ihi.org/resources/Pages/OtherWebsites/InstituteofMedicine.aspx [74], and https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html [78]

[a]DRI + 0.1 g/k/d to replace dialytic losses

[b]DRI + 0.15–0.3 g/k/d (depending on patient age) to replace peritoneal losses

mately be a candidate for recombinant growth hormone therapy [5].

Growth is multifactorial. Growth in children with CKD may be influenced by non-modifiable factors such as primary kidney disease, the age of onset of CKD, severity of renal insufficiency, as well as genetic factors. Ethnicity and socioeconomic status also impact growth outcomes [25, 26]. Modifiable factors impacting growth include metabolic acidosis, altered fluid status and electrolyte abnormalities, poor nutritional intake, renal osteodystrophy, and abnormalities in the growth hormone/insulin-like growth factor axis [27, 28]. When modifiable factors such as nutritional intake, dialysis prescription, acidosis, and

anemia have been addressed and corrected, evaluation for growth hormone therapy can, and should, be pursued [3, 28–32].

Nutrition Assessment

There is no single marker of nutritional adequacy. An accurate and thorough assessment of anthropometric measures, biochemical indices, and dietary intake information, within the context of a patient's presentation, are required to best determine nutrition needs [5].

Anthropometric Evaluation

The standard growth measurements (weight, linear growth, BMI, and head circumference) used to assess healthy children are also utilized to evaluate the nutritional status and estimate nutritional needs for children receiving maintenance dialysis therapy. KDOQI [5] recommends that younger children and those with more severe disease be assessed more frequently than children who are older or have less advanced CKD (Table 26.3). One study determined that children under the age of 5 years required at least twice as many dietetic contacts as older children [33]. Very young children may need to be evaluated as often as weekly [5]. When patients are not physically present, ongoing surveillance via telephone may be used to address weight gain, formula volume and tolerance issues, and feeding challenges.

Weight Determining a child's euvolemic or "dry" weight is complicated by changing urine output, severe oliguria/anuria, the presence of edema, and intradialytic weight changes [5]. The young child with a renal tubular disorder and associated polyuria is at risk of dehydration and volume depletion, potentially leading to underreporting of actual weight. Expected weight gain and growth, or unanticipated weight loss, necessitate the regular review and identification of this regularly changing value [9].

Table 26.3 Minimum frequency (months) for evaluation of anthropometric measures for children on maintenance dialysis

Measure	Age 0- < 1 years	Age 1–3 years	Age >3 years
Dietary intake	0.5–2	1–3	3–4
Height or length/age percentile or SDS	0.5–1	1	1–3
Height or length velocity for age percentile or SDS	0.5–1	1–2	6
Estimated dry weight	0.25–1	0.5–1	1–3
Weight for age percentile or SDS	0.25–1	0.5–1	1–3
BMI for height age percentile or SDS	0.5–1	1	1–3
Head circumference for age percentile or SDS	0.5–1	1–2	N/A
nPCR	N/A	N/A	1

Adapted from the KDOQI Pediatric Nutrition Guidelines [5]

Blood pressure (BP) monitoring is useful in the determination of euvolemic weight. Hypertension may be due to the presence of excess fluid volume, but the BP response may adapt to excess fluid or lag behind improvement in the management of the fluid status. Edema, a potential marker of an altered fluid status, may not manifest until significant extra fluid is present [34]. Noninvasive hematocrit monitoring during HD treatments provides important clues as to whether children on HD have reached dry weight and whether additional fluid removal is needed [35, 36]. Bioimpedance analysis (BIA) may aid in the assessment of euvolemic weight and will be discussed later in this section.

Attention to expected age-appropriate weight gain is critical when evaluating a child's growth trends. The World Health Organization (WHO) growth charts detail the expected daily rates of weight gain in children up to 2 years. Evaluating growth trends using daily weight gain as a guide allow for early detection of faltering growth [37, 38] (Table 26.4).

Linear Growth Despite non-modifiable disease-related factors such as uremia and pubertal delay, continuous age-appropriate height gain is

Table 26.4 Expected weight gain (g) per day by age for children < 2 years

Premie < 2 kg	Premie > 2 kg	0–4 months	4–8 months	8–12 months	12–16 months	16–24 months
15–20 g/kg/d	20–30 g/day	23–34 g/day	10–16 g/day	6–11 g/day	5–9 g/day	4–9 g/day

Adapted from Beer et al. [38]

desired. Recumbent length, as a measure of linear growth, is most accurately measured using a length board. For children over 2 years, standing height should be measured using a stadiometer; however, a recumbent length may be used until age 3 [5, 39]. When measurement of a standing height is not possible, trending surrogate anthropometric measures (arm span, demi-span, or ulna length) aid in determining adequacy of linear growth [40, 41].

Midparental height is used to determine linear growth potential and to guide final height expectations.

- Boy: Inches: (Father's Height + Mother's Height + 5) / 2.
- Centimeters: (Father's Height + Mother's Height + 13) / 2.
- Girl: Inches: (Father's Height – 5 + Mother's Height) / 2.
- Centimeters: (Father's Height – 13 + Mother's Height) / 2.

For example, the child of very short parents may not reach a natural height considered "average" for peers. Conversely, a child of very tall parents whose height is tracking just above the 3rd%ile (SDS, –1.88) is not meeting his growth potential [5, 42].

Body Mass Index KDOQI recommends that BMI be calculated using "height age" until the child has reached final development (Tanner stage 5) or final adult height [5] (Table 26.3). Height age is the age at which the child's current height falls at the 50th%ile. The use of height age prevents underestimation of BMI since many children with CKD have delayed physical maturation [43].

Despite limitations, BMI is the most practical measure available for determining nutritional inadequacy or adiposity. Children with CKD have poor musculature compared to body fat composition, and muscle-to-fat ratio decreases with progression to ESKD. Children with kidney disease also have elevated central adiposity [44–46]. Recent literature supports the use of waist-to-height ratio (WHr) for anthropometric evaluation of adiposity. A WHr of >0.49 suggests obesity is a function of excess fat mass [47].

Head Circumference Head circumference may be altered by comorbidities such as genetic disorders, prematurity, or hydrocephaly. In the absence of comorbid conditions, a reduced head circumference, or a decline in head growth velocity, can indicate chronic inadequate nutritional intake. Head circumference should be measured monthly until a child is 3 years of age [5] (Table 26.3).

Plotting Growth

Evaluation of growth via growth charts is essential to properly assess growth adequacy. The WHO growth standards, which represent expected growth for infants and young children provided with optimal nutrition, should be used for all children below the age of 2 years. After the age of 2 years, country- or region-specific growth charts can be used to better assess population-specific growth patterns [5]. Disease-specific growth charts provide more accurate growth expectation for certain populations with additional medical conditions [48, 49]. The Royal College of Paediatrics and Child Health [50] recommends the use of adjusted growth charts through 1 year of chronological age for children who were born at 32–36 weeks of gestation and until age 2 chronologically for those born at <32 weeks of gestation. The clinician should concurrently evaluate the child's growth on a non-adjusted growth chart to better capture the progress of catch-up growth [51].

Other Measures

Additional tools have been evaluated for their validity in the clinical nutrition assessment in pediatric CKD. Current recommendations regarding BIA or bioimpedance spectroscopy (BIS) strongly suggest that serial measurements be completed by a trained clinician [52]. BIS may be more helpful for trending fluid status and determining euvolemic weight [53]. Mid-Upper Arm Circumference (MUAC) has been validated as a marker of nutritional status in the general pediatric population [54, 55] and is frequently cited in literature to describe the nutritional status of pediatric patients with kidney disease [46, 56–59]. However, MUAC has not been independently evaluated for pediatric CKD or dialysis patients. As discussed later, physical exam of the patient may provide additional insight for determination of actual weight, body composition, and overall nutritional status [60, 61].

Dietary Evaluation

An accurate dietary assessment provides valuable data about nutrient deficits or excesses contributing to biochemical abnormalities and offers information needed in the determination of euvolemic weight [5]. Obtaining an accurate dietary intake history for evaluation may prove challenging as recording intake can be tedious for both patients and families [62]. The most accurate dietary intake assessment tool is a 3- or more-day food record requiring the patient or family to record all food and beverages consumed as the patient eats. Accurate portion sizes and food descriptions are critical [63]. Completing a 3-day food intake record is time-consuming and if not completed in real time includes a potential risk of errors and omissions [62]. Digital technology allows the patient and family to capture intake information by photographing pre- and post-consuming foods and beverages [64]. In the case of an adolescent who is less inclined to complete the record-keeping task, a minimum 3-day food recall conducted by a clinician is recommended [5]. Using food models as visual aids helps increase accuracy. Analysis of usual food patterns, frequently consumed foods, or general dietary information contributes positively to the assessment of the patient's clinical picture [65].

Food insecurity (FI), defined as "the inability to acquire or consume an adequate diet quality or sufficient quantity of food in socially acceptable ways, or the uncertainty that one will be able to do so", is a common problem associated with both poor health outcomes and increased healthcare costs. Families living with FI are less likely to have access to the necessary foods required by their children who have chronic diseases and are prescribed restricted diets [66].

The food insecurity screening tool can be used in the clinic setting. Answering "yes" to either of the validated 2-item food insecurity screen statements quickly identifies households with young children and adolescents at risk:

1. "within the past 12 months, we worried whether our food would run out before we got money to buy more"
2. "within the past 12 months, the food we bought just didn't last and we didn't have enough money to get more" [66, 67]

Nutrition-Focused Physical Exam

In addition to growth and biochemical measures, KDOQI [5] recommends the development and validation of a Subjective Global Assessment (SGA) tool for use in children with CKD. Several SGA tools have been used in the CKD population [68]; a 7-point SGA tool has been validated for use in adults on HD [61]. The SGA method adapted for study and later validated in children is the Subjective Global Nutritional Assessment (SGNA) [60]. The SGNA adds linear growth and weight relative to length/height to the medical history review and limits the nutrition-focused physical review to loss of subcutaneous fat, muscle wasting, and the presence of edema [60, 69–73]. There is some evidence that the SGNA associates well with most objective measures of nutritional status (but not albumin) and is a valid tool for assessing nutritional status of children with CKD [70].

Assessment for nutrient deficiencies can be achieved through completion of a thorough nutrition-focused physical exam (NFPE) using visual inspection and palpitation along with auscultation and percussion [71–73]. A comprehensive exam may include assessing the patient for changes in appearance of the skin, hair, facial features, mouth, neck, and nails and evaluation of the gastrointestinal, skeletal, and nervous systems [73].

Prescribing Nutrition

Energy and Macronutrient Needs

Requirements for energy and nutrients change throughout the life cycle with needs increasing during growth and cell division in infancy, early childhood, and adolescence [74]. Deficits in linear growth and development, acquired during infancy as a result of inadequate nutrition, may not be fully correctable [75]. Resting Energy Expenditure (REE) of children with CKD does not differ significantly from healthy subjects [76]. Calculation of caloric prescriptions for children with chronic kidney disease should follow the same principles used for healthy children [77] (Tables 26.1 and 26.5).

Acceptable macronutrient distribution ranges (AMDRs), expressed as a percentage of total energy, have been established based on epidemiological evidence for reducing the risk of chronic diseases [74, 78]. KDOQI [5] recommends the use of AMDRs to guide macronutrient prescriptions in pediatric CKD (Table 26.6). As macro- and micronutrients are manipulated to meet the special needs due to kidney disease, careful consideration must be paid to the impact of these adjustments on the overall AMDR. For example, lowering protein to reduce uremia will impact the percentage of fat and carbohydrate calories required to make up total energy. Likewise, lowering overall fat content to address dyslipidemia will necessitate calories from additional protein and carbohydrate to make up total energy. Due to the risk of uremia, increased protein is not always clinically appropriate.

Table 26.5 Equations for estimating energy requirements (kcal/d) by age for children

Age	Estimated energy requirement (EER) = Total Energy Expenditure (TEE) + Energy Deposition[a]		
0–3 m	All	EER = [89 × weight (kg) – 100]	+175
4–6 m			+56
7–12 m			+22
13–35 m			+20
3–8 y	Boys	EER = 88.5–61.9 × age (y) + PA × [26.7 × weight (kg) + 903 × height (m)]	+20
9–18 y			+25
3–8 y	Girls	EER = 135.3–30.8 × age (y) + PA × [10 x weight (kg) + 934 × height (m)]	+20
9–18 y			+25
	Estimated total energy expenditure for children who are overweight[b]		
3–18 y	Boys	TEE = 114 – [50.9 × age (y)] + PA × [19.5 × weight (kg) + 1161.4 × height(m)]	
	Girls	TEE = 389 – [41.2 × age (y)] + PA × [15.0 × weight (kg) + 701.6 × height(m)]	

Adapted from the KDOQI Pediatric Nutrition Guidelines [5], http://www.ihi.org/resources/Pages/OtherWebsites/InstituteofMedicine.aspx [74], and https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html [78]

[a]Estimating energy requirements for children at healthy weights

[b]Estimating total energy expenditure for weight maintenance for children who are overweight

Table 26.6 Acceptable macronutrient distribution ranges by age

Acceptable macronutrient distribution ranges for children by age (expressed as %)			
Macronutrient	< than 1 y	1–3 y	4–18 y
Protein	5–20	5–20	10–30
Fat	30–40	25–35	25–35
Carbohydrate	45–55	45–65	45–65
Added sugars[a]			≤25% of total energy

Adapted from the KDOQI Pediatric Nutrition Guidelines [5], http://www.ihi.org/resources/Pages/OtherWebsites/InstituteofMedicine.aspx [74], https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html [78], https://health.gov/dietaryguidelines/2015/guidelines/appendix-7/ [179], and http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/8_Macronutrient%20Summary.pdf [180]

[a]Added sugars are defined as sugars and syrups that are added to foods during processing or preparation

Protein

Children require protein in adequate amounts to ensure growth and prevent protein malnutrition. Dietary protein restriction in children on dialysis is contraindicated and may lead to malnutrition, impaired growth, and subsequent protein energy wasting [79]. Excessive protein intake negatively impacts acid-base balance and potentially increases serum phosphorus, potassium, and uremic toxins. Protein prescriptions must be adjusted based on an individual's biochemical response (Tables 26.1 and 26.2). For infants and children receiving dialysis, careful consideration should be paid to the amount and quality of protein in the context of overall energy intake. Adequate protein in the absence of adequate energy will lead to the body utilizing protein or lean tissue as energy. Provision of adequate protein should take into consideration issues such as the presence of infection, inflammation, catabolism, and protein lost through dialysis therapies (Tables 26.1 and 26.2). With newer high-flux dialyzers and more effective dialysis therapies, protein losses may be greater than previously reported [80].

Carbohydrate and Fat

Carbohydrates should provide 45–65% of total caloric intake [74, 78] with consideration given to the type and sources of carbohydrate for children on dialysis and with an emphasis on adding complex carbohydrates and the associated fiber. Previous recommendations limited complex carbohydrates due to their phosphorus content, but current research no longer supports this dietary modification [81]. Early and frequent efforts should be made to encourage children, teens, and their families to adopt a healthy intake early in the journey of chronic kidney disease. A foundation of healthful eating behaviors, which includes more plant-based foods, will serve patients well post transplantation when the focus on diet shifts toward reducing the risk of developing other chronic diseases [82].

Adjusting the oral intake of carbohydrate to account for additional glucose from PD solutions may prove challenging for the ad lib eater and the formula-fed child. Limiting the use of modular carbohydrates, sugary beverages, and juices may be a solution.

Dietary fat plays an important role in the body, but excessive fat intake should be avoided. Cardiovascular complications arise early in the course of CKD and persist after transplantation. Dyslipidemia is more common and severe in patients with glomerular disease and proteinuria, and in ESKD [83]. Elevated triglycerides and non-high-density lipoprotein (non-HDL) cholesterol have been reported in 44% of children with CKD stages 2–4. As GFR declines, both triglyceride and cholesterol levels increase [84]. Diet and activity modifications are first-line treatments. Adjustments to the type and amount of fat impact elevated lipid levels and long-term cardiovascular health. The American Heart Association (AHA) and Heart and Stroke Foundation guidelines recommend that calories from fat make up no more than 35% of energy intake and more poly- and mono-unsaturated fats be included with a corresponding reduction in the amounts of saturated fats [85, 86].

Micronutrient Needs

Electrolyte Management

Electrolyte management is an important multidisciplinary objective. Dietary manipulation plays an essential role in maintaining electrolytes within safe ranges.

Limiting overall sodium intake is important in CKD. CKiD data reports that the average daily sodium intakes of children with CKD were in excess of the KDOQI recommendation of 1500–2400 mg/day [5, 87]. These findings can likely be extrapolated to dialysis patients given that excessive sodium intake is a worldwide problem [88, 89]. Limiting dietary sodium aids in preventing excess thirst and improving fluid control for the patient with limited or no urine output. Sodium reduction may also prevent hypertension, as well as reduce the risk for cardiovascular disease and left ventricular hypertrophy [5]. Infants and children with renal tubular disorders, such as renal dysplasia or obstructive uropathies, have inappropriate ion exchange resulting in the loss of large amounts of fluid and sodium [90]. These children continue to have

high urine output, and, as a result, sodium supplementation may be necessary. Most infant formulas and breast milk are low in sodium. One study, which used diluted formula to provide adequate fluid for children with polyuria, advised providing 2–4 mEq of sodium supplementation per 100 mL of formula [91]. Higher sodium formulas may decrease or eliminate the need for supplementation. The DRI for sodium should be met to help prevent neurological damage, poor growth, or blindness during infancy [5, 7]. The need for sodium supplementation will often resolve with age and as children begin consuming solid foods.

Very high or low serum levels of potassium, another key electrolyte, can cause serious cardiac outcomes. Most patients with anuria require potassium restriction [5]. Data from CKiD indicates that oral potassium intake is actually quite low and very few children exceed recommended intakes [92]. This finding can likely be extrapolated to children on dialysis in whom fruit and vegetable consumption is low. When hyperkalemia persists, non-dietary causes such as tissue breakdown, protein energy wasting, constipation, or medications (such as ACE inhibitors or ARBs) should also be considered as possible etiologies [93].

In small children with renal tubular disorders, potassium allowances may be very limited. A guideline of 1–3 mmol/kg or 40–120 mg/kg of potassium has been suggested. In the case of a 5-kg infant, the potassium allowance would be only 200–600 mg of potassium daily [5]. One approach to reduce potassium intake is by the pre-treatment of feeds with sodium or calcium ion exchange resins. There are noted risks with this practice, including alteration of other vitamin and mineral levels, and development of potentially serious biochemical derangements [94, 95]. Another option for limiting potassium intake is to use a very low potassium pediatric renal formula, which when combined with a standard formula, decreases potassium load. Feeds should be titrated to meet individual potassium needs [7]. Potassium restriction is not often indicated for PD patients who are high transporters, and in some cases potassium supplementation is indicated. Conversely, a low transporter may need to tightly limit dietary potassium [5, 18, 19] (Table 26.1).

Managing bicarbonate levels in CKD is also important. Excretion of an acid load is impaired, and the resulting acidosis causes poor growth, elevated potassium levels, increased risk of secondary hyperparathyroidism, and the progression of CKD to ESKD [3, 5, 94, 96]. Alkali supplementation in the form of sodium bicarbonate is typically used to increase CO2 levels to above 22 mmol/L as per KDOQI recommendations [5]. The use of low chloride formulas may also improve acidosis.

Bone Mineral Management

Chronic kidney disease- mineral and bone disorder (CKD-MBD) is a complication involving abnormalities in calcium, phosphorus, PTH or vitamin D regulation, variation in the bone itself, or extra-skeletal abnormalities such as soft tissue damage [97]. Early nutrition intervention is key to addressing this phenomenon [98, 99]. Complications due to elevated phosphorus have been shown to present well before the need for dialysis, with bone mineral changes taking place as early as CKD stage 2 [99].

Phosphorus is abundant in today's food supply and easily consumed in excess. Western diets, characterized by increased intake of processed and fast foods containing phosphorus-based food additives, pose a challenge to the management of serum phosphate levels [100]. Eighty-eight percent of adolescents in one HD unit had elevated serum phosphorus levels despite reporting adherence to dietary guidelines [101]. Another study of the typical American diet found additives alone may contribute 1000 mg of phosphorus per day over and above what is naturally found in food [102]. In addition to avoiding excess intake of dairy and meats that are naturally high in phosphorus, the primary intervention should be limiting foods processed with inorganic phosphorus. Phosphorus from nuts, beans, and other plant proteins may be less well absorbed than previously believed due to their high phytate contents. These plant-based sources of phosphorus, which were previously restricted,

are now recommended as part of a healthful intake [81]. It is imperative that the patient receiving dialysis be counseled to limit dietary phosphate intake and take associated phosphate-binding medications [5] (Table 26.7). Excessive phosphate intake leads to an eventual rise in PTH, while a reduction of dietary phosphorus intake helps correct elevated PTH levels. The effects of elevated phosphorus levels are dramatic and can include cardiovascular disease, poor transplant outcomes, and severe bone damage. Even when PTH and serum phosphorus are controlled with medication, excessive phosphorus intake may cause high levels of FGF-23, an early phosphorus-modulating precursor, and damaging bone and organ effects may be taking place [103, 104].

Calcium plays an important role in bone health. Unlike adult dialysis patients, children need calcium for optimal bone accrual and should achieve intakes of 100–200% of the DRI for calcium [5, 98] (Table 26.7). Excessive calcium, whether from diet or calcium-based phosphate binders, should be avoided. An early study showed that adolescents and young adults consuming calcium-based phosphate binders in excess of the maximum recommended calcium intake had cardiovascular damage and calcification by the mid-20s [105]. When hypercalcemia is present, calcium intake should be limited. Excess serum phosphorus draws calcium into the bloodstream, making it available for calcification of soft tissue, leading to bone disease and cardiovascular damage [5].

Vitamin D is another component of bone mineral management. When phosphorus is elevated, PTH increases, and its effectiveness is reduced, in turn reducing serum calcium and active vitamin D. In CKD, activation of vitamin D by the kidney is reduced [106] (see discussion in other chapters in this text). Adequate active vitamin D will help prevent hyperparathyroidism and may reduce the risks of other chronic diseases. The ESPN native vitamin D therapy clinical practice guidelines recommend the use of active vitamin D as first-line treatment of secondary hyperparathyroidism [107]. Children on dialysis routinely receive active vitamin D (1,25-OH) through oral intake or supplementation.

Vitamins

Serum retinol levels are elevated in as many as 77% of children in CKD stages 2–5 and 94% of pediatric dialysis patients [108–110]. Elevated retinol levels are common even when children are not meeting recommended intakes of vitamin A for healthy children. KDOQI recommends against supplementation with vitamin A to reduce the long-term risks such as liver damage since vitamin A is not well-cleared through dialysis [5]. Recent work has also implicated elevated serum retinol levels in hypercalcemia [109] as

Table 26.7 Recommended calcium and phosphorus intake by age in children receiving maintenance dialysis

	Recommended calcium intake (mg/d)		Recommended phosphorus intake (mg/d)		
Age	DRI (mg/d)	Upper limit for CKD stages 2–5, 5D[a]	DRI (mg/d)	Normal phosphorus and high PTH[b]	High phosphorus and high PTH[c]
0–6 m	210	≤420	100	≤100	≤80
7–12 m	270	≤540	275	≤275	≤220
1–3 y	500	≤1000	460	≤460	≤370
4–8 y	800	≤1600	500	≤500	≤400
9–18 y	1300	≤2500	1250	≤1250	≤1000

Adapted from the KDOQI Pediatric Nutrition Guidelines [5], http://www.ihi.org/resources/Pages/OtherWebsites/InstituteofMedicine.aspx [74], https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html [78], and https://health.gov/dietaryguidelines/2015/guidelines/appendix-7/ [179]

[a]200% of the DRI to maximum of 2500 mg elemental calcium, from diet and phosphorus binders

[b]≤100% of the DRI

[c]≤80% of the DRI

elevated retinol levels promote osteoclastic action and inhibit osteoblastic action in bone. If serum calcium levels are high due to an unknown etiology, retinol levels should be assessed. Dietary vitamin A content may be difficult to adjust in an oral eater with a mixed diet; however, modifications to formula and enteral feed prescriptions may be warranted as a greater number of formula-fed infants with higher vitamin A intake have higher retinol and calcium levels [109]. Multivitamin preparations containing vitamin A are contraindicated to prevent any additional intake of vitamin A beyond normal dietary intake.

When kidney function is impaired, fat-soluble vitamins E and K are not well-cleared. While information on these vitamins specific to pediatric dialysis patients is limited, and there is no indication to regularly evaluate or supplement vitamin K, evidence from the general pediatric population suggests that vitamin K is depleted with excess antibiotic use [111]. Given that children receiving dialysis are routinely prescribed antibiotics for treatment of infections (e.g., peritonitis, catheter infections), it is prudent to be aware of side effects (bruising and abnormal coagulation studies) related to inadequate vitamin K. Joyce [110] found vitamin E levels were elevated in 87% of children receiving dialysis. Yet, there is also evidence that vitamin E supplementation improves oxidative stress which consequently improves erythropoietin-resistant anemia [112, 113]. Concern with serum levels not reflecting clinical and intracellular deficiency adds to the challenge of managing vitamin E [113]. There is currently insufficient evidence to recommend vitamin E supplementation.

Levels of 500–1000 mg of supplemental vitamin C intakes have been shown to increase serum oxalate levels, increasing the risk for kidney stones in adult renal patients [114]. However, 100–300 mg vitamin C can be lost during a single dialysis treatment, with plasma levels decreasing about 50% with standard hemodialysis [115]. Young children on PD receiving fortified formula with a moderate supplement were shown to maintain positive vitamin C balances [116]. Daily supplementation with 250 mg of vitamin C showed improved intima media thickness and cardiovascular status in a small study of children with CKD [117], and another study of dialysis patients demonstrated improved lipid profiles likely related to vitamin C-induced reductions in uric acid [118]. While supplemental vitamin C needs for the pediatric dialysis patient remain unclear, excess vitamin C should be avoided.

To address the vitamin needs of children with CKD, KDOQI recommends a standard water-soluble vitamin supplement be given to dialysis patients due to potential dialysate losses and inadequate dietary intakes. While excessive intakes of water-soluble vitamins are unlikely to cause harm, serum levels of B vitamins should be assessed on occasion [5], as some deficiencies, such as riboflavin, folate, and vitamin B12, may contribute to anemia. The B vitamin content of select standard supplements may exceed needs, as evidenced by rates of elevated levels in one patient population study [110]. Currently, no pediatric-specific renal vitamin supplement is available. In practice, reduced doses of adult renal vitamin preparations are used to match age-appropriate needs. While vitamin doses may not perfectly align with the varying pediatric goals, supplementation is superior to inadequate water-soluble vitamin intake. Patient-specific estimates of vitamin and mineral requirements must take into account factors such as age, oral intake, and frequency of dialysis [5]. It is suspected that PD transport status also affects vitamin and mineral needs [110] as is demonstrated by higher potassium losses in those who are higher transporters [18].

Minerals

Minerals more tightly bound to plasma proteins are typically not removed during dialysis and may accumulate in excess. In contrast, minerals more weakly bound to proteins are removed more readily with low serum levels being more common [119]. Elevated serum magnesium has been reported in patients receiving dialysis [56]. Case reports indicate that very elevated magnesium levels that can contribute to symptoms are of concern, but mildly elevated magnesium lev-

els seem to have less clinical significance. Elements such as chromium, manganese, lead, arsenic, aluminum, and vanadium are potentially toxic, especially with environmental or water contamination; therefore, supplementation is not advised [119, 120]. Fluoride supplementation is also contraindicated in the pediatric dialysis patient. Decreased frequency of standard dental fluoride treatments in children with CKD may be prudent as fluoride is poorly cleared with decreased kidney function [121].

There is evidence that copper may have a role in the reduction of oxidative stress. While there are reports of both elevated and depressed copper levels in pediatric dialysis patients, no clear recommendations for supplementation exist [113, 119, 120, 122]. Low copper levels, which can be a manifestation of increased zinc exposure, can result in ESA-resistant anemia. In turn, periodic evaluation of the zinc status [122] is suggested given zinc's important role in many body functions including growth, immune function, and taste and smell. Zinc is commonly reported to be below normal ranges in children receiving dialysis [56, 113, 119, 120, 122]; yet children on dialysis receiving standard supplementation were found to have varying serum levels [108]. Selenium levels are commonly low in the pediatric dialysis patients [113, 119, 120, 122, 123]. Accurate body selenium levels are more difficult to assess than zinc values [121]. Variable levels for these minerals reported within the same study indicate the importance of individualization of micronutrient prescription.

Iron status is affected by decreasing kidney function, abnormal hepcidin level, and varying intake/tolerance of iron supplementation. Iron status has a significant impact on anemia management, as discussed in Chap. 32.

Fluid Management

Fluid control is pivotal in the management of children receiving dialysis to reduce complications such as hypertension and left ventricular hypertrophy that are associated with long-term cardiovascular risk. Daily fluid requirements depend on the primary disease, corresponding urine output and the amount of fluid removed during dialysis [124]. Patients with little or no urine output, or who achieve minimal fluid removal through dialysis, will require fluid restrictions. Careful attention to sodium intake is essential as it greatly impacts thirst and fluid intake and ultimately the ability for patients to successfully manage daily fluid restrictions [125].

Infants and children with polyuria require supplemental fluid intake over and above the usual intake goals, while restriction of fluid is indicated when patients become oliguric or anuric. Both high and low fluid goals make meeting nutritional requirements more challenging [5]. Patients with high fluid needs often forgo calories in favor of drinking large volumes of water in an attempt to normalize serum sodium levels. Although rare in the setting of chronic dialysis, some patients who require additional fluid are unable to achieve daily fluid requirements.

Age-Based Considerations

Infants and Young Children

Children under the age of 5 years are most at risk for inadequate weight gain and growth and spontaneously consume less than their required energy needs [3, 126, 127]. Anorexia and vomiting are common features of infants with CKD. Changes to taste perception can also occur early on in CKD and tend to worsen as renal function decreases. Increased circulating cytokines that impact appetite and satiety result in reduced oral intake [128]. The need for multiple and distasteful medications along with increased fluid requirements can cause oral aversions. While young children have poor growth at the initiation of dialysis, they are most likely to have improved growth with adequate nutrition. This may be due to the fact that the youngest children are the most likely to receive supplemental formula feedings, often via a tube, to achieve total intake [129]. Children who graduate to an "all-oral" diet may consume foods that are high in calories, sugar,

and fat. CKiD data indicates that children who receive 500 or more calories from oral intake daily have calorie-dense diets which may include "empty calorie" items such as fast food, snacks foods and sugary foods, and beverages [16]; however, this may not be the case in regions of the world not consuming a "western" diet [130]. Children with CKD also commonly suffer from severe reflux [131], delayed gastric emptying, uremia, and other issues that decrease appetite [126, 127], and this may have a more pronounced effect in the youngest children who, in the absence of foods with a high savory value, may consume inadequate nutrition.

Enteral and Oral Formula or Breast Milk Feeding

There is currently no one commercially available formula that will "fit all" needs. Enteral product selection and prescriptions should be tailored for positive long-term growth goals. Feed prescriptions vary widely and change often, requiring dietitians to manipulate complex nutrient profiles.

Breast milk is the optimal choice for feeding most infants. Human breast milk provides ideal nutrition, is associated with a low incidence of diarrhea, lowers infection rates, improves immunity, and has been felt to be a contributing factor to a lower risk of obesity in some populations [132]. Breast milk's bioavailability allows for ideal protein and nutrient intake, and its whey content is easily digestible making it a good choice for babies with kidney disease who are prone to delayed gastric emptying [133]. Whenever expressed breast milk (EBM) is available, it should ideally be used as a component of the feed, and avoiding EBM waste should be prioritized [94]. When breast milk is not available or no longer satisfies the nutrition needs of an infant with kidney disease, commercially available formula preparations should be considered, either as supplementation to breast milk or as the primary source of nutrition. While feeding orally is ideal, the majority of infants receiving dialysis will need enteral feeding support [5]. Tube feedings provide an average of 61% of total caloric needs in children with gastrostomies, suggesting the need for nutrition support via supplemental feeding in this population [134]. Furthermore, up to a third of feedings may be lost due to emesis, increasing the need for ongoing surveillance and diet adjustment [135].

Once oral intake is evaluated for adequacy, enteral supplementation can be tailored to meet the total nutritional requirements. Prescribing feeds to achieve biochemical stability is a priority as electrolyte derangements can have serious and sometimes deadly outcomes [5]. Individualizing potassium content is required for children on dialysis who have inappropriate sodium and potassium ion exchange due to renal tubular disorders. Phosphorus restrictions are not commonly needed for the infant or younger child, and most infant formulas are not high in phosphorus. The use of a low-phosphorus product may actually necessitate supplementation. In contrast, as oral intake increases, phosphorus restriction may be indicated.

Managing fluid volume is important in enteral feeding. Abdominal fullness resulting from indwelling dialysate in the PD patient may make it challenging for the patient with polyuria to meet the increased fluid needs. Increased intra-abdominal pressure with PD treatments can also lead to suboptimal formula/food intake. For the patient whose fluids are restricted, feeds can be concentrated in a step-wise fashion with the goal of establishing feed tolerance and optimizing intake while minimizing the symptoms of poor gastric emptying, frequent emesis, and/or vomiting that may result from feeds with increased osmolarity. Additional calories can be added via powdered low electrolyte and mineral modular products. Protein modules can be titrated to individual protein needs. While some renal-specific or nutrient-modified formulas are incomplete and therefore cannot be used as a sole source of nutrition, these formulas can be combined with other standard formulas to meet nutrient needs and to control potassium and phosphorus intakes. Total osmolarity must be kept in mind in terms of renal solute load and tolerance.

Other approaches to control electrolyte and mineral intakes from commercial pediatric formula include pre-treatment of formula with

exchange resins and the use of adult renal formulations. Adult renal formulations are energy dense (1.8 or 2.0 kcal/ml) and have reduced electrolyte and mineral contents [136]. While both these approaches achieve reduction of potassium, the resulting mineral and electrolyte profiles are altered, requiring close monitoring of biochemical indices and vitamin and mineral intakes [94, 95, 136, 137]. Additionally, adult renal preparations are casein-based formulas and may be less well tolerated than whey-based alternates. As the number of formula components and preparation steps increases, so does the chance for errors in preparation [138]. An increasing number of parents and caregivers are expressing a desire to feed their children with "more real food" and home-prepared blenderized tube feeds (BTF). BTF may be better tolerated than commercial formulas resulting in less reflux and constipation and an improved gut microbiome. Successful use of BTF in medically complex children requires significant parental commitment and education regarding preparation techniques, food safety principles, and management of infection risk [139]. The clinician must balance the most important priorities and specific needs in the formula choice [140].

Transition to Oral Feeding

Children with CKD often experience delays in normal childhood development which may be evident in their progression with oral feeding. Introduction of solids at age-appropriate times (e.g., 6 months for term infants) is recommended; however, the child with CKD may struggle with this goal [141, 142]. Many young children with CKD cannot take any feeds orally. Some may struggle with solids when coarser textures are introduced. It is in turn common for toddlers who are well past 1 year of age to need supplemental tube feeding. When a child has consistently demonstrated failure with oral feeding or advancement of solids, it is appropriate to refer the child for therapy. A behavioral psychologist trained in feeding therapy along with a speech language pathologist or an occupational therapist can provide strategies for improving feeding skills [141, 142]. Caregivers may be easily discouraged by the challenges presented when feeding the child with CKD and may benefit from professional support. Progression to age-appropriate feeding, especially post-transplant, is more rapid when the child has had exposure to normal feeding practices at developmentally appropriate times. The use of gastrostomy tubes for feeding is associated with better oral outcomes compared to nasogastric feedings in which a feeding tube may irritate the throat or nose and create negative associations with things near or in the mouth [142–144]. A team approach to managing gastroesophageal reflux, delayed gastric emptying, or other gastrointestinal comorbidities with medication and feeding adjustments helps remove barriers and improves the likelihood of oral feeding advancement. It is important to determine which feeding plan may be most effective for the individual patient. Nocturnal, continuous feeds allow hunger to develop during the day, while daytime bolus feeds emulate physiological feeding patterns. In practice, a combination of daytime and nocturnal feeding may best meet the patient's needs [5, 141, 142].

Reducing stress around mealtimes and feeding in a relaxed environment may promote improved intake. Allowing children to self-feed or dipping a pacifier in texture-appropriate foods may also help some children develop their feeding skills. Promoting nonnutritive oral stimulation can provide a positive oral experience for the child with delayed oral intake. If structural issues are suspected, immediate referral for evaluation prior to any further feeding therapy is recommended [141].

Childhood

Children of school age attend school to continue their social, emotional, and cognitive development. Children with chronic illnesses may face challenges that negatively affect their school experience. Those children with CKD are recorded to have some of the highest rates of absenteeism [145].

Entering school coincides with a stage during which children are developing "eating compe-

tency" which is defined as "being positive, comfortable, and flexible with eating, as well as matter-of-fact and reliable about getting enough to eat of enjoyable and nourishing food" [146]. Dependence on supportive gastrostomy feedings and altered taste perceptions, together with diet and fluid restrictions, prevents children from gaining independence and eating competency in the same way that their healthy peers do. Members of the healthcare team (e.g., dietitian, social worker, psychologist) can support the child with special feeding needs by collaborating closely with schools to develop and provide consistent supportive strategies [145].

Adolescents and Young Adults

The adolescent poses unique challenges for the clinician. Energy needs may decline once the pubertal growth spurt occurs and growth is completed. Emerging independence and psychosocial challenges are major considerations for this population.

Adolescence is a time of growth driven primarily by the sex hormones, as opposed to nutrition as seen in early childhood. High calorie needs, especially in teen males or athletes, increase the risk of inadequate calorie intake or protein energy wasting (PEW) [147]. Puberty is often delayed in children with CKD, and linear growth may be delayed compared to healthy children [148]. Adequate nutrition is essential for achieving full height potential [148].

Overweight and obesity are prevalent in children and adolescents with CKD [149]. Those consuming an oral diet, especially one high in processed and fast foods, are likely to take in excess calories, fat, and sugar [92]. Tube feeding and enteral supplements are not commonly used in adolescents. When the growth spurt ends and needs are decreased, teens may not transition from the high-energy diet to which they are accustomed resulting in unwanted weight gain from excess calories. The latter is especially prevalent in females for whom this growth ends sooner [3, 148].

The social dynamics of adolescents are also an important consideration. Teenagers, more than children in any other age group, prefer to spend time with peers in social situations involving food. More school and social activities are enjoyed away from home, increasing the possibility of nonideal food consumption [150]. To complicate matters, children with CKD have, on average, lower IQs than healthy peers and demonstrate poorer executive functioning and higher impulsivity. Decision-making skills, including those regarding health, are often impaired [151]. Even in healthy individuals, development of the brain's frontal lobe, the center that controls cognitive skills like problem-solving and judgment, is not complete until approximately 25 years of age. This has important implications and may lead to increased risks as a result of poor decision-making in this population [152]. Nonetheless, adolescents often resent juvenilization and will reject patronizing discussions pertaining to medical or nutritional needs. The healthcare professional must find new ways to first present and then reinforce information frequently to optimize learning while at the same time maintaining the independence and individuality of the teenage patient.

Nutrition Considerations for Preparation of Transfer to Adult-Focused Facilities

The newly transferred young adult may feel as though they have limited support after moving from the pediatric unit where high clinician-to-patient ratios are common. In view of this, the pediatric dialysis team has an obligation to appropriately prepare the pediatric patient for the transition and transfer process [153]. Acquiring and demonstrating nutrition knowledge and skills is an integral aspect of the transition process. Patients must understand how dietary intake affects health and health risks. Some of the many skills that patients need for successful transfer are understanding the importance of nutrition-related medications, such as phosphorus binders and vitamin supplements; having the ability to manage and track intake of fluids and other nutrients such as sodium, phosphorus, and potassium;

Table 26.8 Nutritional challenges and priorities by age group

Infants and young children	School-aged children	Adolescents and young adults
Adequate intake and growth	Picky eating	Increasing independence
Establishing healthy eating behaviors	Establishing healthy eating behaviors	Maintaining healthy eating behaviors
Gastrointestinal issues (reflux, delayed gastric emptying)	Early participation in self-care	Prioritization of social needs over healthcare needs
Special nutrition needs associated with prematurity and catch-up growth	School issues including school lunch	Developmental disabilities affecting ability to provide self-care
Weaning from breast milk, tolerating formulas, and enteral feeds	Promoting oral diet	Multiple approaches for nutrition education
Progression of oral diet and physiologic skill development	Balancing oral intake with dependence on supplemental tube feeding	Transition to adult care
Parental barriers (multiple caregivers, complex feeding plans)		
Polyuria, salt wasting, potassium retention		

References [3, 16, 61, 93, 124–153]

and being able to demonstrate appropriate food choices, decision-making in meal planning, restaurant choices, and navigating meals with friends. Skill demonstration may involve food preparation, verbalizing plans for obtaining and scheduling nutrition-related medications, and menu planning [153–155] (Table 26.8).

Special Considerations

Prematurity

ESKD in the NICU remains relatively rare [156]. However, renal conditions diagnosed in utero or in the NICU often progress quickly to ESKD. Renal-specific diet principles need to be layered upon the fundamental nutrition needs of prematurity when the premature infant receives chronic dialysis [156, 157].

In general, nutrient needs are higher for premature compared to term infants and nutrition goals focused on providing nutrients in quantities that meet the needs based on the infant's gestational age. The use of concentrated feeds and fluid restrictions may be required to address respiratory needs; semi-elemental and elemental formulas along with TPN may be prescribed to address higher caloric and protein needs when gut injury occurs. Calcium and phosphorus content of standard infant formulas may not meet the needs of the premature infant, and low serum phosphorus and high alkaline phosphatase levels can be associated with the development of osteopenia [156].

Nutrition care of the newborn with ESKD should address sodium and fluid levels, as well as BUN [158]. Term and premature infants undergo a 10–20% loss of extracellular fluid immediately after birth, which is accompanied by sodium loss. In premature infants, sodium losses may be greater and more prolonged. With renal failure, sodium supplementation needs may be higher, especially if the renal tubules are affected. Maintenance fluids are approximately 100 ml/kg/day, with additional requirements as caloric intake increases. Fluid restriction, necessitating concentration of formula and TPN, is indicated for infants who are oliguric or anuric (60–80 ml/kg/day), while fluid needs may be increased for the infant with polyuria (up to 200 ml/kg/day). In case of hyponatremia, fluid restriction or sodium supplementation is indicated and can be achieved through TPN alterations or supplemental sodium chloride added to formula. Hyperkalemia is common and its content in formula or TPN should be adjusted.

Interpretation of BUN levels should consider hydration status, amino acid oxidation, renal function, energy intake, and degree of illness [158]. In the absence of adequate guidelines for the needs of the preterm infant with CKD, the nutrition plan should provide adequate protein for age and degree of renal function, with careful monitoring of intake [159].

Accommodation must be made for the physiologic higher serum phosphorus range in infants. However, if hyperphosphatemia occurs and persists, the use of lower phosphorus formula or breast milk may be indicated. Liquid calcium carbonate can also be added to formula to bind phosphorus. If serum phosphorus levels decrease when dialysis is initiated, a reduction of calcium carbonate as a binder or the addition of supplemental phosphorus may be required [156].

Protein Energy Wasting/Uremic Failure to Thrive

PEW is defined by the International Society of Renal Nutrition and Metabolism (ISRNM) as "the loss of body protein mass and fuel reserves". The diagnosis of PEW in adults requires the presence of three criteria: reduced muscle mass, reduced body mass with reduced intake, and depressed albumin, transthyretin, or cholesterol. PEW is also highly associated with inflammation [160]. PEW in pediatrics, also termed uremic failure to thrive, alludes to the complexity that growth adds to underlying malnutrition in this population [161]. The link between inflammation and malnutrition has not been well defined in the pediatric population [162].

The only pediatric data on PEW comes from the pediatric CKD population [163]. Using a modified definition, which included poor linear growth, 7–20% of children with CKD exhibited PEW. As CKD progresses to dialysis, appetite decreases, weight loss is common, and uremia increases; it is in turn likely that PEW is more common in the dialysis population than in children with CKD [164, 165]. PEW creates a hormonal milieu in which the body is unable to utilize adipose stores and instead breaks down lean mass [166]. Mak [166] notes that relative obesity may result from an overly aggressive nutrition plan that ultimately does not reverse the abnormalities in body composition. Even when they are not meeting the true definition of PEW, children who are overweight or obese may present with a PEW-like picture [166].

The greater the number of diagnostic criteria for PEW met, the greater is the risk of malnutrition. Two of the three biochemical markers used to identify PEW in adults, reduced transthyretin and cholesterol levels, have not be seen in pediatric CKD [163]. It is unknown if children on dialysis have altered levels of the biochemical markers associated with PEW. In addition to adult biochemical values, an elevated CRP is included in pediatric diagnostic criteria. Reduced body mass is defined as <5th%ile for height age or a decrease in BMI of greater than 10%. Reduced muscle mass is defined as a MUAC for height age < 5th%ile or a decrease in MUAC of greater than 10%. Reporting of a "fair," "poor," or "very poor" appetite is used as a surrogate for reduced intake. An important additional measure for PEW in children is that of growth, defined as a stature of <3rd%ile height for age or a decrease in growth velocity of more than 10%.

Treatment of PEW requires provision of adequate, but not excessive, calories to avoid excess fat deposition while sparing protein [166].

Overweight and Obesity

In recent years, the focus of nutritional assessment and intervention in pediatric renal patients has expanded to address the growing concern of overweight and obesity. The recent International Pediatric Peritoneal Dialysis Network (IPPN) data demonstrates both underweight and obesity as worldwide problems. The identification of children as underweight when starting chronic PD is more prevalent in South and Southeast Asia, Central Europe, and Turkey, while the highest rates of overweight and obesity are present in the Middle East (40%) and the United States (33%). Overall, the prevalence of underweight in the IPPN data was 8.9% and overweight and obesity 19.7%. Higher gross national income was associated with an increased likelihood of overweight and obesity [167]. Abnormal BMIs encompassing either problem are more common in children starting PD than in healthy populations.

Obesity and dyslipidemia are common and modifiable factors that contribute to the complex picture of cardiovascular risk in CKD and ESKD. Wong [25] demonstrated that there is a

U-shaped association between BMI and risk of death in the pediatric dialysis population. Obese ESKD patients are less likely to receive a kidney transplant, with a lower odds of receiving a living donor transplant [165].

The causes of overweight and obesity in the dialysis population are multifactorial. Pediatric renal dietitians routinely recommend supplementation to optimize caloric intake in the young child. Some have suggested obesity may be perceived as more acceptable by family and providers, since poor appetite and growth failure are common concerns in children with CKD [165]. Approximately 92% of younger children aged 2–3 years, and 57–59% of those 9–13 years, in the CKiD cohort had reported intakes in excess of the KDOQI recommendations [87]. The authors estimated that a 50% decrease in the intake of several commonly consumed empty-calorie foods would realize an 11% reduction in energy consumption and may assist these patients in avoiding obesity.

Pediatric dialysis patients are also known to engage in less physical activity, spending as little as 10% of nonschool hours participating in physical exercise and greater than 1000 hours per year in sedentary activity related to dialysis treatments [168, 169]. According to a report from CKiD, only 13% of study participants met the recommended goal of 1 hour of daily physical activity, while 98% exceeded the maximum recommended entertainment screen time of 2 hours per day [170]. Previously discussed diet interventions (fewer simple carbohydrates and less saturated fats), careful and close monitoring and weaning of supplemental tube feedings, together with more effective promotion of physical activity and reduced screen time, are just a few of the strategies designed to mitigate this problem.

Parenteral Nutrition/IDPN

Many children with ESKD are challenged with adherence to a prescribed oral diet and oral supplementation [171]. Meeting the unique nutritional requirements of these children often requires nutritional supplementation via the enteral or parenteral route. Intradialytic parenteral nutrition (IDPN) may be considered as an adjunct therapy to provide the additional protein and energy required to prevent or reverse malnutrition in children undergoing HD who have additional nutritional needs [16].

Parenteral nutrition (PN) may include protein, carbohydrate, fat, minerals and electrolytes, vitamins, and other trace elements. PN is utilized to achieve and maintain an optimal nutrition status of patients who cannot eat or absorb adequate nutrition by mouth or through tube feeding. Whereas standard PN is used infrequently in maintenance dialysis, intradialytic parenteral nutrition (IDPN) is a noninvasive method of providing nutrition to malnourished patients via the HD access during the HD treatment. IDPN provides additional protein and energy to prevent or reverse malnutrition and is accomplished through the provision of fluid volumes that can be removed with ultrafiltration during HD.

Improvement in nutritional status may require 6 weeks to 6 months of IDPN therapy, the goal of which is continued weight maintenance and/or growth once therapy is discontinued. Frequent monitoring of patients receiving IDPN should incorporate biochemical reviews routinely used for patients receiving PN and for those at risk for refeeding syndrome [172].

A recent study examined the use of intralipid (IL) alone as an adjunct therapy to other forms of nutritional supplementation during hemodialysis sessions [16]. The authors explored if IL therapy would spare protein degradation and promote positive nitrogen balance. When used in combination with other forms of nutrition support, the provision of IL was found to be well tolerated, relatively inexpensive, and associated with a positive effect on the nutritional status of pediatric HD patients. However, additional research is needed before IL can be recommended as a standard approach to nutritional rehabilitation.

Nutrition Counseling Strategies

The KDOQI guidelines [5] recommend that nutritional counseling, based on an individualized assessment and plan of care, be considered for all children with CKD and on dialysis.

Intensive counseling should occur at the time of initial presentation and throughout the course of management. Dietary counseling should be positive, with a focus on dietary allowances rather than restrictions. A diet that incorporates personal preferences, cultural and ethnic foods, and provides a degree of pleasure may improve long-term adherence. It is important that dietary intervention takes into account the educational level of both the child and the primary caregivers. Written materials should also be presented in the patient's preferred language of communication and developed at a grade level that can be easily understood. A recent report from the CKiD cohort indicated that 33% of subjects demonstrated low academic achievement, primarily in the mathematics domain [173]. Clinicians' interactions with patients about their medical management routinely include mathematical concepts, a number of portions and amount of feed, volumes of fluid, lab test results, and number of pills to take. It is unclear if and how a low academic ability in mathematics might impact a child's understanding and accommodation of nutrition recommendations.

During patient education sessions, the teach-back method puts the onus of effective communication on the educator rather than the patient. The practitioner provides information to the patient and then asks the patient to repeat the information in their own words to ascertain whether communication was clear and the patient has the knowledge required to make the desired changes. This method of communication [174] may be particularly useful in situations in which a task is being described (e.g., how to prepare a specific renal formula for an infant's oral or tube feeding plan).

During motivational interviewing, which is designed to provide patient ownership of their care, the dietitian works with the patient and/or caregivers in a client-centered style. The goal of motivational interviewing is to help the patient explore and resolve ambivalence to change and elicit behavior change in a manner that shifts the responsibility for identifying solutions from the clinician to the patient [175].

Most importantly, the task of the pediatric renal dietitian is to provide nutritional education or counseling in a style that takes into account each child and family's learning style, level of health literacy, and specific nutrition needs.

Nutrition Considerations in Preparation for Transplant

Patients and their families may mistakenly see transplant as the end of all diet limitations. In reality, healthful nutrition and lifestyle choices aid with allograft longevity and prevention of chronic disease [5, 176].

Nutrition education may focus on the importance of adequate fluid intake for kidney perfusion [5, 176], limitation of sodium (80% of transplant recipients experience hypertension in the first year post transplant) [4], as well as the importance of adequate calcium and vitamin D for bone health [5]. The medication-related side effects of dyslipidemia, hyperglycemia, and hyperkalemia which are commonly observed especially when medication doses are highest [177] can be addressed through nutrition interventions. Excess weight gain is common post-transplant, and pre-transplant nutrition education should include plans for mitigation of this potential outcome [45]. Transplant recipients are more susceptible to foodborne illness and also have lengthier hospitalizations, risk of allograft loss, and increased risk of mortality [178]. Therefore, preparing families for the more stringent food safety requirements during meal preparation is necessary for immunosuppressed patients. Early introduction to and regular review of post-transplant nutrition goals will better prepare the patient and reduce the chances of false expectations regarding post-transplant dietary management.

Summary

Frequent assessment of the pediatric dialysis patient informs accurate and effective nutrition prescription. Each age group under the pediatric umbrella has unique needs. Furthermore, the specific dialysis modality the child is receiving will impact the nutrition prescription. Along with the

fundamentals of nutrition, the skilled dietitian will bring a keen understanding of the various medical and psychosocial factors that impact the achievement of optimal nutrition care. In short, nutrition care of the pediatric dialysis patient is a unique specialty and a complex craft that must be tailored to the individual patient.

References

1. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702.
2. Ku E, Kopple JD, Mcculloch CE, Warady BA, Furth SL, Mak RH, et al. Associations between weight loss, kidney function decline, and risk of ESRD in the chronic kidney disease in children (CKiD) cohort study. Am J Kidney Dis. 2018;71(5):648–56.
3. Rodig NM, Mcdermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, et al. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. Pediatr Nephrol. 2014;29(10):1987–95.
4. North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) 2011 annual dialysis report (2011) Emmes [online]. https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf.
5. National Kidney Foundation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53(3)
6. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. Pediatr Nephrol. 2012;28(4):527–36.
7. Chua AN, Warady BA. Care of the Pediatric Patient on chronic Dialysis. Adv Chronic Kidney Dis. 2017;24(6):388–97.
8. Kaur A, Davenport A. Hemodialysis for infants, children, and adolescents. Hemodial Int. 2014;18(3):573–82.
9. Fischbach M, Edefonti A, Schröder C, Watson A. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.
10. Silverstein DM. Frequent hemodialysis: history of the modality and assessment of outcomes. Pediatr Nephrol. 2017;32(8):1293–300.
11. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14(3):297–303.
12. Geary DF, Piva E, Tyrrell J, Gajaria M, Picone G, Keating L, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147(3):383–7.
13. Hothi DK, Harvey E, Piva E, Keating L, Secker D, Geary DF. Calcium and phosphate balance in adolescents on home nocturnal haemodialysis. Pediatr Nephrol. 2006;21(6):835–41.
14. Thumfart J, Hilliger T, Stiny C, Wagner S, Querfeld U, Müller D. Is peritoneal dialysis still an equal option? Results of the Berlin pediatric nocturnal dialysis program. Pediatr Nephrol. 2015;30(7):1181–7.
15. Goldstein SL, Silverstein DM, Leung JC, Feig DI, Soletsky B, Knight C, et al. Frequent hemodialysis with NxStage™ system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2007;23(1):129–35.
16. Chen W, Ducharme-Smith K, Davis L, Hui WF, Warady BA, Furth SL, et al. Dietary sources of energy and nutrient intake among children and adolescents with chronic kidney disease. Pediatr Nephrol. 2017;32(7):1233–41.
17. Quan A, Baum M. Protein losses in children on continuous cycler peritoneal dialysis. Pediatr Nephrol. 1996;10(6):728–31.
18. Kim H-W, Chang JH, Park SY, Moon SJ, Kim DK, Lee JE, et al. Factors associated with hypokalemia in continuous ambulatory peritoneal Dialysis patients. Electrolyte Blood Press. 2007;5(2):102.
19. Factor KF. Potassium management in pediatric peritoneal dialysis patients: can a diet with increased potassium maintain a normal serum potassium without a potassium supplement? Adv Perit Dial. 2007;23:167–9.
20. Li Y, Greenbaum LA, Warady BA, Furth SL, Ng DK. Short stature in advanced pediatric CKD is associated with faster time to reduced kidney function after transplant. Pediatr Nephrol. 2019; https://doi.org/10.1007/s00467-018-4165-2. [epub ahead of print]
21. Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherrard DJ, et al. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis. 2000;36(4):811–9.
22. Goldstein SL, Gerson AC, Furth S. Health-related quality of life for children with chronic kidney disease. Adv Chron Kid Dis. 2007;14(4):364–9.
23. Rosenkranz J, Reichwald-Klugger E, Oh J, Turzer M, Mehls O, Schaefer F. Psychosocial rehabilitation and satisfaction with life in adults with childhood-onset of end-stage renal disease. Pediatr Nephrol. 2005;20(9):1288–94.
24. Bertram JF, Goldstein SL, Pape L, Schaefer F, Shroff RC, Warady BA. Kidney disease in children: latest advances and remaining challenges. Nat Rev Nephrol. 2016;12(3):182–91.
25. Abubakar A, Van de Vijver F, Van Baar A, Mbonani L, Kalu R, Newton C, Holding P. Socioeconomic status, anthropometric status, and psychomotor development of Kenyan children from resource-limited settings: a path-analytic study. Early Hum Dev. 2008;84(9):613–21.
26. Gurzkowska B, Kułaga Z, Litwin M, Grajda A, Świąder A, Kułaga K, et al. The relationship between selected socioeconomic factors and basic anthropometric parameters of school-aged children and adolescents in Poland. Eur J Pediatr. 2013;173(1):45–52.
27. Harambat J, Cochat P. Growth after renal transplantation. Pediatr Nephrol. 2008;24(7):1297–306.

28. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. Pediatr Nephrol. 2006;21(7):917–30.
29. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2009;25(3):867–73.
30. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7.
31. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR. Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol. 2000;15(3–4):259–65.
32. Salas P, Pinto V, Rodriguez J, Zambrano MJ, Mericq V. Growth retardation in children with kidney disease. Int J Endocrinol. 2013;2013:1–8.
33. Coleman JE, Norman LJ, Watson AR. Provision of dietetic care in children on chronic peritoneal dialysis. J Ren Nutr. 1999;9(3):145–8.
34. Gunal AI. How to determine 'dry weight'? Kidney Int Suppl. 2013;3(4):377–9.
35. Candan C, Sever L, Civilibal M, Caliskan S, Arisoy N. Blood volume monitoring to adjust dry weight in hypertensive pediatric hemodialysis patients. Pediatr Nephrol. 2008;24(3):581–7.
36. Michael M, Brewer ED, Goldstein SL. Blood volume monitoring to achieve target weight in pediatric hemodialysis patients. Pediatr Nephrol. 2004;19(4):432–7.
37. The WHO Child Growth Standards [Internet]. World Health Organization. World Health Organization; 2016 [cited 2018 Oct 23]. Available from: https://www.who.int/childgrowth/standards/en/.
38. Beer SS, Bunting KD, Canada N, Rich S, Spoede E, Turybury K, editors. Texas Children's Hospital pediatric nutrition reference guide 2016, 11th ed. Texas Children's Hospital Nutrition Committee.
39. World Health Organization, Department of Nutrition for Health and Development 2008 WHO Anthropometry Training Module. http://www.who.int/childgrowth/training/module_b_measuring_growth.pdf. Accessed October 21, 2018.
40. Forman MR, Zhu Y, Hernandez LM, Himes JH, Dong Y, Danish RK, et al. Arm span and ulnar length are reliable and accurate estimates of recumbent length and height in a multiethnic population of infants and children under 6 years of age. J Nutr. 2014;144(9):1480–7.
41. Haapala H, Peterson MD, Daunter A, Hurvitz EA. Agreement between actual height and estimated height using segmental limb lengths for individuals with cerebral palsy. Am J Phys Rehab. 2015;94(7):539–46.
42. Tanner JM, Goldstein H, Whitehouse RH. Standards for Childrens height at ages 2-9 years allowing for height of parents. Arch Dis Child. 1970;45(244):755–62.
43. Gao T, Leonard MB, Zemel B, Kalkwarf HJ, Foster BJ. Interpretation of body mass index in children with CKD. Clin J Am Soc Nephrol. 2012;7(4):558–64.
44. Rashid R, Neill E, Smith W, King D, Beattie TJ, Murphy A, et al. Body composition and nutritional intake in children with chronic kidney disease. Pediatr Nephrol. 2006;21(11):1730–8.
45. Foster BJ, Kalkwarf HJ, Shults J, Zemel BS, Wetzsteon RJ, Thayu M, et al. Association of Chronic Kidney Disease with muscle deficits in children. J Am Soc Nephrol. 2010;22(2):377–86.
46. Garcia De Alba Verduzco J, Fabiola Hurtado Lopez E, Ponton Vazquez C, de la Torre Serrano A, Romero Velarde E, Manuel Vasquez Garibay E. Factors associated with anthropometric indicators of nutritional status in children with chronic kidney disease undergoing peritoneal dialysis, hemodialysis, and after kidney transplant. J Ren Nutr. 2018;28(5):352–8.
47. Sgambat K, Roem J, Mitsnefes M, Portale AA, Furth S, Warady B, et al. Waist-to-height ratio, body mass index, and cardiovascular risk profile in children with chronic kidney disease. Pediatr Nephrol. 2018;33(9):1577–83.
48. Butler MG, Lee J, Manzardo AM, Gold J-A, Miller JL, Kimonis V, et al. Growth charts for non-growth hormone treated Prader-Willi Syndrome. Pediatrics. 2014;135(1)
49. Zemel BS, Pipan M, Stallings VA, Hall W, Schadt K, Freedman DS, et al. Growth charts for children with Down Syndrome in the United States. Pediatrics. 2015;136(5)
50. Royal College of Paediatrics and Child Health (2009) Plotting Preterm Infants, https://www.rcpch.ac.uk/sites/default/files/Plotting_preterm_infants.pdf accessed on December 15, 2018.
51. Coleman JE, Edefonti A, Watson AR 2003 Pediatric ISPD guidelines: assessment of growth and nutritional status in children on chronic peritoneal dialysis. https://www.ispd.org/media/pdf/hoca.pdf. Accessed July 31, 2018.
52. Mastrangelo A, Paglialonga F, Edefonti A. Assessment of nutritional status in children with chronic kidney disease and on dialysis. Pediatr Nephrol. 2013;29(8):1349–58.
53. Eng CSY, Bhowruth D, Mayes M, Stronach L, Blaauw M, Barber A, et al. Assessing the hydration status of children with chronic kidney disease and on dialysis: a comparison of techniques. Nephrol Dial Transplant. 2017;33(5):847–55.
54. Addo OY, Himes JH, Zemel BS. Reference ranges for midupper arm circumference, upper arm muscle area, and upper arm fat area in US children and adolescents aged 1–20 y. Am J Clin Nutr. 2016;105(1):111–20.
55. Modi P, Nasrin S, Hawes M, Glavis-Bloom J, Alam NH, Hossain MI, et al. Midupper arm circumference outperforms weight-based measures of nutritional status in children with diarrhea. J Nutr. 2015;145(7):1582–7.
56. Pontón-Vázquez C, Vásquez-Garibay EM, Hurtado-López EF, Serrano ADLT, García GP, Romero-Velarde E. Dietary intake, nutritional status, and body composition in children with end-stage kidney disease on hemodialysis or peritoneal Dialysis. J Ren Nutr. 2017;27(3):207–15.

57. Apostolou A, Printza N, Karagiozoglou-Lampoudi T, Dotis J, Papachristou F. Nutrition assessment of children with advanced stages of chronic kidney disease – a single center study. Hippokratia. 2014;18(3):212–6.
58. Canpolat N, Caliskan S, Sever L, Tasdemir M, Ekmekci OB, Pehlivan G, et al. Malnutrition and its association with inflammation and vascular disease in children on maintenance dialysis. Pediatr Nephrol. 2013;28(11):2149–56.
59. Vega MW, Srivaths PR. Air displacement plethysmography versus bioelectrical impedance to determine body composition in pediatric hemodialysis patients. J Ren Nutr. 2017;27(6):439–44.
60. Secker DJ, Jeejeebhoy KN. Subjective global nutritional assessment for children. Am Clin Nutr. 2007;85(4):1083–9.
61. Steiber A, Leon JB, Secker D, Mccarthy M, Mccann L, Serra M, et al. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. J Ren Nutr. 2007;17(5):336–42.
62. Yang J, Lynch KF, Uusitalo UM, Foterek K, Hummel S, Silvis K, et al. Factors associated with longitudinal food record compliance in a paediatric cohort study. Public Health Nutr. 2015;19(05):804–13.
63. Mcpherson R, Hoelscher DM, Alexander M, Scanlon KS, Serdula MK. Dietary assessment methods among school-aged children: validity and reliability. Prev Med. 2000;31(2)
64. Martin CK, Nicklas T, Gunturk B, Correa JB, Allen HR, Champagne C. Measuring food intake with digital photography. J Hum Nutr Diet. 2013;27:72–81.
65. Collins CE, Watson J, Burrows T. Measuring dietary intake in children and adolescents in the context of overweight and obesity. Int J Obes. 2009;34(7):1103–15.
66. Berkowitz SA, Fabreau GE. Food insecurity: what is the Clinician's role? CMAJ. 2015;187(14):1031–2.
67. Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. Pediatrics. 2010;126(1):e26–32.
68. Steiber AL, Kalantar-Zadeh K, Secker D, Mccarthy M, Sehgal A, Mccann L. Subjective global assessment in chronic kidney disease: a review. J Ren Nutr. 2004;14(4):191–200.
69. Secker DJ, Jeejeebhoy KN. How to perform subjective global nutritional assessment in children. J Acad Nutr Diet. 2012;112(3)
70. Secker D, Cornelius V, Teh JC. Validation of subjective global (nutritional) assessment (SGNA) in children with CKD. J Ren Nutr. 2011;21(2):207.
71. Corkins KG. Nutrition-focused physical examination in pediatric patients. Nutr Clin Pract. 2015;30(2):203–9.
72. Corkins KG, Teague EE. Pediatric nutrition assessment. Nutr Clin Pract. 2016;32(1):40–51.
73. Esper DH. Utilization of nutrition-focused physical assessment in identifying micronutrient deficiencies. Nutr Clin Pract. 2015;30(2):194–202.
74. Institute of Medicine (IOM) [Internet]. Institute for Healthcare Improvement. [cited 2019 Feb 6]. Available from: http://www.ihi.org/resources/Pages/OtherWebsites/InstituteofMedicine.aspx.
75. Battelino N, Rus R, Novljan G. Nutritional requirements in children with chronic kidney disease. Clin Nutr ESPEN. 2016;14:44–6.
76. Aquino TMD, Avesani CM, Brasileiro RS, Carvalhaes JTDA. Resting energy expenditure of children and adolescents undergoing hemodialysis. J Ren Nutr. 2008;18(3):312–9.
77. Anderson CE, Gilbert RD, Elia M. Basal metabolic rate in children with chronic kidney disease and healthy control children. Pediatr Nephrol. 2015;30(11):1995–2001.
78. Health Canada. Dietary Reference Intakes Tables [Internet]. Canada.ca. Innovation, Science and Economic Development Canada; 2006 [cited 2019 Feb 6]. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html.
79. Chaturvedi S, Jones C. Protein restriction for children with chronic kidney disease. Coch Data Sys Rev. 2007;Chaturvedi 2007.
80. Salame C, Eaton S, Grimble G, Davenport A. Protein losses and urea nitrogen underestimate total nitrogen losses in peritoneal dialysis and hemodialysis patients. J Ren Nutr. 2018;28(5):317–23.
81. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:257–64.
82. Tuso P. A plant-based diet, atherogenesis, and coronary artery disease prevention. Perm J. 2015;19:62–7.
83. Tian J, Niu L, An X. Cardiovascular risks in chronic kidney disease pediatric patients (review). Exper Therap Medi. 2017;14(5):4615–9.
84. Khurana M, Silverstein DM. Etiology and management of dyslipidemia in children with chronic kidney disease and end-stage renal disease. Pediatr Nephr. 2015;30(12):2073–84.
85. Dietary Recommendations for Healthy Children [Internet]. About Heart Attacks. [cited 2019 Feb 18]. Available from: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/dietary-recommendations-for-healthy-children.
86. Heart healthy activity [Internet]. Heart and Stroke Foundation of Canada. [cited 2019 Feb 18]. Available from: https://www.heartandstroke.ca/get-healthy/healthy-kids/heart-healthy-activity.
87. Hui WF, Betoko A, Savant JD, et al. Assessment of dietary intake of children with chronic kidney disease. Pediatr Nephrol. 2017;32:485–94.
88. Kloss L, Meyer JD, Graeve L, Vetter W. Sodium intake and its reduction by food reformulation in the European Union — a review. NFS J. 2015;1:9–19.

89. Ongan D, Inanc N, Cicek B. Comparing school lunch and canteen foods consumption of children in Kayseri. Turkey Pak J Med Sci. 2014;30(3):549–53.
90. Rodriguez-Soriano J, Arant BS, Brodehl J, Norman ME. Fluid and electrolyte imbalances in children with chronic renal failure. Am J Kidney Dis. 1986;7(4):268–74.
91. Parekh RS, Flynn JT, Smoyer WE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12:2418–36.
92. Chen W, Ducharme-Smith K, Davis L, et al. Dietary sources of energy and nutrient intake among children and adolescents with chronic kidney disease. Pediatr Nephrol. 2017;32:1233–41.
93. Beto J, Bansal VK. Hyperkalemia evaluating dietary and nondietary etiology. J Ren Nutr. 1992;2(1):28–9.
94. Taylor JM, Oladitan L, Carlson S, Hamilton-Reeves JM. Renal formulas pretreated with medications alters the nutrient profile. Pediatr Nephrol. 2015;30:1815–23.
95. Le Palma K, Rampolla-Pavlick E, Copelovitch L. Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware of high prevalence of electrolyte derangements in clinical practice. Clin Kidney J. 2018;11(2):166–71.
96. Harambat J, Kunzmann K, Azukaitis K, et al. Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. Kidney Int. 2017;92(6):1507–14.
97. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kid Int. 2006;69:1945–53.
98. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral bone disorder (CKD-MBD). Kidney Int. 2017;7(suppl 1):1–59.
99. Wesseling-Perry K, Pereira RC, Tseng CH, et al. Early skeletal and biochemical alterations in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2012;7:146–52.
100. Carrigan A, Klinger A, Choquette SS, et al. Contribution of food additives to sodium and phosphorus content of diets rich in processed foods. J Ren Nutr. 2014;24(1):13–9.
101. Taylor JM, Oladitan L, Degnan A, et al. Psychosocial factors that create barriers to managing serum phosphorus levels in pediatric dialysis patients: a retrospective analysis. J Ren Nutr. 2016;26(4):270–5.
102. Uribarri J, Calvo MS. Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? Semin Dial. 2003;16(3):186–8.
103. Portale AA, Wolf M, Juppner H, et al. Disordered FGF23 and mineral metabolism in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):344–53.
104. Wesseling-Perry K, Tsai EW, Ettenger RB, et al. Mineral abnormalities and long-term graft function in pediatric renal transplant recipients: a role for FGF-23? Nephrol Dial Transplant. 2011;26:3779–84.
105. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478–83.
106. Hanudel MR, Salusky IB. Treatment of pediatric chronic kidney disease-mineral and bone disorder. Curr Osteoporosis Rep. 2017;15:198–206.
107. Shroff R, Wan M, Nagler EV, et al. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease stages 2-5 and on dialysis. Nephrol Dial Transplant. 2017;32:1098–113.
108. Fassinger N, Imam A, Klurfeld DM. Serum retinol, retinol-binding protein, and transthyretin in children receiving dialysis. J Ren Nutr. 2010;20(1):17–22.
109. Manichkavasagar B, McArdle AJ, Yadav P, et al. Hypervitaminosis A is prevalent in children with CKD and contributes to hypercalcemia. Pediatr Nephrol. 2015;30:317–25.
110. Joyce T, Court Brown F, Wallace D, Reid CJD, Sinha MD. Trace element and vitamin concentrations in paediatric dialysis patients. Pediatr Nephrol. 2018;33:159–65D.
111. Bhat RV, Deshmukh CT. A study of vitamin K status in children on prolonged antibiotic therapy. Indian Pediatr. 2003;40:36–40.
112. Nemeth I, Turi S, Haszon I, Bereczki C. Vitamin E alleviates the oxidative stress of erythropoietin in uremic children on hemodialysis. Pediatr Nephrol. 2000;14:13–7.
113. Zwolinska D, Grzeszczak W, Szczepanska M, Kilis-Pstruslnska K, Szprynger K. Lipid peroxidation and antioxidant enzymes in children on maintenance dialysis. Pediatr Nephrol. 2006;21:705–10.
114. Pru C, Eaton J, Kjellstand C. Vitamin C intoxication and hyperoxalemia in chronic hemodialysis patients. Nephron. 1985;39:112–6.
115. Naseri M, Shahri HMM, Horri M, et al. Antioxidant vitamins status in children and young adults undergoing dialysis: a single center study. Indian J Nephrol. 2015;25(4):206–12.
116. Kriley M, Warady BA. Vitamin status of pediatric patients receiving long-term peritoneal dialysis. Am J Clin Nutr. 1991;53:1476–9.
117. Sabri MR, Tavana EN, Ahmadi A, Gheissari A. Effect of vitamin C on endothelial function of children with chronic renal failure: an experimental study. Adv Biomed Res. 2015;4:260.
118. El Mashad GM, ElSayed HM, Nosair NA. Effect of vitamin C supplementation on lipid profile, serum uric acid, and ascorbic acid in children on hemodialysis. Saudi J Kidney Dis Transpl. 2016;27:1148–54.
119. Filler G, Felder S. Trace elements in dialysis. Pediatr Nephrol. 2013;29(8):1329–35.

120. Tonelli M, Wiebe N, Hemmelgarn B, et al. Trace elements in hemodialysis patients: a systematic review and meta-analysis. BMC Med. 2009;7:25.
121. Spak CJ, Berg U, Ekstrand J. Renal clearance of fluoride in children and adolescents. Pediatrics. 75(3):575–80. Whitford GM. Fluoride metabolism and excretion in children. J Public Health Dent. 1999;59(4):224–8.
122. Esmaeili M, Rakhshanizadeh F. Serum trace elements in children with end-stage renal disease. J Ren Nutr. 2019;29(1):48–54.
123. Ortac E, Ozkaya O, Saraymen R, et al. Low hair selenium and plasma glutathione peroxidase in children with chronic renal failure. Pediatr Nephrol. 2006;21:1739–45.
124. Allinovi M, Saleem MA, Burgess O, Armstrong C, Hayes W. Finding covert fluid: methods for detecting volume overload in children on dialysis. Pediatr Nephrol. 2016;31(12):2327–35.
125. Tomson CRV. Advising dialysis patients to restrict fluid intake without restricting sodium intake is not based on evidence and is a waste of time. Nephrol Dial Transpl. 2001;16(8):1538–42.
126. Salusky IB, Fine RN, Nelson P, Blumenkrantz MJ, Kopple JD. Nutritional status of children undergoing continuous ambulatory peritoneal dialysis. Am J Clin Nutr. 1983;38(4):599–611.
127. Paglialonga F, Edefonti A. Nutrition assessment and management in children on peritoneal dialysis. Pediatr Nephrol. 2008;24(4):721–30.
128. Mak RH, Cheung WW, Roberts CT. The growth hormone–insulin-like growth factor-I axis in chronic kidney disease. Growth Hormon IGF Res. 2008;18(1):17–25.
129. Weaver DJ, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
130. Yılmaz D, Sönmez F, Karakaş S, Yavaşcan Ö, Aksu N, Ömürlü IK, et al. Evaluation of nutritional status in children during predialysis, or treated by peritoneal dialysis or hemodialysis. J Trop Pediatr. 2016;62(3):178–84.
131. Ruley EJ, Bock GH, Kerzner B, Abbott AW, Majd M, Chatoor I. Feeding disorders and gastroesophageal reflux in infants with chronic renal failure. Pediatr Nephrol. 1989;3(4):424–9.
132. The World Health Organization's infant feeding recommendation [Internet]. World Health Organization. World Health Organization; 2015 [cited January 19, 2019]. Available from: https://www.who.int/nutrition/topics/infantfeeding_recommendation/en/.
133. Hawkins NM, Coffey S, Lawson MS. Potential Aluminium toxicity in infants fed special infant formula. J Pediatr Gast Nutr. 1994;19(4):377–81.
134. Coleman J. Gastrostomy buttons for nutritional support on chronic dialysis. Nephrol Dial Transplant. 1998;13(8):2041–6.
135. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2009;25(4):699–704.
136. Hobbs DJ, Gast TR, Ferguson KB, Bunchman TE, Barletta G-M. Nutritional Management of Hyperkalemic Infants with Chronic Kidney Disease, using adult renal formulas. J Ren Nutr. 2010;20(2):121–6.
137. Thompson K, Flynn J, Okamura D, Zhou L. Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate®) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. J Ren Nutr. 2013;23(5):333–9.
138. Evans S, Daly A, Ashmore C, Gokmen-Ozel H, Dileva R, Dumbleton B, et al. Nutritional content of modular feeds: how accurate is feed production? Arch Dis Child. 2013;98(3):184–8.
139. Novak P, Wilson KE, Ausderau K, Cullinane D. The use of Blenderized tube feedings. ICAN: Infant Child Adol Nutr. 2009;1(1):21–3.
140. Nelms CL. Optimizing enteral nutrition for growth in pediatric Chronic Kidney Disease (CKD). Front Pediatr. 2018;6
141. Samaan S, Secker D. Oral feeding challenges in infants with chronic kidney disease. ICAN: Infant Child Adolesc Nutr. 2014;6(3):164–71.
142. Warady BA, Kriley M, Belden B, Hellerstein S, Alon U. Nutritional and behavioral aspects of nasogastric tube feeding in infants, receiving chronic peritoneal dialysis. Adv Perit Dial. 1990;6:265–8.
143. Mekahli D, Shaw V, Ledermann SE, Rees L. Long-term outcome of infants with severe chronic kidney disease. Clin J Am Soc Nephrol. 2009;5(1):10–7.
144. Pugh P, Watson A. Transition from gastrostomy to oral feeding following renal transplantation. Adv Perit Dial. 2006;22:153–7.
145. Lum A, Wakefield CE, Donnan B, Burns MA, Fardell JE, Marshall GM. Understanding the school experiences of children and adolescents with serious chronic illness: a systematic meta-review. Child Care Health Dev. 2017;43(5):645–62.
146. Ellyn Satter Institute [Internet]. [cited January 19, 2019]. Available from: https://www.ellynsatterinstitute.org/.
147. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2012;27:173–81.
148. Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D. Stature in children with chronic kidney disease: analysis of NAPRTCS database. Pediatr Nephrol. 2006;21:793–9.
149. United States Renal Data System. 2017 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2017. Accessed at: https://www.usrds.org/2017/view/v2_07.aspx on February 11, 2019.

150. Morris A, Love H, van Aar Z, Liles C, Roskell C. The problematic world of following a renal diet outside the home. J Ren Care. 2015;41(4):253–9.
151. Chen K, Didsbury M, Zwieten AV, Howell M, Kim S, Tong A, et al. Neurocognitive and educational outcomes in children and adolescents with CKD. Clin J Am Soc Nephrol. 2018;13(3):387–97.
152. Anderson JE. Brain development in adolescents: new research – implications for physicians and parents in regard to medical decisions making. Issues L Med. 2015;30(2):193–7.
153. Ferris MED-GD, Villar-Vilchis MD, Guerrero R, Barajas-Valencia VM, Vander-Schaaf EB, Pomposo AD, et al. Self-management and health care transition among adolescents and young adults with chronic kidney disease: medical and psychosocial considerations. Adv Chron Kidney Dis. 2017;24(6):405–9.
154. Raina R, Wang J, Krishnappa V, Ferris M. Pediatric renal transplantation: focus on current transition care and proposal of the "RISE to transition" protocol. Ann Transplant. 2018;23:45–60.
155. Bell LE, Ferris ME, Fenton N, Hooper SR. Health care transition for adolescents with CKD—the journey from pediatric to adult care. Adv Chron Kidney Dis. 2011;18(5):384–90.
156. Spinozzi NS, Nelson P. Nutrition support in the newborn intensive care unit. J Ren Nutr. 1996;6(4):188–97.
157. Misurac J. Chronic kidney disease in the neonate: etiologies, management, and outcomes. Semin Fetal Neonatal Med. 2017;22(2):98–103.
158. Ridout E, Melara D, Rottinghaus S, Thureen PJ. Blood urea nitrogen concentration as a marker of amino-acid intolerance in neonates with birthweight less than 1250 g. J Perinatol. 2004;25(2):130–3.
159. Tsang RC, Uauy R. Nutrition of the preterm infant: scientific basis and practical guidelines. Cincinnati: Digital Educational Publishing Ltd; 2005.
160. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. Kidney Int. 2008;74(3):393.
161. Nourbakhsh N, Rhee CM, Kalantar-Zadeh K. Protein-energy wasting and uremic failure to thrive in children with chronic kidney disease: they are not small adults. Pediatr Nephrol. 2014;29(12):2249–52.
162. Sylvestre LC, Fonseca KPD, Stinghen AEM, Pereira AM, Meneses RP, Pecoits-Filho R. The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2007;22(6):864–73.
163. Abraham AG, Mak RH, Mitsnefes M, White C, Moxey-Mims M, Warady B, et al. Protein energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2014;29(7):1231–8.
164. Ayestaran FW, Schneider MF, Kaskel FJ, Srivaths PR, Seo-Mayer PW, Moxey-Mims M, et al. Perceived appetite and clinical outcomes in children with chronic kidney disease. Pediatr Nephrol. 2016;31(7):1121–7.
165. Ku E, Glidden DV, Hsu C-Y, Portale AA, Grimes B, Johansen KL. Association of Body Mass Index with patient-centered outcomes in children with ESRD. J Am Soc Nephrol. 2015;27(2):551–8.
166. Mak RH. Cachexia in children with chronic kidney disease. Curr Opin Supp Pall Care. 2016;10(4):293–7.
167. Schaefer F, Benner L, Borzych-Duzalka D, et al. Global variation of nutritional status in children undergoing chronic peritoneal dialysis: a longitudinal study of the International Pediatric Peritoneal Dialysis Network. Sci Rep. 2019;9:4886.
168. Weaver DJ, Mitsnefes M. Cardiovascular disease in children and adolescents with chronic kidney disease. Semin Nephrol. 2018;38(6):559–69.
169. Schaar B, Thys S, Hoppe B. Endurance training during maintenance hemodialysis in pediatric and adolescent patients—theory and best practice suggestions. Pediatr Nephrol. 2019; https://doi.org/10.1007/s00467-018-4182-1. [Epub ahead of print]
170. Clark SL, Denburg MR, Furth SL. Physical activity and screen time in adolescents in the chronic kidney disease in children (CKiD) cohort. Pediatr Nephrol. 2015;31(5):801–8.
171. Haskin O, Sutherland SM, Wong CJ. The effect of intradialytic Intralipid therapy in pediatric hemodialysis patients. J Ren Nutr. 2017;27(2):132–7.
172. Juarez MD. Intradialytic parenteral nutrition in pediatrics. Front Pediatr. 2018;4
173. Harshman LA, Johnson RJ, Matheson MB, Kogon AJ, Shinnar S, Gerson AC, et al. Academic achievement in children with chronic kidney disease: a report from the CKiD cohort. Pediatr Nephrol. 2018;34(4):689–96.
174. Dinh HTT, Bonner A, Clark R, Ramsbotham J, Hines S. The effectiveness of the teach-back method on adherence and self-management in health education for people with chronic disease: a systematic review. JBI Database System Rev Implement Rep. 2016;14(1):210.
175. Sanders KA, Whited A, Martino S. Motivational interviewing for patients with chronic kidney disease. Semin Dial. 2013;26(2):175–9.
176. Asfaw M, Mingle J, Hendricks J, et al. Nutrition management after pediatric solid organ transplantation. Nutr Clin Pract. 2014;29(2):192.200.
177. Coelho T, Tredger M, Dhawan A. Current status of immunosuppressive agents for solid organ transplantation in children. Pediatr Transplant. 2012;16:106–22.
178. Food Safety for Transplant Recipients: https://permanent.access.gpo.gov/gpo51931/UCM312793.pdf, USDA, 2011, accessed January 1, 2020.
179. Dietary Guidelines 2015–2020: https://health.gov/dietaryguidelines/2015/guidelines/appendix-7/. Accessed January 1, 2010.
180. National Academies Dietary Reference Intakes Macronutrients: http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/8_Macronutrient%20Summary.pdf. Accessed January 1, 2020.

Controlled Enteral and Parenteral Nutrition in Children on Dialysis

27

Bethany J. Foster and Anne Tsampalieros

Introduction

Growth retardation is common among children with chronic kidney disease (CKD). As a result, adequacy of nutritional intake is a frequent preoccupation of professionals caring for these children. While optimized oral intake is preferred, this is not always feasible. When oral intake is insufficient to meet requirements for normal growth and development, enteral or, less commonly, parenteral nutritional supplementation is needed. Enteral nutrition, via nasogastric or gastrostomy tube, is always preferred over the parenteral route.

This chapter will review the rationale for nutritional supplementation in pediatric CKD, causes of inadequate intake, indications for enteral and parenteral nutritional supplements, and evidence for the benefits of each method of supplementation. We will also consider the advantages and disadvantages of nasogastric versus gastrostomy tube feeding, highlight the potential complications of each, and review the challenges of transitioning to full oral feeding after a period of tube feeding.

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Rationale for Nutritional Supplementation in Pediatric CKD

Growth impairment, defined as a height-for-age or height velocity-for-age standard deviation score (SDS) of less than −1.88, [1, 2], is a common complication of pediatric CKD. In the period 1992–2001, 40.5% of children undergoing kidney transplant had a height more than 2.0 SD below the average for children of the same age and sex. Although this percentage dropped to 32.8% in the interval 2002–2011, growth restriction remains very prevalent [3]. Severe (height-for-age SDS < −3.0) and moderate (−3.0 > height-for-age SDS < −2.0) growth failure are associated with an increased risk of mortality [4] and poorer quality of life [5]. Children starting dialysis with a height-for-age less than the first percentile (SDS < −2.5) had a twofold higher risk of death compared to those with a height-for-age greater than −2.5 SDS [6].

The severity of growth failure is correlated with the degree of renal impairment and is most pronounced once the GFR falls below 25 ml/min/1.73m^2 [7–9]. A report from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), including more than 5000 children, showed that over 35% of children with a creatinine clearance <75 ml/min/1.73m^2 had a

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height below the third percentile at the time of enrollment into the study [7, 10]. The proportion of children with a height SDS < -1.88 was higher when GFR was lower: height SDS was <−1.88 in 31.1% of children with GFR >25 ml/min/1.73m^2, 47.2% of those with GFR between 10 and 25 ml/min/1.73m^2 and 68.4% of those with GFR <10 ml/min/1.73m^2. Growth failure is also more severe at younger ages: the average height SDS in infants aged 0–1 years at registry entry was −2.30 and in young children between 2 and 5 years was −1.69, whereas in adolescents (>12 years), it was −0.96 [7]. Additionally, infants born with CKD were found to have lower height SDS compared to those with acquired diseases [7, 11]. Infancy is a particularly high-risk interval given that one third of total postnatal growth occurs during this period [12].

Inadequate calorie intake is one among many factors contributing to growth failure in CKD and is the dominant contributor in infants and very young children [8, 13–15]. Anorexia is common [13–15]; a number of factors may lead to anorexia including gastroesophageal reflux, delayed gastric emptying, altered taste, and increased levels of cytokines such as leptin, IL-1, IL-6, and TNF-α [14, 16–19]. Disruption in the levels of appetite-regulating hormones such as leptin and ghrelin leads to both a lack of appetite and early satiety [14, 18–21]. Other reasons for inadequate intake include fluid and dietary restrictions and frequent vomiting [22, 23]. Children with polyuric CKD may favor water consumption over intake of food. Those on PD may have diminished appetite due to a sense of abdominal fullness.

While nutrition is important throughout childhood, the contribution of nutritional intake to growth depends heavily on the phase of growth [24–26]. Normal postnatal growth can be divided into infantile, childhood, and pubertal phases. Growth during the infantile phase is driven primarily by nutritional intake. Therefore, inadequate intake in infancy manifests with growth failure. Routine calorie supplementation in infants with CKD has been shown to improve growth [27–30]. Healthy infants transition from the infantile to the childhood growth phase between 6 and 12 months. However, the childhood phase may be delayed until 2–3 years in children with CKD [14, 31]. During the childhood phase, growth depends mainly on growth hormone. The pubertal phase of growth, which in CKD is often delayed and of shorter duration than normal [32, 33], is driven by both growth hormone and sex hormone [13, 34]. Outside infancy, energy intake among children with CKD is usually appropriate relative to body size [2, 35]; there is no good evidence that nutritional supplements enhance growth in older children.

Weight loss is another important indication for nutritional supplementation in children with CKD [2]. Wasting, defined as low weight-for-height, was initially thought to be due exclusively to inadequate nutritional intake or malnutrition [36, 37]. However, there is now evidence that other factors such as systemic inflammation, abnormal neuropeptide signaling, and endocrine perturbations may contribute to wasting in the context of CKD [36, 38, 39]. Children with cachexia/wasting syndrome may have an increased metabolic rate or anorexia with altered body composition (reduced muscle mass and body weight, with normal or increased fat mass); therefore, increasing food consumption or altering the diet may not help children with cachexia. In contrast, malnutrition can be corrected by supplying more food or improving the diet [36, 40].

Neurocognitive dysfunction, including memory deficits, academic difficulties, and deficits in executive functioning, may also be a consequence of CKD and ESRD [41–44]. Because infancy is a period of rapid neurodevelopment, infants are at greatest risk for neurodevelopmental disorders. Earlier reports [45–48] found developmental delay in up to 60–85% of infants with severe renal insufficiency. However, these reports predate recognition of the roles of aluminum exposure and malnutrition in neurodevelopmental disturbances. Subsequent small observational studies showed superior developmental outcomes associated with early intervention including aggressive nutrition and dialysis [48, 49]. Nutritional intervention has the potential to have an important positive impact on neurodevelopment during infancy [14].

Indications for Supplemental Nutritional Support

The 2008 Kidney Disease Outcomes Quality Initiatives (KDOQI) nutrition guidelines recommend: *Supplemental nutritional support should be considered when the usual intake of a child with CKD stages 2–5 or 5D fails to meet his or her energy requirements and the child is not achieving expected rates of weight gain and/or growth for age. (Evidence Grade B) Oral intake of an energy-dense diet and commercial nutritional supplements should be considered the preferred route for supplemental nutritional support for children with CKD stages 2–5 and 5D. (Evidence Grade B) When energy requirements cannot be met with oral supplementation, tube feeding should be considered* [2] *(Evidence Grade B).*

It is important to remember that a normal rate of weight gain for age depends on a normal rate of linear growth. Outside infancy, a child with growth failure should not be subjected to a long trial of nutritional support before starting growth hormone therapy.

Indications for Tube Feeding

Most infants and toddlers with moderate to severe CKD show substantially decreased spontaneous oral intake [50, 51], and the majority require tube feeding. Dietary intake should be regularly monitored in infants and toddlers with CKD. Tube feeding should be considered for children unable to meet their estimated energy requirements (EER) orally who are either underweight, are growth restricted (weight-for-age or length-for-height SDS less than −1.88), or are failing to maintain normal weight gain or growth [2]. Early intervention, with a goal of *preventing* growth retardation, is a key principle of nutritional management in infants and toddlers with CKD. Height potential lost during infancy is extremely difficult to catch up later, and even short periods of poor growth during infancy may result in substantial loss of height potential. Evidence of stunting is not required to justify intervention. Greater final height is achieved in children in whom tube feedings are started before important height deficits are noted [52]. Catch-up growth is most likely during infancy [13]. The goal of tube feeding is to ensure intake of at least 100% of the EER; greater energy intake is required for catch-up growth. This may be challenging especially for those who have volume restrictions, delayed gastric emptying, frequent emesis, or gastroesophageal reflux [5].

Tube feeding is rarely required for older children with CKD, in whom intakes are usually normal relative to body size [35]. It is possible that poor intake is a consequence of the poor growth, rather than the cause. A study of 33 children with CKD showed an almost 12% increase in spontaneous calorie intake during treatment with recombinant human growth hormone [53]. Older children with CKD should have dietary intake monitored regularly [2]. If intake is found to be inadequate, an underlying reason should be sought. Causes of poor nutritional intake among older children include progressive uremia, gastrointestinal disorders, and eating disorders. Progressive uremia may require initiation or intensification of dialysis [54]. Growth hormone therapy may promote greater oral intake by stimulating metabolic demand. If nutritional supplements are deemed necessary, the oral route should be the first choice. Tube feedings should be limited to children with progressive weight loss or growth failure who are unable to take adequate calories orally [2].

Evidence for Benefits of Tube Feeding: Infants

The literature on tube feeding in children with CKD is difficult to interpret. There have been no randomized trials assessing the impact of tube feeding on growth or other outcomes. In addition, confounding factors including severity of CKD, type and intensity of renal replacement therapy, and age of the child – all of which may independently influence growth and/or response to nutritional supplementa-

tion – make comparisons between studies challenging. Numerous studies of infants with CKD showed significant increases in height velocity following NG or gastrostomy tube feeding [12, 27–29, 52, 55–57]. In studies including both infants and older children, growth benefits due to tube feeding were evident among infants when the outcomes of older children were separated from those of infants [29, 58, 59]. Results of studies published in 2000 onward are summarized in Table 27.1. The largest study to date included 153 infants under the age of 24 months maintained on peritoneal dialysis (PD), 55% of whom received gastrostomy or NG tube feeds [12]. BMI- and height-for-age SDS were significantly higher in children receiving gastrostomy feeds compared to those who received NG feeds or no tube feeding. Catch-up growth occurred only in those receiving gastrostomy tube feeding.

Tube feeding is also an important means of delivering sodium and fluid supplements to infants with high urinary sodium and water losses due to polyuric CKD [27, 28, 52], and to infants treated with PD, who may also experience large sodium losses through the dialysate [13]. These high fluid volumes and large doses of sodium are rarely taken orally. Linear growth is impaired by a negative sodium balance [60]. Furthermore, volume depletion due to sodium and water losses has also been reported to result in neurologic injury [2].

While there had been initial concerns that children (specifically infants) who received enteral tube feeds may have disproportionate gains in weight compared to height [29, 58] and thus may be predisposed to becoming overweight after having their gastrostomy removed, a later study demonstrated otherwise. Sienna et al. [61] found that while children with CKD who received tube feeds for a median of 2.9 years, starting at a median age of 1.7 years, had increases in weight- and BMI-for-age Z-scores, these did not continue to increase significantly up to 5 years after having their gastrostomy removed.

Evidence for Benefits of Tube Feeding: Older Children

There is no strong evidence supporting the benefit of tube feeding in promoting growth in older children and adolescents with CKD. Although adequate nutrition is certainly necessary to support normal growth in older children, CKD-related disturbances in the effects of growth hormone and in normal puberty are more important drivers of poor growth than inadequate nutrition in this age group [34, 62–64]. Indeed, undernutrition is increasingly uncommon, while obesity is a problem of increasing prevalence among older children with end-stage renal disease (ESRD) [65]. A recent study of over 4000 children and adolescents with ESRD across 25 European countries found that 40.8% of children 12–15 years old were overweight or obese, while only 1.4% were underweight. In contrast, only 9% of children under 1 year of age were overweight or obese, and 15.8% were underweight [66].

Selected older children who are observed to have inadequate intake and are unable to tolerate oral supplements may benefit from supplemental tube feeding [2]. However, this represents the minority of older children with CKD. Therapies with proven benefit in improving growth, such as growth hormone [67], should not be delayed by prolonged trials of supplemental calories.

Nasogastric (NG) Versus Gastrostomy Tube Feeding

Home tube feeding either with a NG tube or gastrostomy has been used successfully in infants discharged from the neonatal intensive care unit [68] and has been found to promote growth and decrease the length of hospital stay [68–70].

There are two methods for delivering enteral tube feeds: nasogastric or gastrostomy.

Nasogastric tube feeding The use of NG feeding in children with CKD began in the 1980s [71, 72]. NG tube feeding is suitable to provide nutri-

Table 27.1 Summary of studies assessing the use of enteral feeding among children with CKD in association with growth

Study year published	Population	Study design	Intervention	Duration	Outcome
Kari et al. [28] 2000	*N* = 81 Age: 0.7* (0 to 4.5) years GFR: <20 ml/min/1.73m^2 Group 1: Conservative therapy: *N* = 25 Group 2: Preemptive transplant: *N* = 20 Group 3: Dialysis *N* = 36	Case series	Tube feeds: *N* = 66 100% estimated average requirement for calories Conservative: Tube feeds *N* = 20 Preemptive transplant: Tube feeds *N* = 14 Dialysis: Tube feeds *N* = 32	1.9* (0.1 to 6.8) years	The study demonstrated catch-up growth among infants and young children treated with tube feeding
Ledermann et al. [55] 2000	*N* = 20 Age: 0.34 (0.02 to 1) years All on peritoneal dialysis	Case series	Tube feeds: *N* = 18 NG: *N* = 9 G-tube: *N* = 8 NG and G-tube: *N* = 1 Two did not receive tube feeds Goal RDA > 100% for calories	Follow up 1 and 2 years from the start of peritoneal dialysis	Mean height-for-age SDS at the start was −1.8 ± 1.1 and − 1.1 ± 1.2 at 1 year (p = 0.046) and −0.8 ± 1.4 at 2 years (p = 0.06) Mean weight-for-age SDS at the start of PD was −1.6 ± 1.5, 0.3 ± 1.5 at 1 year (p = 0.008) and 0.3 ± 1.8 at 2 years (p = 0.008)
Ellis et al. [115] 2001	*N* = 137 Age: All <6 years at the start of dialysis <3 months: *N* = 51 3–23 months: *N* = 52 2–5 years: *N* = 34 Peritoneal dialysis: *N* = 126 Hemodialysis: *N* = 8	Cohort study using data from North American Pediatric Renal Transplant Cooperative Study	Supplemental feeds received in *N* = 96 NG only: *N* = 52 G-tube only: *N* = 27 NG and G-tube: *N* = 8 NG + other[a]: *N* = 3 Others: N = 5 The rest received no supplemental feeds Did not report caloric intake	30 days, 6 months, and 1 year post dialysis initiation	No significant difference in height-for-age SDS in those who received supplemental feeding at the start of dialysis compared to those who did not Change in height-for-age SDS was −0.69 ± 0.68 in those receiving enteral feeds versus −0.63 ± 0.66 in those who did not

(continued)

Table 27.1 (continued)

Study year published	Population	Study design	Intervention	Duration	Outcome
Parekh et al. [52] 2001	*N* = 24 GFR: <65 ml/min/1.73m^2 Age not reported Dialysis: *N* = 7 Transplant: *N* = 0 No renal replacement therapy: *N* = 17	Cohort Controls from: 1. USRDS pediatric growth study [116] (*N* = 42) 2. Abitbol [117] (*N* = 12)	G tube: *N* = 15 Oral and NG or G-tube: *N* = 3 Oral: *N* = 6 ≥100% RDA for calories Supplemented with sodium	1 and 2 year follow-up	Net increase in height-for-age SDS of +0.15 over 2 years in the treatment group Treatment group had a 1.37 greater increase in height-for-age SDS at 1 year compared to untreated patients in the USRDS [116] $p = 0.017$ and a 1.83 greater increase in height-for-age SDS at 2 years compared to Abitbol [117] controls $p = 0.003$
Waller et al. [57] 2003	*N* = 99 Age: 1.6 (0.4 to 6.0) GFR: <41 mL/min/1.73m^2 (median 22) All received conservative therapy	Cohort study	Tube feeds (NG and G-tube): *N* = 41 The rest of the participants were fed orally	3.6 (1.8 to 4.9) years	Overall height-for-age SDS increased by 0.09 per year; however no significant difference in change in height among those receiving tube feeds versus not (change in height-for-age SDS/year of 0.13 versus 0.05) $p = 0.16$ Weight- and BMI-for-age SDS increased significantly in those receiving enteral feeds vesus not receiving Change in weight SDS/year 0.47 versus 0.22 $p = 0.005$) and change in BMI-for-age SDS/year 0.56 versus 0.24 $p = 0.002$
Waller et al. [118] 2005	*N* = 162 Age: 9.9* (0.3 to 17.1) years GFR: <60 ml/min Conservative: *N* = 96 Hemodialysis: *N* = 7 Peritoneal dialysis: *N* = 19 Transplanted: *N* = 40	Cohort study	G-tube: *N* = 28 The rest of the participants were fed normally	1.1* (0.15 to 1.7) years	Overall patients grew normally (i.e., change in height-for-age SDS per year and change in weight SDS per year were not different compared to an expected mean change of 0) There was no significant difference in growth in those fed via G-tube compared to those fed normally

Table 27.1 (continued)

Study year published	Population	Study design	Intervention	Duration	Outcome
Cansick et al. [56] 2007	*N* = 35 Age: 2.8 (0.25 to 8.90) years Peritoneal dialysis: *N* = 14 Hemodialysis: *N* = 4 Both: *N* = 17	Case series	Tube feeds: *N* = 32 By G-tube and/or NG ≥100% RDA for calories Study does not specify what the remaining three received	Until 10 years of age, transplanted or started growth hormone	Children <2 years showed catch-up growth in the first year on dialysis (height-for-age SDS 0.31* (−0.78 to 3.13). No catch-up growth in older children
Hijazi et al. [119] 2009	*N* = 52 Age: 4.4 ± 5.3, (0.5–18) months Peritoneal dialysis: *N* = 50 Hemodialysis: *N* = 2	Cohort study comparing growth in two different eras Era 1: Born 1983–1995 *N* = 23 Era 2: Born 1996–2008 *N* = 29	G-tube: *N* = 20 NG: *N* = 32 ≥100% RDA for calories 21 patients were on growth hormone	25 years of follow-up	Height-for-age SDS at most recent encounter in children from era 2 (−1.4 ± 0.9) was higher than that in era 1 (−3.0 ± 1.5); $p = 0.001$
Sienna et al. [61] 2010	*N* = 20 Age: 1.7* (0.9 to 15.6) years GFR: 13.8*(3.9 to 61.8) ml/min/1.73m^2 Hemodialysis: *N* = 2 Peritoneal dialysis: *N* = 6 CKD: *N* = 11 Unknown: *N* = 1 Comparison group: *N* = 82 Age: 9.2 ± 3.1 years GFR: 45.3*(7.4 to 140.1) ml/min/1.73m^2 Hemodialysis: *N* = 3 Peritoneal dialysis: *N* = 3	Cohort study	G-tube fed (*N* = 20) ≥100% RDA 9/20 were on growth hormone Comparison group included children with CKD who did not have a G-tube during the study period (*N* = 82)	2.9* (0.9 to 11.8) years	Mean height-for-age Z-score at G-tube insertion was −2.35 ± 1.86 and at removal was −1.51 ± 0.99 this was a nonsignificant increase and was not significantly different from comparison population Mean BMI-for-age Z-score increased in those receiving G-tube feeds: At G-tube insertion, it was −1.22 ± 1.68 and at removal was 0.43 ± 0.86 $p < 0.05$ No significant increase in the comparison group

(continued)

Table 27.1 (continued)

Study year published	Population	Study design	Intervention	Duration	Outcome
Rees et al. [12] 2011	*N* = 153 Age: <24 months All: 3.1* (0.1 to 5.8) months NG: 1.73* (0.1 to 5.4) G-tube: 2.2* (0.2 to 7.96) Peritoneal dialysis: *N* = 153	Cohort study using data from the International Pediatric Peritoneal Dialysis Network registry	NG: *N* = 54 G-tube: *N* = 33 Demand fed: *N* = 66	6, 12, 18, and 24 months	Length improved with G-tube feeding: Change in height-for-age SDS for demand feeding was −1.35/year, −0.72/year for NG tube feeding and − 0.50/year for G-tube feeding ($p < 0.05$ for g-tube versus demand) BMI improved in both NG and G-tube fed compared to demand fed: Change in BMI-for-age SDS -0.54/year for demand feeding versus +0.97/year for NG and +1.24/year for G-tube ($p < 0.05$)
Rees et al. [20] 2013	*N* = 18 Age: 7.1 (2.1 to 13.3) years GFR: 16 mL/min/1.73m^2 On dialysis at start of feeds: *N* = 9 Started dialysis 1 year after feeds initiated: *N* = 4 Transplanted: *N* = 5	Case series	All received tube feeds but does not specify route	12 and 24 months	Height-for-age SDS at the start was −2.61 and after 1 year −2.38 (NS) and −2.20 after 24 months (NS)
Prestidge et al. [120] 2015	*N* = 17 Age: 7.2* years (10 weeks to 17.2 years) Peritoneal dialysis: *N* = 17	Case series	G-tube: *N* = 17	1 year post G-tube insertion (*n* = 9) Followed until transplantation (*n* = 5) Two patients died and one was not accounted for	Height-for-age SDS pre-enteral feeds −1.2 [−2.7,1.4] and post was −1.1 [−3.4,0.9] Height-for-age SDS -1.1 [−1.9,-0.4] to −0.8 [−1.8,-0.5] P-values not provided

Data in this table is limited to the studies which were published in 2000 and after
Results presented as mean ± standard deviation, mean (range), median [interquartile range], or *median with range
NG nasogastric, *G-tube* gastrostomy, *RDA* recommended daily allowance, *USRDS* US renal data system
[a]Other denotes oral gastric tube, transpyloric tube, gastrojejunostomy tube, parenteral, or a combination of these

tional support for a short period of time and is the preferred method for infants weighing less than 4 kilograms [73]. A variety of flexible NG tubes with different external diameters are commercially available. Polyvinyl chloride tubes have a life span ranging between 5 and 7 days, whereas silk tubes may last up to 4–6 weeks. NG tubes are easily placed at the bedside. The NG tube is inserted through the nostril and passed though the oropharynx and into the stomach. Placement

must be checked prior to use. Methods used to verify placement include auscultation for air insufflation with a stethoscope or aspirating contents from the tube and assessing the color and pH with a litmus paper, which should turn red if acidic stomach secretions are present [31, 74, 75]. NG tubes require daily care in order to prevent blockage. This includes flushing before and after every feed or medication or every 8 hours if the tube is not being used.

NG tubes have the advantages of placement without the need for surgery and a lack of peritonitis risk for the children who are on PD. However, NG tube use may be complicated by pulmonary aspiration, nasoseptal erosion, sinusitis, and otitis media. Additional disadvantages include an increased gag reflex, an increased risk of reflux and vomiting, and discomfort at the back of the throat which may lead to aversion to oral intake. The need for repeated replacement of the tube following vomiting may further contribute to oral aversion. Finally, the altered cosmetic appearance of an NG tube may have a negative psychological impact on both caregivers and the child him or herself [5, 12, 76–78].

Gastrostomy Tube Feeding When nutritional support is anticipated for more than 6 weeks, a gastrostomy should be considered [79]. Gastrostomies can be placed endoscopically or by an open procedure. Percutaneous gastrostomy is less invasive than open and may be inserted under endoscopic guidance (PEG) and laparoscopic or radiologic assistance. Percutaneous gastrostomy has the benefit of a faster recovery time compared to an open gastrostomy [79]. In the open technique, a small incision is made and the stomach is brought anteriorly and sutured to the abdominal wall. If a tube is used, it may be changed to a button device after 3–4 weeks [76]. The advantage of gastrostomy button devices over tubes is that they are smaller and more discreet. There are different types of buttons: the Bard and the MIC-KEY. Each type has a stem which inserts into the abdominal wall as well as a valve in the lumen to prevent leakage of stomach contents. With the MIC-KEY the valve is located closer to the skin, whereas with the Bard it is in the more distal portion [76]. The Bard device lasts longer than the MIC-KEY, but the MIC-KEY is easier to change. Both gastrostomy tubes and buttons may be left in place for months to years. The main advantages of gastrostomy over NG tubes are the potential for improvement in reflux symptoms, avoidance of the potential upper airway complications of NG tubes, a better cosmetic profile, and the potential avoidance of oral aversion sometimes associated with NG tubes.

However, gastrostomies are not free of complications. Complications are reported to be minor in 10–15% of cases and major in 3–5% [52, 76, 80–85]. Complications include tube blockage, tube displacement, balloon rupture, closure of the tract, leakage around the gastrostomy exit site with skin irritation, granulation or enlarged stoma site, exit site infection, gastrocutaneous or colocutaneous fistula, hemorrhage, and worsening of gastroesophageal reflux due to distortion of gastric anatomy. Complications specific to PEG tubes include intra-abdominal leakage, peritonitis for those also on PD, and gastrocolic fistula [76].

Ricciuto et al. [85] compared prolonged NG and gastrostomy use in a retrospective chart review of 166 children who were a median of 5.3 months old at the start of tube feeding. Underlying disease varied from neurologic/genetic causes to prematurity, and median tube feeding duration was 24.9 months. The incidence of oral food refusal was higher in those fed by NG than gastrostomy (especially if for longer than 3 months). Furthermore, the proportion of children who were wasted (defined as a BMI-for-age (if older than 2 years) or weight-for-age (if less than 2 years) below the third percentile) did not change in those fed by NG, whereas it decreased among those receiving gastrostomy feeds. However, the complication rate for gastrostomy was almost double that for NG (80% vs 46%). Most gastrostomy-related complications were fairly minor, including granulation tissue, skin irritation, tube displacement, and cellulitis. NG-related complications included feeding intolerance, facial irritation, and epistaxis.

Complications requiring hospital visits occurred at a greater rate in gastrostomy-fed infants (2.2 visits per 1000 days) than in those fed by NG (0.7 visits per 1000 days) [85]. The reported complication rate was much higher than that previously published, which may reflect the relatively large proportion of neurologically impaired and critically ill children in the study. Similarly, Khalil et al. [84] found the incidence of tube-related complications requiring an emergency room visit to be significantly higher among those receiving gastrostomy (33.6%) versus NG (9.5%) feeds among 322 infants discharged from the neonatal intensive care unit. The most common gastrostomy-related complications were inadvertent tube displacement or removal (39.1%) and gastrostomy site issues (21.4%).

Gastrostomies in Peritoneal Dialysis Patients The 2012 International Society of Peritoneal Dialysis guidelines provided specific recommendations for the placement and care of gastrostomies [86]. They recommended that a gastrostomy tube be inserted prior to or at the same time as the PD catheter insertion. This can be done either by open surgical technique or laparoscopically (Evidence Grade 1C). For those children already on PD, an open surgical approach is recommended. An open technique may limit contamination of the peritoneal cavity as the stomach is secured to the abdominal wall [86, 87]. In order to lower the risk of peritonitis, prophylactic antibiotics (a single dose of parenteral cefazolin prior to the procedure) is recommended for either open surgical or PEG tube placement [86, 88]. A meta-analysis including ten randomized controlled trials with over 1000 patients found that those who received prophylactic antibiotics had a significantly lower risk of peristomal infection compared to those who did not receive prophylactic antibiotics [88]. There are reports of a higher risk of fungal infection among those who have "advanced malnutrition" [89], and therefore it is recommended that these patients undergo a period of NG feeding to improve their nutritional status prior to gastrostomy insertion; antifungal prophylaxis at the time of the procedure is also suggested [86]. Lastly it is suggested that PD be withheld for a period of time after gastrostomy placement regardless of the placement technique used. The ideal duration that PD should be withheld is not known; however between 1 and 4 days has been suggested [87]. It is then important to restart dialysis with a low exchange volume and gradually increase.

Practical Aspects of Enteral Tube Feeding

Enteral tube feeding may be used to either supplement a child's insufficient oral intake or to provide all of their nutritional requirements [90]. This can be accomplished through the use of a feeding pump at night or manually, by syringe. The method of tube feed delivery as boluses or continuous infusion will depend on a variety of factors including the child's age, the volume to be provided, nutrient requirements, presence of recurrent emesis, and the comfort level of the caregiver [2]. Some children may only require intermittent bolus feeds or "top-ups" if oral intake is inadequate, while others may need all nutrition be provided by tube as a combination of overnight feeding with additional daytime boluses [5, 31]. In older children, enteral tube feeds may be supplied mainly during the night in order to optimize hunger and encourage oral intake during the day. This approach also allows the child to participate in normal daytime activities and socialize without being "tied down" to their feeding tube [2, 5, 90]. Nutrition options used for tube feeding include breast milk, infant formula, or specialized infant or pediatric formulas for younger children and high calorie or protein supplements for older children [90]. Another way to increase calorie intake is to deliver concentrated formula with a higher caloric density per unit volume than standard formula. However, this can be challenging given the additional electrolytes and renal solute load delivered in concentrated formula; close monitoring for intolerance is necessary [5, 91].

Table 27.2, reproduced from the 2008 KDOQI guidelines [2], provides suggested rates for both boluses and continuous infusions. In order to

Table 27.2 Suggested rates for initiating and advancing tube feeds 2008 KDOQI Nutrition guidelines [2]

Age (years)	Initial hourly infusion	Daily increases	Goal[a]
Continuous feedings			
0–1	10–20 mL/h or 1–2 mL/hr./kg	5–10 ml/8 h or 1 ml/kg/h	21–54 ml/h or 6 ml/kg/h
1–6	20–30 ml/h or 2–3 ml/kg/h	10–15 ml/8 h or 1 ml/kg/h	71–92 ml/h or 4–5 ml/kg/h
6–14	30–40 ml/h or 3–4 ml/kg/h	15–20 ml/8 h or 0.5 ml/kg/h	108–130 ml/h or 3–4 ml/kg/h
>14	50 ml/h or 5 ml/kg/h	25 ml/8 h or 0.4–0.5 ml/kg/h	125 ml/h
Bolus feedings			
0–1	60–80 ml q4h or 10–15 ml/kg q feed	20–40 ml q 4 h	80–240 ml q4h or 20–30 ml/kg/feed
1–6	80–120 ml q4h or 5–10 ml/kg q feed	40–60 ml q 4 h	280–375 ml q4h or 15–20 ml/kg/feed
6–14	120–160 ml q4h or 3–5 ml/kg q feed	60–80 ml q 4 h	430–520 ml q4h or 10–20 ml/kg/feed
>14	200 ml q4h or 3 ml/kg q feed	100 ml q 4 h	500 ml q4h or 10 ml/kg/feed

Note: Calculating rates based on age and per kilogram body weight is useful for small-for-age patients
[a]Goal is expected maximum that child will tolerate; individual children may tolerate higher rates or volumes. Proceed cautiously for jejunal feedings. Goals for individual children should be based on energy requirements and energy density of feeding and therefore may be lower than expected maximum

ensure the feeds are well tolerated, children should be monitored for complications such as vomiting or diarrhea when changes to either the hourly infusion rate or caloric density of the feed are made [31, 91].

Gastrointestinal Disturbances in Children with CKD

Children with CKD often have recurrent vomiting [92]. Vomiting may occur secondary to gastroesophageal reflux, increased intra-abdominal pressure from dialysate during PD, delayed gastric emptying, and inadequate clearance of polypeptide hormones such as gastrin [20, 76]. In a study of 12 infants with CKD who presented with decreased oral intake and vomiting, gastroesophageal reflux was found to be present in 8/12 (67%) and delayed gastric emptying and gastric dysrhythmia in 55% [93]. Another study of 22 infants with CKD and poor oral intake found gastroesophageal reflux in over 70% [94]. Other causes for vomiting may be related to the formula composition or method of feeding. These include formula that is too concentrated, excessive volume or rate of administration, or an intolerance to the formula [31].

Impaired Oromotor Development

As many infants with CKD receive a large portion, if not all, of their feeds via a feeding tube, the age at which feeding skills develop and progress is often delayed due to a lack of feeding experience [23]. Voluntary oral intake decreases in infants with CKD as renal disease progresses [15]. Children who receive tube feeds for a prolonged period of time, especially for greater than 1 year, need help learning to feed orally [77]. Common problems include difficulty latching to the nipple while bottle feeding, poor coordination with sucking and swallowing, gagging with bottle feeds, and feeding aversion which presents as completely refusing the bottle or self-induced gagging when offered oral feeds [23, 77].

Children who received primarily NG feeds are at risk of oral hypersensitivity, a hyperactive gag reflex, and poor oromotor coordination [95]. All children who receive tube feeding should be encouraged to continue with some oral intake or oral stimulation such as sucking and tasting food, because limited practice with oral feeding may impair oral motor skill development [2]. In a study of preterm infants (without CKD), those who received oral stimulation while tube fed were able to transition to oral feeding sooner than

those who did not [96]. Participating in family meals, even if only to play with food and observe others eating, may also be beneficial.

Transition to Oral Feeding

Transitioning from tube feeds to an exclusively oral diet should be the goal after kidney transplantation [5]. Almost all patients across numerous studies were able to switch to exclusive oral feeding within a median of 2 to 10 months post-transplant [28, 59, 77, 97, 98] (Table 27.3). The largest study [28], which included 66 children who had been tube fed a median of 1.9 years, reported 64/66 (96.7%) were able to transition off enteral feeds within 6 months post kidney transplantation. Reasons for a longer transition to oral feeds, or an inability to stop tube feeds, included cognitive impairments or other significant comorbidities [23, 28, 77, 98]. Younger age at initiation of NG feeds, particularly initiation at under 1 year of age, was also associated with greater difficulty in transitioning to oral feeding [97]. To help with the transition to oral feeding, Warady et al. [77] recommend a multidisciplinary approach including support from a renal dietician and a clinical psychologist. Feeding support groups may be helpful to encourage and support parents through the process [98].

Intradialytic Parenteral Nutrition (IDPN) and Intraperitoneal Nutritional Supplementation

As CKD progresses in severity, anorexia often worsens, leading to inability to maintain adequate oral nutritional intake [2]. While enteral supplementation is the preferred method, barriers such as strict fluid restrictions may prevent nutritional goals from being met [99]. In such instances, intradialytic parenteral nutrition (IDPN) may be considered for those on hemodialysis [100]. IDPN is a noninvasive method of providing nutrition to hemodialysis patients. IDPN usually includes a mixture of amino acids, dextrose, and lipid emulsion and is administered during each dialysis session [101] through the venous limb; extra volume can be removed with ultrafiltration [102]. IDPN is only able to provide a small percentage of daily caloric needs, and thus it must be considered a supplement [102, 103].

IDPN has the following advantages: it provides a significant amount of protein in a short period of time; can be administered during scheduled hemodialysis sessions, minimizing effort

Table 27.3 Summary of studies assessing transitioning to oral feeding post-transplantation

Study year published	Size of cohort	Age at initiation of tube feeding	Length of time tube feeding	Time to transition to oral feeds post kidney transplant	Outcome proportion transitioned to full oral feeds post-transplantation
Warady et al. [77] 1990	$N = 8$	0–1 month	19.8 ± 13.5 months	2* (1 to 18) months	6/8
Dello Strologo et al. [97] 1997	$N = 12$	6.5* (0.16 to 48) months	18.4 ± 8 months	6* (0 to 24) months	12/12
Coleman et al. [59] 1998	$N = 22$	2.3* (0.2 to 10.3) years	14.5 (2.5 to 56) months	2.8 (0.8 to 8.3) months	13/22
Kari et al. [28] 2000	$N = 66$	0.7* (0 to 4.5) years	1.9* (0.1 to 6.8) years	Within 6 months after transplantation	64/66
Pugh et al. [98] 2006	$N = 22$	1.7* (0.25 to 4.25) years	2.9* (1.0 to 5.58) years in those <2 years 1.7* (0.5 to 6.0) in those 2–5 years	Within 10 months after transplantation	18/22

This table was adapted from Samaan et al. [23]
Results presented as mean ± standard deviation or * median with range

required by the patient or family; and requires no separate access. Complications of IDPN include hyperglycemia [104], hyperlipidemia (defined as a 50% increase in baseline triglyceride levels), hypersensitivity (egg allergy), and symptoms of refeeding syndrome such as hypokalemia and hypophosphatemia [102]. Nausea, vomiting, chest pain, and headaches have also been reported [104–107]. The high cost is also a disadvantage [101, 102].

KDOQI recommends a trial of IDPN in malnourished children, defined as BMI-for-height-age < fifth percentile, who are receiving maintenance dialysis and are unable to meet their nutritional requirements through oral and tube feeds [2] (Grade C evidence).

Studies on the use of IDPN [99, 105–108] as a means of improving weight or BMI were all limited by small sample sizes (range 3–15 patients) and were mainly restricted to older children and young adults (median age range 12.5–20 years) (Table 27.4). Only one study [105] showed a significant increase in weight and BMI. Goldstein et al. [105] reported a reversal in weight loss with progressive weight gain within 6 weeks of initiating IDPN among the three adolescents included. A subsequent study [106] from the same center showed a nonstatistically significant increase in weight and BMI among six of the nine participants with gastrointestinal illnesses. The largest ($N = 15$) and most recent study [99] reported a significant improvement in dry weight after starting IDPN consisting only of lipids ($p = 0.04$); however, there were no significant improvements in either weight-for-age SDS or height-for-age SDS.

Patients treated with chronic PD are at risk of protein loss [13, 109–113]. While intraperitoneal amino acid supplementation is an option for children on PD [13, 22, 24], it has been trialed in only a few small pediatric studies (fewer than ten children), most of short duration (less than 12 months) [109–111, 113, 114]. Two of these studies showed no improvement in growth [110, 111], while the other two studies did not assess weight or height [109, 113]. A case report of a 5-year-old child on chronic PD treated with 1.1% amino acid solution for a year showed significant improvements in appetite, weight, and height velocity [114]. Given the paucity of studies to date, whether intraperitoneal supplementation has a beneficial role in the pediatric population remains to be determined.

Summary

Infants with CKD often have poor appetite, leading to low caloric intake and ultimately poor growth. Tube feeding is necessary to achieve adequate caloric intake in the majority of infants with advanced CKD. Even infants with ESRD can achieve normal growth and weight gain with preemptive enteral feeding intervention. Early intervention is critical for infants given the impact poor nutritional intake can have on neurocognitive development as well as growth. Older children may also benefit from tube feeding, but this is rarely necessary. Gastrostomy tube feeding may be more effective in improving linear growth compared to NG feeding; however, prospective studies are needed. IDPN may be considered for children on hemodialysis who are unable to meet energy requirements through oral or tube feeding. However IDPN is costly and has not been as well-studied in the pediatric ESRD population.

Table 27.4 Summary of studies assessing the use of intradialytic parenteral nutrition and intraperitoneal nutritional supplementation among children with end-stage renal disease

Intradialytic parenteral nutrition						
Study year published	**Population**	**Study design**	**Intervention**	**Duration**	**Outcome(s) of interest**	**Conclusion**
Zachwieja [108] 1994	*N* = 10 Age: 10 to 18 years Hemodialysis Healthy children *N* = 134 aged 6 to 18 years to provide reference for normal plasma levels of free amino acids	Case series	Amino acid supplementation dosed at 0.25 g/kg and carnitine 25 mg/kg after dialysis Three times per week hemodialysis sessions of 4–5 hours Comparison group of healthy controls	Total 3 months duration; 1 month supplemented, o1 month taken off, 1 month supplemented again	Plasma levels of essential amino acid did not improve Mean increase of 4.5 ± 1.7% in dry body weight from the start of study to end among children receiving amino acid and carnitine supplementation	No significant improvement
Goldstein et al. [105] 2002	*N* = 3 Age: 18* (17 to 25) years Hemodialysis	Case series	IDPN composed of dextrose (70%), novoamine (15%), and 20% lipid solution RDA 150%	Compared 4 months prior to starting IDPN with the first 5 months of IDPN	Monthly percent change in weight and BMI in pre-IDPN period versus IDPN interval	Weight decreased 0.6 ± 2.7% per month and BMI decreased 1.3 ± 2.7% per month pre-IDPN Weight increased 1.8 ± 2.1% per month and BMI increased 1.3 ± 2.1% per month during IDPN
Krause et al. [107] 2002	N = 4 Age: 17* (4 to 18) years Hemodialysis	Case series	IDPN composed of amino acids (8.5%), glucose (10 or 15% dextrose), and 20% fat emulsion (max 0.2 g/kg/day) administered three times per week for 4 hours	7 to 12 weeks	There was no change in weight or BMI immediately after the start of IDPN There was an increase in body weight (from a mean of 25 to 26.7 kg) and BMI (from a mean of 13.5 to 16.6 kg/m^2) 3 months after cessation of IDPN treatment	Short-term IDPN improved appetite and oral caloric intake

Orellana et al. [106] 2005	*N* = 9 Age: 19.9 (16 to 26) years Hemodialysis	Case series	IDPN composed of dextrose (70%), novoamine (15%), and 20% lipid solution three times per week	Median of 9 months, range of 3 to 22 months	Six of nine participants had an increase in weight and BMI, which was measured as the mean monthly change for the 5 months before and up to 5 months after the start of IDPN	Overall nonsignificant change in percent body weight and BMI
Haskin et al. [99] 2017	*N* = 15 Age: 12.5* (1 to 20) years On maintenance hemodialysis, a median of 4.3 months IQR [3.4, 23.6] prior to starting intralipid therapy	Case series	Intradialytic intralipid therapy Median dose 0.5 g/kg, IQR [0.23, 1.0 g/kg]	Median 3 months, IQR [4.5, 7.25]	Dry weight-for-age SDS at start −1.17 ± 1.12 and at the end −1.22 ± 1.03 $p = 0.59$ BMI-for-age SDS at the start of therapy −0.89 ± 1.37 and at the end −0.9 ± 1.39 p = 0.9 Height-for-age SDS at the start −0.98 ± 0.94 and at the end −1.06 ± 0.9 $p = 0.5$	No statistically significant improvement in dry weight, BMI-, or height-for age SDS
Intraperitoneal amino acid supplementation						
Study year published	**Population**	**Study design**	**Intervention**	**Duration**	**Outcome(s) of interest**	**Conclusion**
Canepa [110] 1991	*N* = 8 Age: 7.9 (1.1 to 15.8) years Chronic ambulatory peritoneal dialysis	Case series: Pre-post comparison Age-matched children (*N* = 10) without CKD provided reference for serum levels	1% amino acid solution consisting of 16 amino acids	Total 12–18 months: 6 months dextrose followed by 6–12 months of amino acid solution for morning exchange	Height-for-age did not show significant change before or after amino acid dialysis	Growth was comparable in the dextrose and amino acid dialysis periods
Qamar [111] 1994	*N* = 7 Age: 9.3 (0.7 to 16.5) years Chronic ambulatory peritoneal dialysis	Case series: Pre-post comparison	Amino acid dialysate containing ten essential and four nonessential amino acids compared to 2.5% dextrose dialysate	Total 6 months: 3 months amino acid or dextrose then crossed over to alternate regimen for 3 months	No significant difference in the change in height between those receiving amino acid dialysate versus glucose	Growth rates were comparable in the amino acid and glucose dialysis groups

Results presented as mean ± standard deviation or * median with range
IDPN intradialytic parenteral nutrition, *RDA* recommended daily allowance, *IQR* interquartile range

References

1. Iorember FM. Malnutrition in chronic kidney disease. Front Pediatr. 2018;6:161.
2. Working Group. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53 (3 Suppl 2):S11–104.
3. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
4. Furth SL, Hwang W, Yang C, Neu AM, Fivush BA, Powe NR. Growth failure, risk of hospitalization and death for children with end-stage renal disease. Pediatr Nephrol. 2002;17(6):450–5.
5. Nelms CL. Optimizing enteral nutrition for growth in pediatric Chronic Kidney Disease (CKD). Front Pediatr. 2018;6:214.
6. Furth SL, Stablein D, Fine RN, Powe NR, Fivush BA. Adverse clinical outcomes associated with short stature at dialysis initiation: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics. 2002;109(5):909–13.
7. Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D. Stature in children with chronic kidney disease: analysis of NAPRTCS database. Pediatr Nephrol. 2006;21(6):793–9.
8. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. Clin Kidney J. 2016;9(4):583–91.
9. Silverstein DM. Growth and nutrition in pediatric chronic kidney disease. Front Pediatr. 2018;6:205.
10. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: the 2001 annual report of the NAPRTCS. Pediatr Nephrol. 2003;18(8):796–804.
11. Mekahli D, Shaw V, Ledermann SE, Rees L. Long-term outcome of infants with severe chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(1):10–7.
12. Rees L, Azocar M, Borzych D, Watson AR, Buscher A, Edefonti A, et al. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22(12):2303–12.
13. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702.
14. Foster BJ, McCauley L, Mak RH. Nutrition in infants and very young children with chronic kidney disease. Pediatr Nephrol. 2012;27(9):1427–39.
15. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR. Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol. 2000;15(3–4):259–65.
16. Bellisle F, Dartois AM, Kleinknecht C, Broyer M. Alteration of the taste for sugar in renal insufficiency: study in the child. Nephrologie. 1995;16(2):203–8.
17. Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. Pediatr Nephrol. 2010;25(4):711–24.
18. Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. Kidney Int. 2006;69(5):794–7.
19. Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, et al. Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. J Am Soc Nephrol. 1998;9(6):1074–9.
20. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. Pediatr Nephrol. 2013;28(4):527–36.
21. Mak RH, Cheung W, Purnell J. Ghrelin in chronic kidney disease: too much or too little? Perit Dial Int. 2007;27(1):51–5.
22. Paglialonga F, Edefonti A. Nutrition assessment and management in children on peritoneal dialysis. Pediatr Nephrol. 2009;24(4):721–30.
23. Samaan SSD. Oral feeding challenges in infants with chronic kidney disease. ICAN: Infant Child Adolesc Nutrit. 2014;6(3):164–71.
24. Brewer ED. Pediatric experience with intradialytic parenteral nutrition and supplemental tube feeding. Am J Kidney Dis. 1999;33(1):205–7.
25. Fine RN. Growth in children undergoing continuous ambulatory peritoneal dialysis/continuous cycling peritoneal dialysis/automated peritoneal dialysis. Perit Dial Int. 1993;13(Suppl 2):S247–50.
26. Brewer ED. Supplemental enteral tube feeding in infants undergoing Dialysis – indications and outcome. Semin Dial. 1994;7(6):429–34.
27. Claris-Appiani A, Ardissino GL, Dacco V, Funari C, Terzi F. Catch-up growth in children with chronic renal failure treated with long-term enteral nutrition. JPEN J Parenter Enteral Nutr. 1995;19(3):175–8.
28. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7.
29. Ledermann SE, Shaw V, Trompeter RS. Long-term enteral nutrition in infants and young children with chronic renal failure. Pediatr Nephrol. 1999;13(9):870–5.
30. Warady BA. Growth retardation in children with chronic renal insufficiency. J Am Soc Nephrol. 1998;9(12 Suppl):S85–9.
31. Foster BJ, Borzych D. Technical aspects of Controlled Enteral Nutrition in Pediatric Dialysis. In: Warady BA, Schaefer F, Fine RN, Alexander R, editors. Pediatric Dialysis: Springer; New York. 2012. p. 439–51.
32. Haffner D, Zivicnjak M. Pubertal development in children with chronic kidney disease. Pediatr Nephrol. 2017;32(6):949–64.
33. Schaefer F, Seidel C, Binding A, Gasser T, Largo RH, Prader A, et al. Pubertal growth in chronic renal failure. Pediatr Res. 1990;28(1):5–10.

34. Karlberg J. On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr Scand Suppl. 1989;356:26–37.
35. Foreman JW, Abitbol CL, Trachtman H, Garin EH, Feld LG, Strife CF, et al. Nutritional intake in children with renal insufficiency: a report of the growth failure in children with renal diseases study. J Am Coll Nutr. 1996;15(6):579–85.
36. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2012;27(2):173–81.
37. Mitch WE. Insights into the abnormalities of chronic renal disease attributed to malnutrition. J Am Soc Nephrol. 2002;13(Suppl 1):S22–7.
38. Mak RH, Cheung W, Cone RD, Marks DL. Mechanisms of disease: cytokine and adipokine signaling in uremic cachexia. Nat Clin Pract Nephrol. 2006;2(9):527–34.
39. Mak RH, Cheung W. Cachexia in chronic kidney disease: role of inflammation and neuropeptide signaling. Curr Opin Nephrol Hypertens. 2007;16(1):27–31.
40. Mak RH, Cheung W. Energy homeostasis and cachexia in chronic kidney disease. Pediatr Nephrol. 2006;21(12):1807–14.
41. Johnson RJ, Warady BA. Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy. Pediatr Nephrol. 2013;28(8):1283–91.
42. Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB, et al. Neurocognitive outcomes in children with chronic kidney disease: current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev. 2006;12(3):208–15.
43. Gipson DS, Hooper SR, Duquette PJ, Wetherington CE, Stellwagen KK, Jenkins TL, et al. Memory and executive functions in pediatric chronic kidney disease. Child Neuropsychol. 2006;12(6):391–405.
44. Hulstijn-Dirkmaat GM, Damhuis IH, Jetten ML, Koster AM, Schroder CH. The cognitive development of pre-school children treated for chronic renal failure. Pediatr Nephrol. 1995;9(4):464–9.
45. Greenbaum LA, Warady BA, Furth SL. Current advances in chronic kidney disease in children: growth, cardiovascular, and neurocognitive risk factors. Semin Nephrol. 2009;29(4):425–34.
46. Rotundo A, Nevins TE, Lipton M, Lockman LA, Mauer SM, Michael AF. Progressive encephalopathy in children with chronic renal insufficiency in infancy. Kidney Int. 1982;21(3):486–91.
47. McGraw ME, Haka-Ikse K. Neurologic-developmental sequelae of chronic renal failure in infancy. J Pediatr. 1985;106(4):579–83.
48. Warady BA, Kriley M, Lovell H, Farrell SE, Hellerstein S. Growth and development of infants with end-stage renal disease receiving long-term peritoneal dialysis. J Pediatr. 1988;112(5):714–9.
49. Geary DF, Ikse KH, Coulter P, Secker D. The role of nutrition in neurologic health and development of infants with chronic renal failure. Adv Perit Dial. 1990;6:252–4.
50. Ratsch IM, Catassi C, Verrina E, Gusmano R, Appiani A, Bettinelli A, et al. Energy and nutrient intake of patients with mild-to-moderate chronic renal failure compared with healthy children: an Italian multicentre study. Eur J Pediatr. 1992;151(9):701–5.
51. Norman LJ, Macdonald IA, Watson AR. Optimising nutrition in chronic renal insufficiency–growth. Pediatr Nephrol. 2004;19(11):1245–52.
52. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12(11):2418–26.
53. Zadik Z, Frishberg Y, Drukker A, Blachar Y, Lotan D, Levi S, et al. Excessive dietary protein and suboptimal caloric intake have a negative effect on the growth of children with chronic renal disease before and during growth hormone therapy. Metabolism. 1998;47(3):264–8.
54. Tom A, McCauley L, Bell L, Rodd C, Espinosa P, Yu G, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134(4):464–71.
55. Ledermann SE, Scanes ME, Fernando ON, Duffy PG, Madden SJ, Trompeter RS. Long-term outcome of peritoneal dialysis in infants. J Pediatr. 2000;136(1):24–9.
56. Cansick J, Waller S, Ridout D, Rees L. Growth and PTH in prepubertal children on long-term dialysis. Pediatr Nephrol. 2007;22(9):1349–54.
57. Waller S, Ledermann S, Trompeter R, van't Hoff W, Ridout D, Rees L. Catch-up growth with normal parathyroid hormone levels in chronic renal failure. Pediatr Nephrol. 2003;18(12):1236–41.
58. Ramage IJ, Geary DF, Harvey E, Secker DJ, Balfe JA, Balfe JW. Efficacy of gastrostomy feeding in infants and older children receiving chronic peritoneal dialysis. Perit Dial Int. 1999;19(3):231–6.
59. Coleman JE, Watson AR, Rance CH, Moore E. Gastrostomy buttons for nutritional support on chronic dialysis. Nephrol Dial Transplant. 1998;13(8):2041–6.
60. Wassner SJ, Kulin HE. Diminished linear growth associated with chronic salt depletion. Clin Pediatr (Phila). 1990;29(12):719–21.
61. Sienna JL, Saqan R, Teh JC, Frieling ML, Secker D, Cornelius V, et al. Body size in children with chronic kidney disease after gastrostomy tube feeding. Pediatr Nephrol. 2010;25(10):2115–21.
62. Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model. I. From birth to three years. Acta Paediatr Scand. 1987;76(3):478–88.
63. Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a mathematical model. II. From 3 to 21 years of age. Acta Paediatr Scand Suppl. 1987;337:12–29.
64. Karlberg J, Schaefer F, Hennicke M, Wingen AM, Rigden S, Mehls O. Early age-dependent growth impairment in chronic renal failure. European

Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol. 1996;10(3):283–7.
65. Foster BJ, Martz K, Gowrishankar M, Stablein D, Al-Uzri A. Weight and height changes and factors associated with greater weight and height gains after pediatric renal transplantation: a NAPRTCS study. Transplantation. 2010;89(9):1103–12.
66. Bonthuis M, van Stralen KJ, Verrina E, Groothoff JW, Alonso Melgar A, Edefonti A, et al. Underweight, overweight and obesity in paediatric dialysis and renal transplant patients. Nephrol Dial Transplant. 2013;28(Suppl 4):iv195–204.
67. Arnold WC, Danford D, Holliday MA. Effects of caloric supplementation on growth in children with uremia. Kidney Int. 1983;24(2):205–9.
68. Sturm LD. Implementation and evaluation of a home gavage program for preterm infants. Neonatal Netw. 2005;24(4):21–5.
69. Ortenstrand A, Winbladh B, Nordstrom G, Waldenstrom U. Early discharge of preterm infants followed by domiciliary nursing care: parents' anxiety, assessment of infant health and breastfeeding. Acta Paediatr. 2001;90(10):1190–5.
70. Collins CT, Makrides M, McPhee AJ. Early discharge with home support of gavage feeding for stable preterm infants who have not established full oral feeds. Cochrane Database Syst Rev. 2003;4:CD003743.
71. Strife CF, Quinlan M, Mears K, Davey ML, Clardy C. Improved growth of three uremic children by nocturnal nasogastric feedings. Am J Dis Child. 1986;140(5):438–43.
72. Rees L, Rigden SP, Ward GM. Chronic renal failure and growth. Arch Dis Child. 1989;64(4):573–7.
73. Braegger C, Decsi T, Dias JA, Hartman C, Kolacek S, Koletzko B, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;51(1):110–22.
74. Lyman B, Kemper C, Northington L, Yaworski JA, Wilder K, Moore C, et al. Use of temporary enteral access devices in hospitalized neonatal and pediatric patients in the United States. JPEN J Parenter Enteral Nutr. 2016;40(4):574–80.
75. Irving SY, Lyman B, Northington L, Bartlett JA, Kemper C, Novel Project Work G. Nasogastric tube placement and verification in children: review of the current literature. Crit Care Nurse. 2014;34(3):67–78.
76. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25(4):699–704.
77. Warady BA, Kriley M, Belden B, Hellerstein S, Alan U. Nutritional and behavioural aspects of nasogastric tube feeding in infants receiving chronic peritoneal dialysis. Adv Perit Dial. 1990;6:265–8.
78. McClave SA, DeMeo MT, DeLegge MH, DiSario JA, Heyland DK, Maloney JP, et al. North American summit on aspiration in the critically ill patient: consensus statement. JPEN J Parenter Enteral Nutr. 2002;26(6 Suppl):S80–5.
79. Volpe A, Malakounides G. Feeding tubes in children. Curr Opin Pediatr. 2018;30(5):665–70.
80. Ramage IJ, Harvey E, Geary DF, Hebert D, Balfe JA, Balfe JW. Complications of gastrostomy feeding in children receiving peritoneal dialysis. Pediatr Nephrol. 1999;13(3):249–52.
81. Wood EG, Bunchman TE, Khurana R, Fleming SS, Lynch RE. Complications of nasogastric and gastrostomy tube feedings in children with end stage renal disease. Adv Perit Dial. 1990;6:262–4.
82. Wirth R, Bauer J, Sieber C. Necrotizing Candida infection after percutaneous endoscopic gastrostomy: a fatal and rare complication. JPEN J Parenter Enteral Nutr. 2008;32(3):285–7.
83. Vervloessem D, van Leersum F, Boer D, Hop WC, Escher JC, Madern GC, et al. Percutaneous endoscopic gastrostomy (PEG) in children is not a minor procedure: risk factors for major complications. Semin Pediatr Surg. 2009;18(2):93–7.
84. Khalil ST, Uhing MR, Duesing L, Visotcky A, Tarima S, Nghiem-Rao TH. Outcomes of infants with home tube feeding: comparing nasogastric vs gastrostomy tubes. JPEN J Parenter Enteral Nutr. 2017;41(8):1380–5.
85. Ricciuto A, Baird R, Sant'Anna A. A retrospective review of enteral nutrition support practices at a tertiary pediatric hospital: a comparison of prolonged nasogastric and gastrostomy tube feeding. Clin Nutr. 2015;34(4):652–8.
86. Warady BA, Bakkaloglu S, Newland J, Cantwell M, Verrina E, Neu A, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86.
87. Ledermann SE, Spitz L, Moloney J, Rees L, Trompeter RS. Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol. 2002;17(4):246–50.
88. Jafri NS, Mahid SS, Minor KS, Idstein SR, Hornung CA, Galandiuk S. Meta-analysis: antibiotic prophylaxis to prevent peristomal infection following percutaneous endoscopic gastrostomy. Aliment Pharmacol Ther. 2007;25(6):647–56.
89. Murugasu B, Conley SB, Lemire JM, Portman RJ. Fungal peritonitis in children treated with peritoneal dialysis and gastrostomy feeding. Pediatr Nephrol. 1991;5(5):620–1.
90. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ, European Paediatric Dialysis Working G. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). Pediatr Nephrol. 2013;28(9):1739–48.
91. Spinozzi N, Nelson P. Nutrition Suppot in the newborn intensive care unit. J Ren Nutr. 1996;6:188–97.
92. Ravelli AM. Gastrointestinal function in chronic renal failure. Pediatr Nephrol. 1995;9(6):756–62.

93. Ravelli AM, Ledermann SE, Bisset WM, Trompeter RS, Barratt TM, Milla PJ. Foregut motor function in chronic renal failure. Arch Dis Child. 1992;67(11):1343–7.
94. Ruley EJ, Bock GH, Kerzner B, Abbott AW, Majd M, Chatoor I. Feeding disorders and gastroesophageal reflux in infants with chronic renal failure. Pediatr Nephrol. 1989;3(4):424–9.
95. Kamen RS. Impaired development of oral-motor functions required for normal oral feeding as a consequence of tube feeding during infancy. Adv Perit Dial. 1990;6:276–8.
96. Fucile S, Gisel E, Lau C. Oral stimulation accelerates the transition from tube to oral feeding in preterm infants. J Pediatr. 2002;141(2):230–6.
97. Dello Strologo L, Principato F, Sinibaldi D, Appiani AC, Terzi F, Dartois AM, et al. Feeding dysfunction in infants with severe chronic renal failure after long-term nasogastric tube feeding. Pediatr Nephrol. 1997;11(1):84–6.
98. Pugh P, Watson AR. Transition from gastrostomy to oral feeding following renal transplantation. Adv Perit Dial. 2006;22:153–7.
99. Haskin O, Sutherland SM, Wong CJ. The effect of intradialytic Intralipid therapy in pediatric hemodialysis patients. J Ren Nutr. 2017;27(2):132–7.
100. Warady BA, Neu AM, Schaefer F. Optimal care of the infant, child, and adolescent on dialysis: 2014 update. Am J Kidney Dis. 2014;64(1):128–42.
101. Sabatino A, Regolisti G, Antonucci E, Cabassi A, Morabito S, Fiaccadori E. Intradialytic parenteral nutrition in end-stage renal disease: practical aspects, indications and limits. J Nephrol. 2014;27(4):377–83.
102. Juarez MD. Intradialytic parenteral nutrition in pediatrics. Front Pediatr. 2018;6:267.
103. Cherry N, Shalansky K. Efficacy of intradialytic parenteral nutrition in malnourished hemodialysis patients. Am J Health Syst Pharm. 2002;59(18):1736–41.
104. Dudley J, Rogers R, Sealy L. Renal consequences of parenteral nutrition. Pediatr Nephrol. 2014;29(3):375–85.
105. Goldstein SL, Baronette S, Gambrell TV, Currier H, Brewer ED. nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. Pediatr Nephrol. 2002;17(7):531–4.
106. Orellana P, Juarez-Congelosi M, Goldstein SL. Intradialytic parenteral nutrition treatment and biochemical marker assessment for malnutrition in adolescent maintenance hemodialysis patients. J Ren Nutr. 2005;15(3):312–7.
107. Krause I, Shamir R, Davidovits M, Frishman S, Cleper R, Gamzo Z, et al. Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. J Ren Nutr. 2002;12(1):55–9.
108. Zachwieja J, Duran M, Joles JA, Allers PJ, van de Hurk D, Frankhuisen JJ, et al. Amino acid and carnitine supplementation in haemodialysed children. Pediatr Nephrol. 1994;8(6):739–43.
109. Hanning RM, Balfe JW, Zlotkin SH. Effectiveness and nutritional consequences of amino acid-based vs glucose-based dialysis solutions in infants and children receiving CAPD. Am J Clin Nutr. 1987;46(1):22–30.
110. Canepa A, Perfumo F, Carrea A, Giallongo F, Verrina E, Cantaluppi A, et al. Long-term effect of amino-acid dialysis solution in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1991;5(2):215–9.
111. Qamar IU, Levin L, Balfe JW, Balfe JA, Secker D, Zlotkin S. Effects of 3-month amino acid dialysis compared to dextrose dialysis in children on continuous ambulatory peritoneal dialysis. Perit Dial Int. 1994;14(1):34–41.
112. Canepa A, Perfumo F, Gusmano R. Amino acids solutions and nutritional impact in children. Contrib Nephrol. 1999;129:195–204.
113. Canepa A, Carrea A, Menoni S, Verrina E, Trivelli A, Gusmano R, et al. Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. Kidney Int. 2001;59(5):1967–73.
114. Brem AS, Maaz D, Shemin DG, Wolfson M. Use of amino acid peritoneal dialysate for one year in a child on CCPD. Perit Dial Int. 1996;16(6):634–6.
115. Ellis EN, Yiu V, Harley F, Donaldson LA, Hand M, Warady BA, et al. The impact of supplemental feeding in young children on dialysis: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 2001;16(5):404–8.
116. US Renal Data System 1998 Annual Data Report. Bethesda: National Institute of Diabetes and Digestive and Kidney Disease; 1998.
117. Abitbol CL, Zilleruelo G, Montane B, Strauss J. Growth of uremic infants on forced feeding regimens. Pediatr Nephrol. 1993;7(2):173–7.
118. Waller SC, Ridout D, Cantor T, Rees L. Parathyroid hormone and growth in children with chronic renal failure. Kidney Int. 2005;67(6):2338–45.
119. Hijazi R, Abitbol CL, Chandar J, Seeherunvong W, Freundlich M, Zilleruelo G. Twenty-five years of infant dialysis: a single center experience. J Pediatr. 2009;155(1):111–7.
120. Prestidge C, Ronaldson J, Wong W, Stack M, Kara T. Infectious outcomes following gastrostomy in children receiving peritoneal dialysis. Pediatr Nephrol. 2015;30(5):849–54.

28

Growth and Pubertal Development in Children and Adolescents Receiving Chronic Dialysis

Dieter Haffner and John D. Mahan

Introduction

Body growth is an exceedingly complex and temporally regulated biological process which depends on adequate nutrition as well as metabolic and endocrine homeostasis. Infancy, mid-childhood, and puberty are characterized by distinct growth patterns (Fig. 28.1), with nutrition being most critical during infancy, the somatotropic hormone axis during mid-childhood, and the gonadotropic hormones during puberty [1, 2]. Chronic kidney disease (CKD) interferes with this complex network at various levels, and pediatric patients are at high risk of growth failure and disproportionate growth patterns (Fig. 28.2) [3, 4]. Approximately 50% of children requiring renal replacement therapy (RRT) before their 13th birthday have a final height below the normal range [5–12]. The younger the patient at onset of CKD, the higher is the risk of severe growth retardation and stunting, putting additional strain on patients and families and making psychosocial integration even more difficult [13]. Beyond this, the degree of growth retardation and mortality are closely associated, suggesting that the growth rate is a sensitive marker of overall patient wellbeing [14–16]. There is, however, evidence that alongside advancements in the medical and technical management of CKD and RRT, height prognosis has substantially improved during the past few decades [5, 8, 9, 17]. Yet this is not the case in all parts of the world, particularly in those regions with inadequate local resources, where height prognosis remains dismally low [5, 18]. Beyond careful monitoring of growth, adequate measures to prevent and treat growth failure are of crucial importance for pediatric CKD patients at all ages and any degree of renal failure. In fact, while this chapter focuses on the growth of children on maintenance dialysis, it should be emphasized that early intervention is critical since measures such as the correction of malnutrition and CKD-mineral bone disease (CKD-MBD) and treatment with recombinant human growth hormone (rhGH) are considerably more effective when started before the initiation of dialysis. Unfortunately, there is still substantial variation in pediatric nephrology practice in addressing short stature and rhGH utilization in children with CKD [19]. Standardized care is of utmost importance in order to improve growth outcomes in short children with CKD [20–22].

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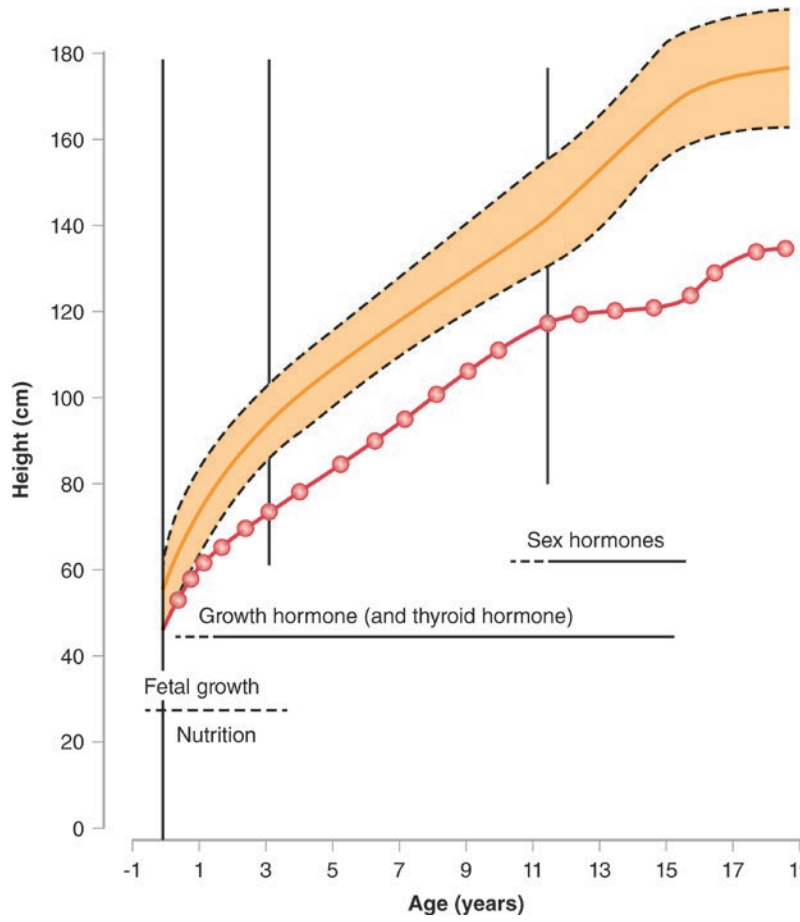


Fig. 28.1 Typical growth pattern in congenital chronic kidney disease (red dots) if measures such as adequate nutrition and growth hormone therapy and early renal transplantation with minimized steroid exposure are not provided. Relative loss in the nutrient-dependent infantile and gonadal hormone-dependent puberty phases and percentile-parallel growth in the mainly GH-dependent growth period in mid-childhood are shown. The shaded area represents the normal range, 3rd to 97th centiles. (Reproduced with permission of Ref. [2])

Final Height and Height Prediction

When interpreting the final heights of patients treated for CKD in childhood, it has to be remembered that data obtained at any time will reflect treatment practices spanning the previous two decades. Furthermore, most reports of final heights do not or incompletely discriminate according to patient characteristics (e.g., diagnoses, ages of onset of CKD, types, and duration of RRT) and, in particular registries, do not separate out children with comorbidities that affect growth in their own right. With those limitations in mind, reduced adult heights have been reported in up to 50% of pediatric CKD patients [5, 7, 8, 11, 12, 23–26]. Mean final heights vary from 148 to 158 cm for females and 162 to 168 cm for males (with third centiles of 151 and 163 cm, respectively).

However, there is evidence that over the years, the final height in ESKD patients is improving [5, 7, 9]. This is likely due to a combination of factors such as better growth attained pre-transplant as a result of the provision of adequate nutrition and rhGH therapy, preemptive transplantation thus avoiding dialysis, and the development of protocols that minimize the use of corticosteroids. In Germany, the overall mean standardized height in children on RRT has increased over the past 20 years from −3.0 SD to −1.8 SD [9]. An analysis from the ESPN/EDTA registry revealed an improvement in final height from −2.06 SDS in children who reached adulthood in 1990–1995 to −1.33 SDS in 2006–2011 (Fig. 28.3) [5]. Older age at the start of RRT, starting RRT more recently, cumulative time with a transplant, and greater height SDS at initiation of RRT were independently associated with a higher final adult

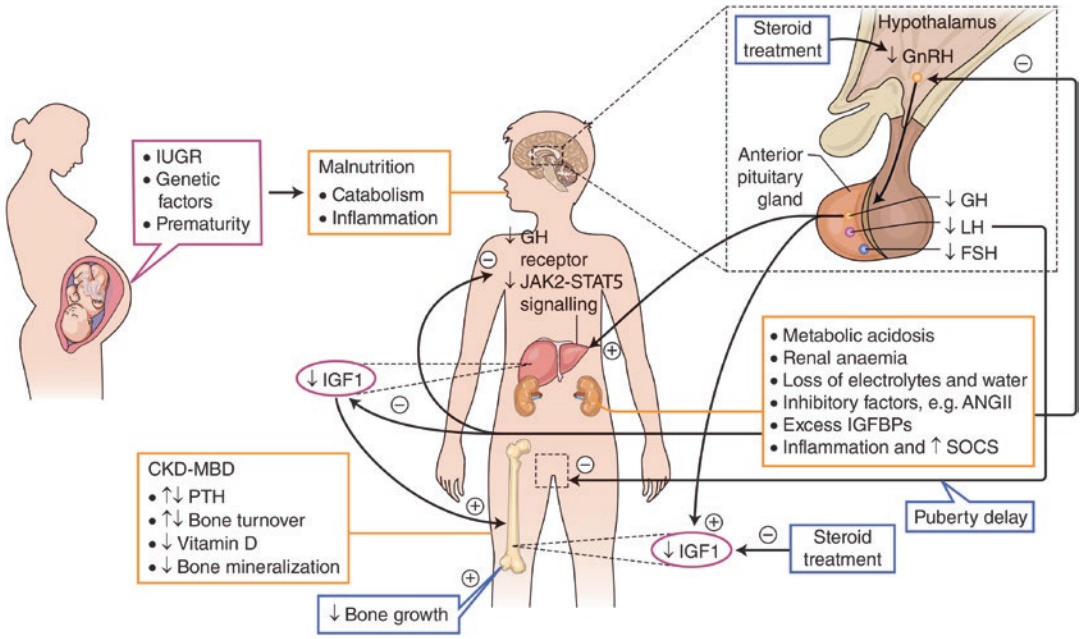


Fig. 28.2 The etiology of growth failure in CKD is multifactorial and includes intrauterine growth restriction (IUGR), genetic factors such as parental height and primary renal disease, prematurity, and malnutrition which especially limits growth in children with congenital CKD. Mineral and bone disorder (CKD-MBD), metabolic acidosis, anemia, loss of electrolytes and water, and disturbances of the somatotropic and gonadotropic hormone axes are additional factors. CKD is a state of growth hormone (GH) insensitivity, characterized by deficiency of functional insulin-like growth factor I (IGF-I), to reduced GH receptor expression in target organs like the liver, disturbed GH receptor signaling via the Janus kinase-signal transducers, activators of transcription (JAK2-STAT5) due to inflammation-induced SOCS (suppressor of cytokine signaling), and increased IGF-binding capacity due to excess IGFBPs. Finally, reduced release of hypothalamic gonadotropin-releasing hormone (GnRH), due to uremia-related inhibitory factors such as angiotensin II (AngII), and steroid treatment may result in decreased circulating levels of bioactive luteinizing hormone (LH), hypogonadism, and reduced pubertal growth spurt. PTH, parathyroid hormone; FSH, follicle-stimulating hormone; IGFBP, insulin-like growth factor binding proteins. (Reproduced with permission of Ref. [22])

height SDS. In general, the poorest growth outcomes were associated with an earlier start and longer duration of dialysis or a diagnosis of a metabolic disorder such as cystinosis and hyperoxaluria, whereas those treated with rhGH did the best [5, 11, 27, 28].

The applicability of adult height prediction methods in children suffering from CKD is questionable. Final height was overpredicted by 3–10 cm in several validation studies testing final height prediction in children with CKD [12, 23, 29]. Most likely, this reflects the complexity and thus unpredictability of growth and development under the condition of chronic uremia, with a highly variable and dynamic impact of disease progression, medications, renal replacement treatment modalities, skeletal maturation, and pubertal timing.

Clinical Presentation

Children with congenital CKD are prone to marked growth retardation already in utero and during the first 2 years of life. Whereas growth during mid-childhood tends to be percentile-parallel, height velocity decreases disproportionately during the last 2–3 prepubertal years in these children. Eventually, growth potential is irreversibly lost in the peripubertal period due to a delayed pubertal growth spurt that is also of insufficient magnitude (Fig. 28.1).

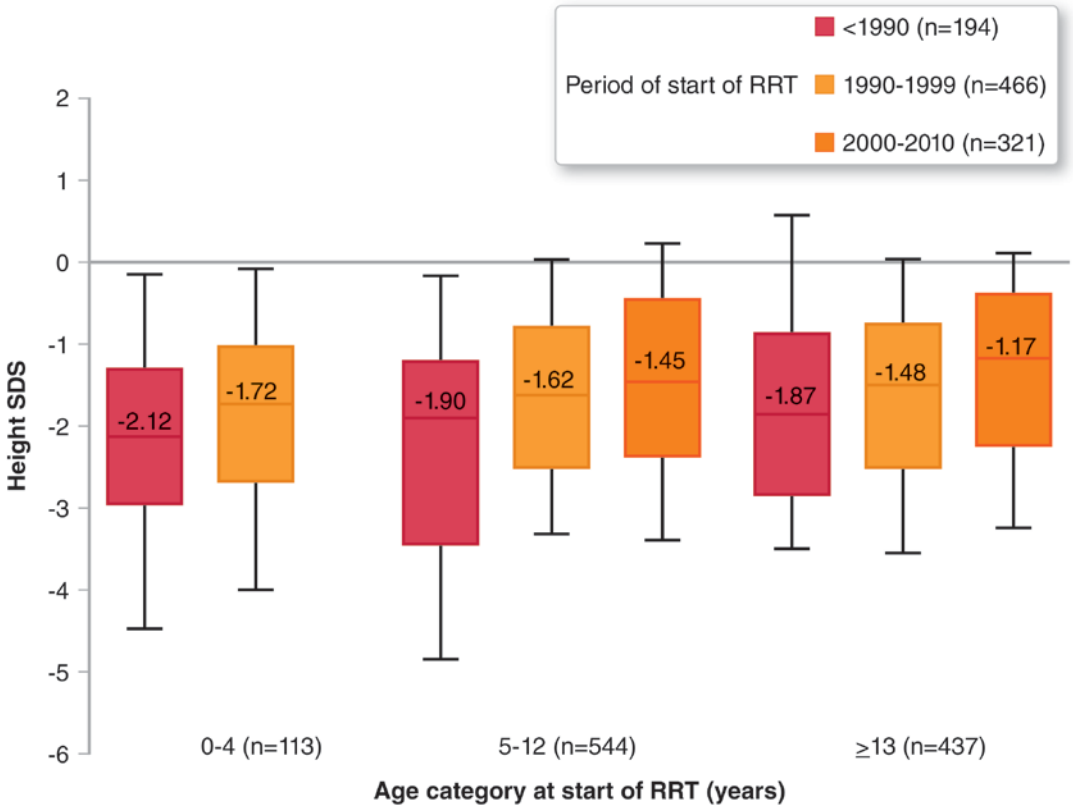


Fig. 28.3 Changes in final height SDS over time according to age and period of start of RRT ($n = 981$). The horizontal line in the middle of the box represents the median; the bottom and top of the box represent the lower and upper quartiles, respectively; and the ends of the whiskers represent the 10th and the 90th percentiles. (Reproduced with permission of Ref. [5])

Intrauterine Growth

Reduced fetal growth has been described in several studies in children with CKD [30–34]. Both prematurity and low birth weights are often seen. The incidence is particularly high in infants on dialysis, but it also occurs in children with less severe CKD. Although registry data do not always distinguish between infants who do or do not have comorbidities (and the latter often have below normal mean birth weight and length), it has been shown that of over 400 children with a mean GFR of around 40 ml/min/1.73 m^2 in the CKiD study, low birth weight (LBW, <2500 g) occurred in 17%, prematurity (gestational age <36 weeks) in 12%, and small for gestational age (SGA, birth weight <10th percentile for gestational age) in 14%. Interestingly, 40% had also received intensive care unit (ICU) care at birth. The comparable overall incidence of abnormal birth history in the US population is 7–8%. Low birth weight, prematurity, SGA, and requirement for ICU care were all risk factors for poor growth outcomes, independent of renal function [33]. Likewise, intrauterine growth retardation and neonatal distress were shown to be important independent predictors of poor growth outcome in a cohort of 509 German children with CKD stage 3–5 [34]. Potential explanations for these findings could be poor intrauterine growth conditions (e.g., maternal malnutrition, smoking) or genetic abnormalities which may cause both intrauterine growth retardation and kidney hypoplasia.

Growth During Infancy

Approximately one third of total postnatal growth occurs during the first 2 years of life. Therefore, any growth-suppressing conditions during this early period of life result in severe growth retardation and probably irreversible loss of growth potential [35, 36]. A retrospective study in infants with severe CKD clearly demonstrated that the most critical period for loss of height potential is the first 6 months of life. Growth at this time is particularly dependent on adequate nutrition, which may be very hard to attain because of prematurity, poor feeding, vomiting, and episodes of fasting as a result of surgery or sepsis [32]. In addition, and as mentioned previously, infants with comorbidities often present with much more severe growth failure than infants without comorbidities (Fig. 28.4). In infants with ESKD, i.e., those with severe congenital CKD, the decrease in mean standardized height can be as much as 0.6 SD per month [2]. At 3 years of age, these children may have already lost 3 SD scores (SDS). According to the Infancy-Childhood-Puberty model, approximately 1 SDS may be lost during each of the following three periods, fetal life, during the first postnatal months, and between 9 and 18 months of age, the latter being due to either delayed onset of the "childhood" growth phase or regression to the infancy phase growth pattern. It has been suggested that the growth failure that occurs during fetal life and the first postnatal months reflects abnormal metabolic and/or nutritional influences and the impaired growth present around the first birthday may be related to a partial insensitivity to GH. The increasing incidence of renal replacement therapy offered even to multimorbid infants makes the achievement of normal growth during infancy particularly challenging [30, 32].

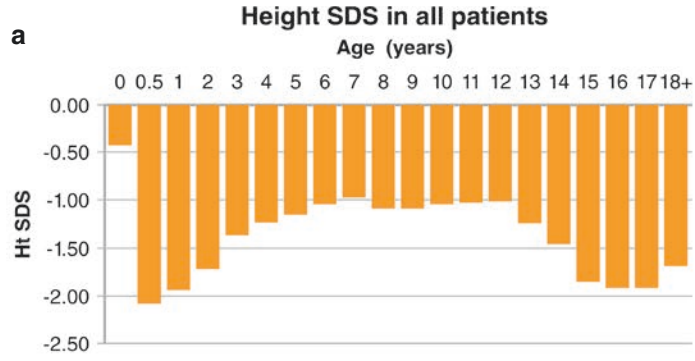
Growth During Mid-childhood

Patients with congenital CKD usually show percentile-parallel growth during the mid-childhood years. In this period, growth is closely correlated with the degree of renal dysfunction. Although there is no critical threshold of GFR, growth patterns are typically stable if the GFR remains above 25–35 ml/min/1.73 m^2 and tends to diverge from the percentiles below this level [37–39]. In one study, a mean cumulative loss of 6 cm from predicted final height was observed in children with a mean GFR below 25 ml/min/1.73 m^2 between early childhood and the age of 10 years [37]. In addition, metabolic acidosis (serum bicarbonate < 18 mEq/l) was shown to be associated with poor growth, whereas other sequelae of CKD such as anemia and malnutrition seem to be less important determinants of statural growth in mid-childhood [40]. Abnormal growth patterns also occur in children who acquire CKD in this age range.

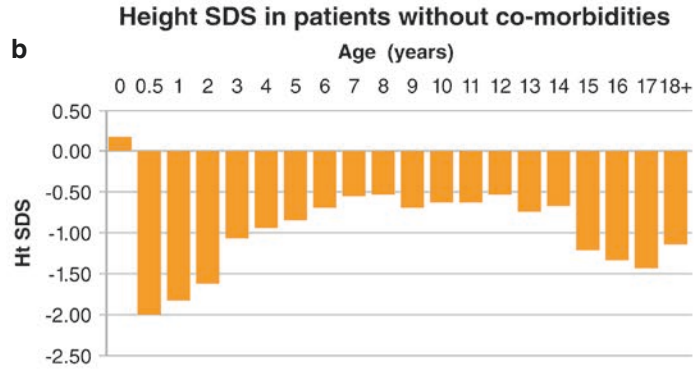
The Pubertal Phase

Pubertal Development

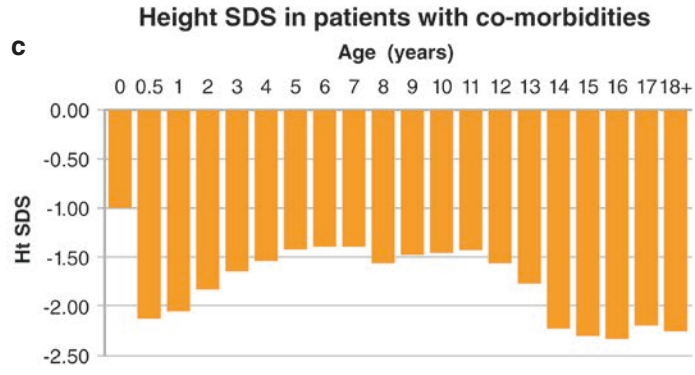
Delayed onset and progression of pubertal development has historically been a common feature in children started on RRT [29]. Indeed, data from the late 1980s demonstrated a delay of pubertal onset by 2–2.5 years [29]. At least 50% of adolescents with ESKD achieved the pubertal milestones later than 95% of their healthy peers [29, 41]. Moreover, despite the achievement of pubertal stage 4 or 5, a substantial proportion of dialysis patients presented with permanently impaired reproductive function [42]. However, these observations were made more than 20 years ago, when many patients were on long-term dialysis treatment before being transplanted. Fortunately, in the last 20 years, most children requiring RRT before pubertal age present with normal or only slightly delayed pubertal onset. In two studies, mean age at pubertal onset as well as age at menarche did not differ between children on RRT and healthy children; in addition, the serum levels of pubertal reproductive hormones were normal in the great majority of patients [9, 43]. It is important to note that the age at onset of puberty is positively associated with the age at transplantation. Thus, early renal transplantation is a prerequisite for the prevention of pubertal delay in children with ESKD [23, 43].



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	40	57	72	76	73	71	67	65	66	62	69	62	53	52	44	46	40	40	31	32
BMI	13	13	13	14	14	15	16	16	17	19	20	20	21	21	23	22	23	23	23	25



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	33	38	39	38	37	35	33	33	30	29	31	27	28	23	23	17	17	12	17
BMI	14	12	12	14	14	15	16	16	17	18	20	21	20	22	23	23	23	23	22	25



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	24	34	37	35	34	32	32	33	32	30	31	26	24	21	23	23	23	19	15
BMI	12	13	13	14	14	15	15	16	17	19	19	20	21	22	23	22	22	22	23	25

Fig. 28.4 Course of mean standardized height and body mass index (BMI) of children presenting within the first 6 months of life with a glomerular filtration rate less than 20 ml/min/1.73 m^2 receiving tube feeding in order to provide at least 100% of the recommended daily allowance (RDA) of healthy children. (**a**) Height SDS and BMI values for all patients. (**b**) Height SDS and BMI values for patients without comorbidities. (**c**) Height SDS and BMI values for patients with comorbidities. (Reproduced with permission of Ref. [32])

Nevertheless, patients who demonstrate delayed puberty – that is, boys with a testicular volume <4 ml at the age of 14 years and girls with breast stage <B2 at age 13.5 years – should be referred to a pediatric endocrinologist for full workup and potential induction of puberty [22].

Pubertal Growth

During the last two decades, in parallel with the improvement in sexual maturation has been an improvement in pubertal height gain [5, 9, 23, 29]. Longitudinal growth in 384 German children on RRT who were followed between 1998 and 2009 was compared with 732 children enrolled in the European Dialysis and Transplant Association (EDTA) registry between 1985 and 1988 (Fig. 28.5) [9]. In line with previous studies, the pubertal growth spurt in the patients in the earlier EDTA study was delayed by approximately 2.5 years. In many of these patients, no clear pubertal growth spurt was present, and consequently standardized height decreased during pubertal age. In contrast, a clear pubertal growth spurt was present, and the onset of the pubertal growth spurt was within the normal range in the majority of patients followed up more recently. Consequently, standardized height even improved during puberty and until adult height. Thus, whereas 20 years ago a loss of about 1.0 SD was expected during puberty, currently a normal or only slightly reduced pubertal growth spurt can be expected if long-term dialysis is avoided.

Segmental Growth

It has been postulated that during malnutrition there is preferential preservation of growth of vital organs at the expense of less vital tissues such as the limbs, so that malnutrition during childhood results in disproportionate stunting with impairment of leg growth and preserved trunk and head growth [44]. To that end, relative leg length is increasingly used as a biomarker of childhood nutrition in epidemiological studies [45–47]. Information pertaining to segmental growth has been collected in the CKD Growth and Development Study, a study in which more than 800 pediatric CKD patients before and after transplantation have been enrolled since 1998. Patients undergo yearly detailed anthropometric assessments at two pediatric nephrology centers in Northern Germany in this prospective observational study. Patients with a long-term history of CKD and RRT demonstrated an age-related disproportionate growth pattern [3, 4, 48]. Growth impairment and disproportionality was most obvious in early childhood. Sitting height was mostly preserved, whereas growth of the legs and arms was most severely affected (Fig. 28.6a). This resulted in a markedly elevated sitting height index (ratio of sitting height to total body height). Leg length was more affected in prepubertal compared to pubertal patients. Consequently, body disproportion was less pronounced in pubertal patients. In addition to transplant function and steroid exposure, congenital CKD, small for gestational age, young age, and use of rhGH in the pre-transplant period were significantly associated with growth outcome (stature and degree of body disproportion) in these patients. Noteworthy was the finding that kidney transplantation resulted in complete normalization of body proportions until attainment of adult height in the vast majority of patients affected (Fig. 28.6b) [4].

Etiology of Growth Failure in Chronic Kidney Disease

There is no single cause of growth failure in CKD (Table 28.1). Children may suffer from various acquired or congenital renal abnormalities, manifesting in early or late childhood and differing widely with respect to severity and rate of progression. Likewise, a broad spectrum of concomitant complications (e.g., metabolic acidosis, electrolyte disturbances, and malnutrition) has to be considered (Fig. 28.2). Furthermore, children with CKD may undergo various therapeutic interventions and different modes of renal replacement therapy of variable timing and duration during their growth period. While some factors, such as nutritional

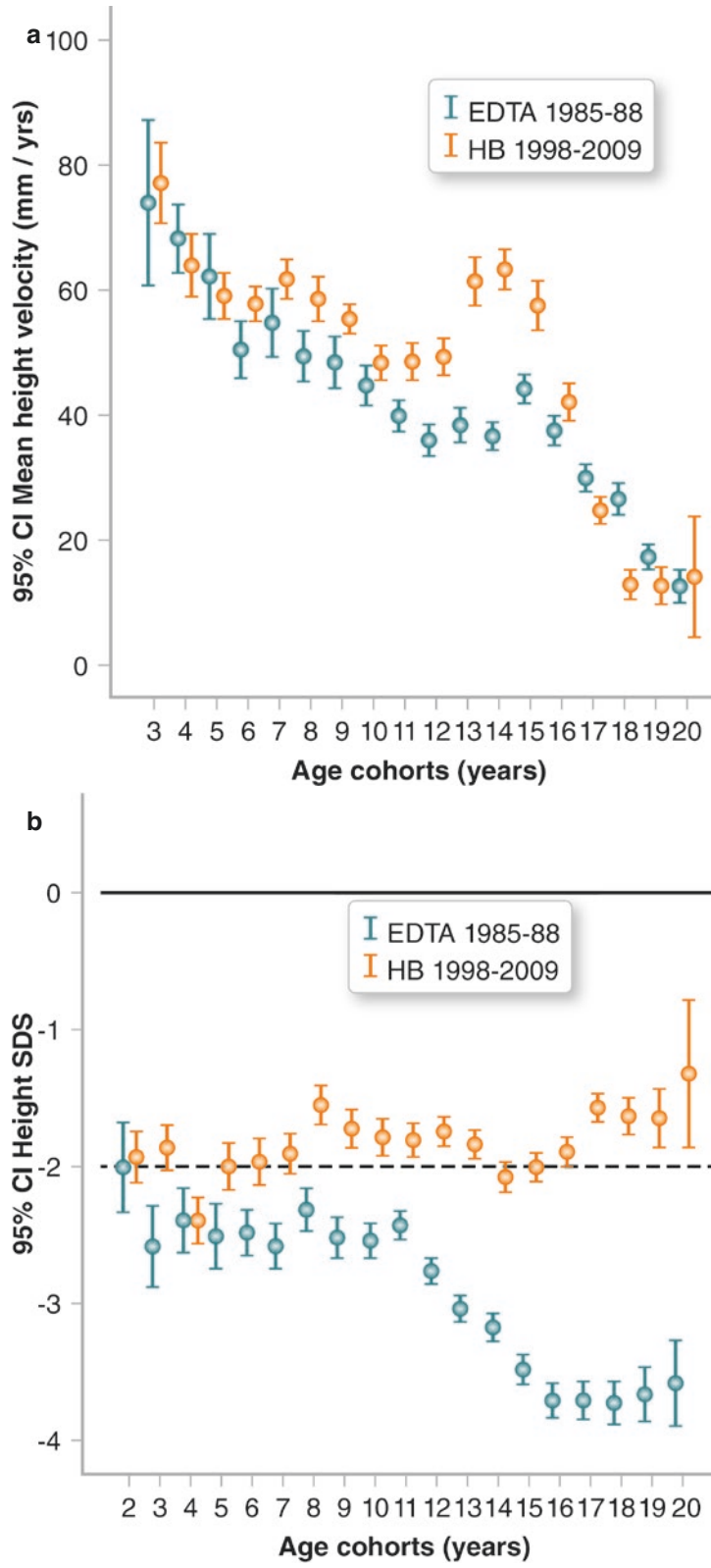


Fig. 28.5 (**a**) Mean height velocity of European children with renal replacement therapy in the EDTA study 1985–1988 (blue lines) versus the Hannover/Berlin (H/B) pediatric population cohort 1998–2009 (orange lines) in different age cohorts. (Reproduced with permission of Ref. [9]). (**b**) Age-dependent height standard deviation score of European children on renal replacement therapy 1985–1988 (EDTA study, $n = 732$, blue error bars) and in the HB group ($n = 384$, orange error bars). EDTA, European Dialysis and Transplant Association, CI confidence interval. (Reproduced with permission of Ref. [9])

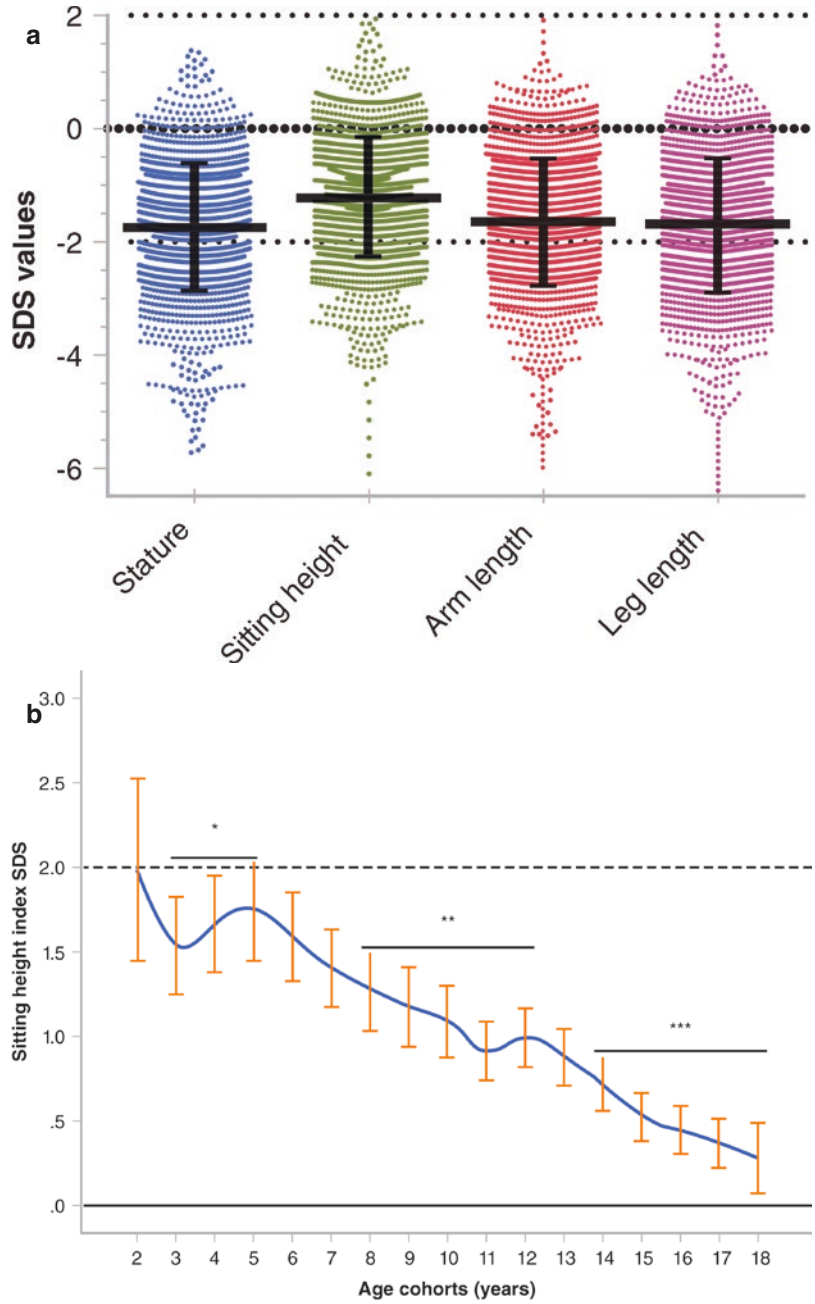


Fig. 28.6 (**a**) Mean SD scores (SDS) for stature, sitting height, and arm and leg lengths in 389 patients who had received transplants. (**b**) Mean sitting height index (ratio between trunk length and total body height) as a function of age in 389 renal transplant recipients. *$P < 0.05$ for age cohorts of 3 years versus 5 years; **$P < 0.05$ for age cohorts of 2–5 years versus 8–12 years; ***$P < 0.05$ for age cohorts of 8–12 years versus 14–18 years. Data are given as mean and 95% confidence interval. Horizontal lines refer to the normal mean (0 SDS) and lower (−2.0 SDS) and upper (2.0 SDS) normal range. (Reproduced with permission of Ref. [4])

and hormonal abnormalities, and hematological and metabolic derangements, such as acidosis, electrolyte imbalance, CKD-MBD, and anemia, are potentially correctable, the effects of others, such as birth parameters, associated syndromes, and parental heights, are not [49]. In addition, differences in economics (based on gross national income) and socioeconomic status substantially impact growth outcome in various countries. The effect of these economic factors has been shown to be independent of well-known factors that impair growth such as congenital CKD, anuria, and dialysis vintage, as outlined below [18].

Table 28.1 Factors that contribute to growth failure in children with CKD

Genetic factors
Parental heights
Gender
Syndromic kidney diseases
Birth-related factors
Prematurity
Small for gestational age
Intensive care requirement
Comorbidities (e.g., central nervous system, liver, or heart involvement)
Age at onset of CKD
Severity of CKD and residual renal function in patients on dialysis
Anemia
Metabolic disturbances
Salt and water metabolism
Metabolic acidosis
CKD-MBD
Malnutrition
Altered taste sensation
Anorexia
Vomiting
Dietary restrictions
Nutrient losses in dialysate
Infections and inflammation
Protein-energy wasting
Infections and inflammation
Uremic toxins
Oxidative stress
Inflammatory cytokines
Hormonal disturbances affecting:
The somatotropic hormone axis
The gonadotropic hormone axis
PTH and vitamin D metabolism or action
Gastrointestinal hormones

Reproduced with permission of Ref. [22]
CKD chronic kidney disease, *MBD* mineral and bone disorder, *PTH* parathyroid hormone

Underlying Renal Disease

Congenital anomalies of the kidneys and urinary tract (CAKUT), characterized by renal hypoplasia or dysplasia with and without reflux or obstructive uropathy, are the most common causes of ESKD during infancy and childhood. Renal dysplasia is often associated with electrolyte and/or water losses, and losses of both are likely to contribute to growth failure [50]. Thus, it is important to compensate for these losses and to provide appropriate treatment of concomitant urinary tract infections as part of successful growth management.

In children suffering from glomerulopathies, growth rates might decline even with rather mild renal insufficiency. The nephrotic state per se and glucocorticoid treatment are known risk factors for growth delay [51]. Congenital nephrotic syndrome is usually associated with severe early infantile growth failure, which may occur even with preserved global renal function. The poor growth seems to be secondary to persistent edema, recurrent infections, losses of peptide and protein-bound hormones, and/or protein-calorie malnutrition [52, 53]. In Finnish-type congenital nephrotic syndrome, aggressive nutritional support is vital, and bilateral nephrectomy and initiation of peritoneal dialysis may be necessary to improve growth. In other types of congenital nephrotic syndrome, unilateral nephrectomy and treatment with prostaglandin synthesis inhibitors and renin-angiotensin system (RAS) antagonists can reduce proteinuria and thereby improve growth and the overall clinical condition [52, 54].

Nephropathic cystinosis results in complex tubular dysfunction and is associated with severe growth failure early in infancy, even when glomerular function is not yet compromised [55, 56]. Progressive growth failure is further augmented in these children by generalized deposition of cystine crystals altering the function of growth plates, bone marrow, hypothalamus, pituitary gland, and thyroid gland. However, early initiation of treatment with the cystine-depleting agent cysteamine improves growth and delays the development of ESKD by approximately 10 years [55, 57]. Consequently, height at the start of RRT in this population has significantly improved during the last decade [58]. In patients with primary hyperoxaluria, supplementary treatment with citrate and pyridoxine can delay progression of renal failure and possibly improve longitudinal growth [59]. In patients with systemic oxalosis, combined liver and kidney transplantation is a curative option; however, real catch-up growth after combined transplantation is rarely observed, even in prepubertal oxalosis

patients [28]. Most important is the recognition that every measure directed to preserve kidney function except glucocorticoid therapy has a beneficial impact on growth in children with CKD.

Consequences of Renal Disease

Protein-Calorie Malnutrition

Nutritional imbalances, particularly protein-energy malnutrition, are frequently seen in children suffering from CKD. Infants and young children are particularly vulnerable to malnutrition because of low nutritional stores and high energy demands which are, in turn, necessary to achieve high growth rates in this age group [20, 32, 60]. Anorexia in CKD is due to a combination of altered taste sensation, decreased clearance of cytokines that affect appetite and satiety, obligatory losses of salt and water leading to preference for salty foods and large volumes of water, and the need for multiple medications. Vomiting is common, particularly in infants. PD results in raised intra-abdominal pressure, which may also have an adverse effect on appetite and cause vomiting. Malnutrition is a crucial clinical issue since it is also significantly associated with increased mortality in children suffering from CKD [14–16].

The term malnutrition-inflammation complex syndrome (MICS) has been coined to describe the association between chronic inflammation and malnutrition in dialyzed children and adults. Another term, protein-energy wasting (PEW), was also recently coined which more or less describes the same pathophysiological scenario [61, 62]. Possible causes of MICS/PEW include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, cytokine induction by exposure to bio-incompatible dialysis materials, decreased clearance of inflammatory cytokines, volume overload, and other dialysis-related factors. MICS may contribute to erythropoietin hyporesponsiveness, early cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients and may also lead to GH insensitivity and growth failure in children on dialysis [63–66]. Indeed, an in vitro study demonstrated that uremia attenuates GH-stimulated insulin-like growth factor I (IGF-I) expression in the liver, which was further aggravated by inflammation [63].

There is no consensus about how to determine the degree of severity of MICS or how to manage it. Anorexia manifests early in the course of renal failure and usually progresses with declining renal function [38]. In addition, protein synthesis is decreased in uremia, and catabolism is increased [67]. In CKD patients, spontaneous energy intake is directly correlated with decreased growth if it is less than 80% of recommended dietary allowance [68]. Unfortunately, further augmentation of energy above 100% of recommended dietary allowance tends to result in obesity rather than additional length/height gain [69–72]. Other approaches to prevent MICS may include the preferential use of biocompatible dialysis materials to minimize inflammatory responses and intensified dialysis protocols to increase cytokine clearance and improve volume status. Preliminary results support the efficacy of these measures in improving growth hormone sensitivity and inducing catch-up growth (see below).

Metabolic Acidosis

Metabolic acidosis (serum bicarbonate < 22 mEq/l) usually occurs when the GFR is below 50% of normal, although nutritional intake (protein and acid load), catabolism, and alterations in electrolyte balance contribute to its development. Subsequent metabolic and endocrine aberrations are triggered by metabolic acidosis and aggravate uremic growth failure. In fact, metabolic acidosis is significantly associated with decreased length gain and increased protein breakdown in children with CKD [73–75]. Studies on metabolic acidosis in uremic animals have revealed a complex pattern of interrelated pathophysiological reactions. Metabolic acidosis increases glucocorticoid production and protein degradation while concomitantly suppressing spontaneous pituitary GH secretion, decreasing expression of the GH receptor and IGF-I receptor, and decreasing IGF-I

serum concentrations; these effects highlight the necessity for adequate control of metabolic acidosis in children with CKD [76, 77]. Likewise, metabolic acidosis was noted to be undertreated in the CKiD population and associated with poor growth which further supports the concept that interventions targeting metabolic acidosis may improve growth in this population [40].

CKD-Mineral and Bone Disorder (CKD-MBD)

It is widely accepted that skeletal deformities due to CKD-MBD can contribute to uremic growth failure [78, 79]. Pronounced secondary hyperparathyroidism (sHPT) can interfere with longitudinal growth by destruction of the growth plate architecture, epiphyseal displacement, and metaphyseal fractures. Severe destruction of the metaphyseal bone architecture may result in complete growth arrest. Although treatment with 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) reverts sHPT and improves growth in uremic rats, this has not been demonstrated in children with CKD [80–82]. The situation is even more complicated since skeletal growth is the net result of proliferation and differentiation of growth plate chondrocytes with subsequent mineralization of the extracellular matrix. According to current knowledge, this biological process is under the control of three hormones, namely, PTH, $1,25(OH)_2D_3$ (calcitriol), and fibroblast growth factor 23 (FGF23), as well as numerous paracrine and autocrine signals [83].

The contribution of sHPT to uremic growth failure has not been fully elucidated. Under physiological conditions, growth plate chondrocytes proliferate and differentiate under the influence of PTH, mainly mediated by the induction of local IGF-I synthesis [84]. However, bones and growth plates are relatively resistant to PTH in chronic uremia [85]. Hence, low or normal PTH levels, which are indicative of low bone turnover in experimental uremia as well as in children with CKD stage 5D, have been suspected to impair longitudinal growth [86]. However, low bone turnover is rarely seen in children on dialysis (approx. 4%) [87]. In addition, one well-designed direct histomorphometric assessment in children on dialysis showed no association between low bone turnover and statural growth [88].

The IPPN offers the most up-to-date information pertaining to the association between PTH and growth in a large cohort of pediatric PD patients. The annual prospective change in standardized height of this patient cohort tended to correlate inversely with time-integrated mean PTH levels (Fig. 28.7): patients with mean PTH levels >500 pg/ml (i.e., >9 times upper limit of

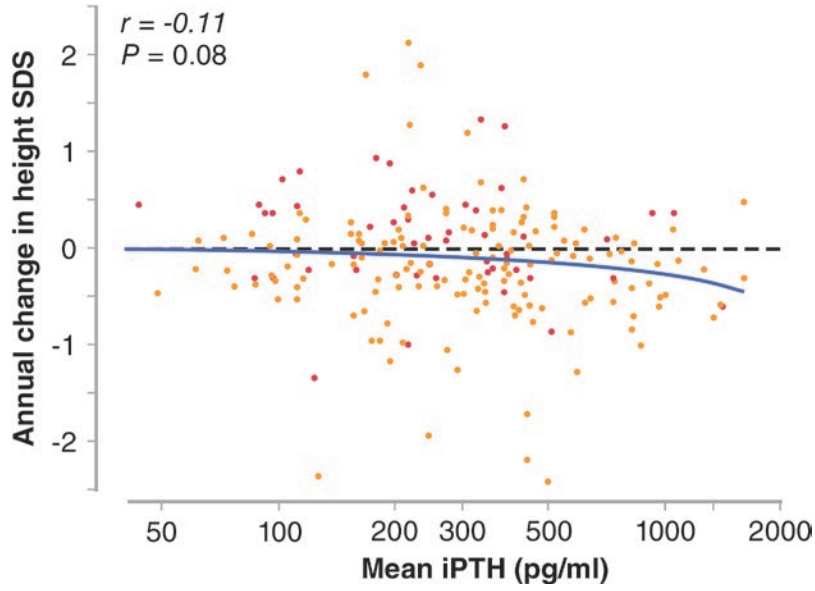


Fig. 28.7 Time-averaged mean plasma intact parathyroid hormone (iPTH) concentrations and change in standardized height in 214 pre- and early pubertal children on peritoneal dialysis followed prospectively for at least 12 months. Full circles indicate patients receiving recombinant human growth hormone. (Reproduced with permission of Ref. [89])

normal (ULN)) showed a significant loss in height SDS as compared to children with lower PTH levels (−0.28 versus −0.05 SDS per year; $P < 0.05$) [89]. Thus, dialyzed children with normal or up to nine times ULN elevated PTH levels retain the potential for normal growth, whereas patients with high PTH levels (>500 pg/ml) are at increased risk of growth failure.

Anemia

Longstanding anemia in CKD patients has profound systemic consequences including anorexia and catabolism due to altered energy turnover and multiple system dysfunctions. In fact, retardation of growth and development is a hallmark in patients with longstanding chronic anemia of non-renal origin, e.g., thalassemia major. From a theoretical point of view, anemia may suppress growth secondary to reduction of appetite, intercurrent infections, cardiac complications, and severely reduced oxygen supply to cartilage. The advent of recombinant human erythropoietin (EPO) and thus the possibility to correct anemia in CKD patients facilitated study of the impact of anemia on longitudinal growth. Although short-term stimulatory effects of EPO on longitudinal growth have been reported anecdotally, there is no data demonstrating correlation between successful treatment with EPO and improved growth in children with CKD [90, 91].

Physical Activity

Physical activity is often reduced in children with CKD and associated with abnormalities in serum markers of bone formation and remodeling such as bone alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase 5b (TRAP5b) [92]. Although endurance exercise improves bone formation in subtotal nephrectomized young rats [93], studies demonstrating better growth after increased physical activity in children with CKD are lacking.

Endocrine Changes

Uremia interferes with the metabolism and regulation of various peptide hormones, leading to inappropriate circulating hormone concentrations and/or altered hormone action. Distinct alterations of the gonadotropic and somatotropic hormone axes have been identified which are considered crucial pathomechanisms of uremic growth failure (Fig. 28.2).

Gonadotropic Hormone Axis

Gonadal Hormones

The reduced conversion of T to DHT secondary to diminished 5α-reductase activity might at least partially explain the delayed pubertal development in boys with advanced CKD [94, 95]. In addition, the accumulation of sex hormone-binding proteins that occurs with impaired renal clearance lowers the serum concentration of unbound (free) T [96]. Beyond this, the plasma concentration of inhibin, a gonadotropin feedback inhibitor produced by Sertoli cells, is increased in pubertal boys with CKD [97]. In adult women, plasma estradiol levels tend to decrease parallel to GFR reduction, and adolescent girls show low-normal or decreased estradiol levels in relation to pubertal age [98]. However, these observations were all made more than 20 years ago. At least in recently transplanted children, this issue appears to be resolved. In a recent study, the majority of transplanted children without prior long-term dialysis had normal estradiol and testosterone levels [43]. This may at least partly explain the improvement of pubertal development in patients on RRT documented during the last few decades [9].

Gonadotropins

Plasma concentrations of LH and FSH in combination with decreased or low-normal gonadal hormones suggest a state of compensated hypergonadotropic hypogonadism in uremia [99].

However, in CKD patients, the usually inadequate degree of hypergonadotropism relative to the level of hypogonadism is compatible with an additional defect of pituitary gonadotropin release. Analysis of spontaneous pulsatile LH secretion in children with CKD has provided new insights into the underlying pathophysiology [100, 101]. In CKD, mean LH plasma levels are elevated despite significantly reduced pituitary LH secretion, due to the markedly impaired renal metabolic clearance of LH. These alterations are much more pronounced in patients on dialysis compared to pre-dialysis [100]. When renal function is restored by renal transplantation, pulsatile LH secretion normalizes, and hypergonadotropic FSH and/or LH levels are only rarely observed [43, 99].

Since the onset of puberty is heralded by the appearance of nocturnal LH secretion episodes, the uremia-related impairment of pulsatile LH release suggests that the delayed pubertal onset in CKD is driven by hypothalamic abnormalities. Indeed, experimental evidence suggests that the reduced release of hypothalamic gonadotropin-releasing hormone (GnRH) is due to uremia-related inhibitory factors and/or to an increased tone of the inhibitory neurotransmitter gamma-aminobutyric acid [102, 103]. Beyond the quantitative alterations of gonadotropin release, uremia affects also the biological quality of circulating gonadotropins. In pubertal and adult CKD patients, the proportion of bioactive LH in relation to the total immunochemically measurable amount of LH is reduced. This might be due to altered glycosylation and/or accumulation of less active isoforms [104].

In summary, insufficient activation of the hypothalamic GnRH pulse generator, likely mediated via circulating inhibitors, appears to be the key abnormality underlying delayed puberty and altered sexual functions in children on dialysis therapy. However, renal transplantation is able to completely normalize all these alterations in the majority of patients if long periods on dialysis treatment are avoided.

Somatotropic Hormone Axis

Growth Hormone Secretion and Metabolism

In pediatric and adult CKD patients, fasting GH concentrations are normal or even increased, depending on the degree of renal failure. GH, a 22-kilodalton protein, is almost freely filtered by the glomerulus (sieving coefficient ~0.82) and thereby ultimately cleared from the circulation [105]. Indeed, a linear relationship between GFR and the metabolic clearance rate of GH has been shown; GH clearance is reduced by approximately 50% in patients with ESKD [105, 106]. The prolonged plasma half-life of GH, rather than increased endogenous secretion, explains the increased circulating GH concentrations in uremia. Pituitary GH secretion is unaltered in prepubertal patients, but decreased in adolescents with CKD, suggesting insufficient stimulation by gonadal steroids during puberty [107, 108]. In addition, malnutrition and metabolic acidosis negatively impact GH secretion rates in children with CKD [76].

Growth Hormone Receptor and GH Signaling

Studies in experimental uremia showed that CKD is a state of GH insensitivity. GH-induced hepatic IGF-I synthesis is diminished, due to either decreased expression of the GH receptor (GH-R) or a postreceptor signaling defect [63, 109, 110]. Whereas reduced expression of GH-R encoding mRNA in the liver and growth plate chondrocytes has been consistently seen, hepatic but not growth plate cartilage GH-R protein levels were found to be comparable in uremic and non-uremic animals when corrected for uremia-associated anorexia by pair feeding [109–111]. Thus, while decreased GH-R abundance in growth plate cartilage is likely to contribute to uremic growth failure, a postreceptor GH signaling defect has been identified as cause of the diminished hepatic IGF-I secretion upon GH stimulation. In fact, aberrant GH-dependent

JAK-STAT signaling has been noted with uremia (Fig. 28.8). Normally, activation of the JAK-STAT cascade by tyrosine phosphorylation is triggered by GH binding to its receptor. This then leads to transcriptional activation of IGF-I synthesis as well as synthesis of the proteins of the suppressor of cytokine signaling (SOCS) family. The latter are responsible for dephosphorylation of the GH-activated activated cascade and as such provide a GH-regulated negative feedback loop. However, under the conditions of chronic uremia, the equilibrium

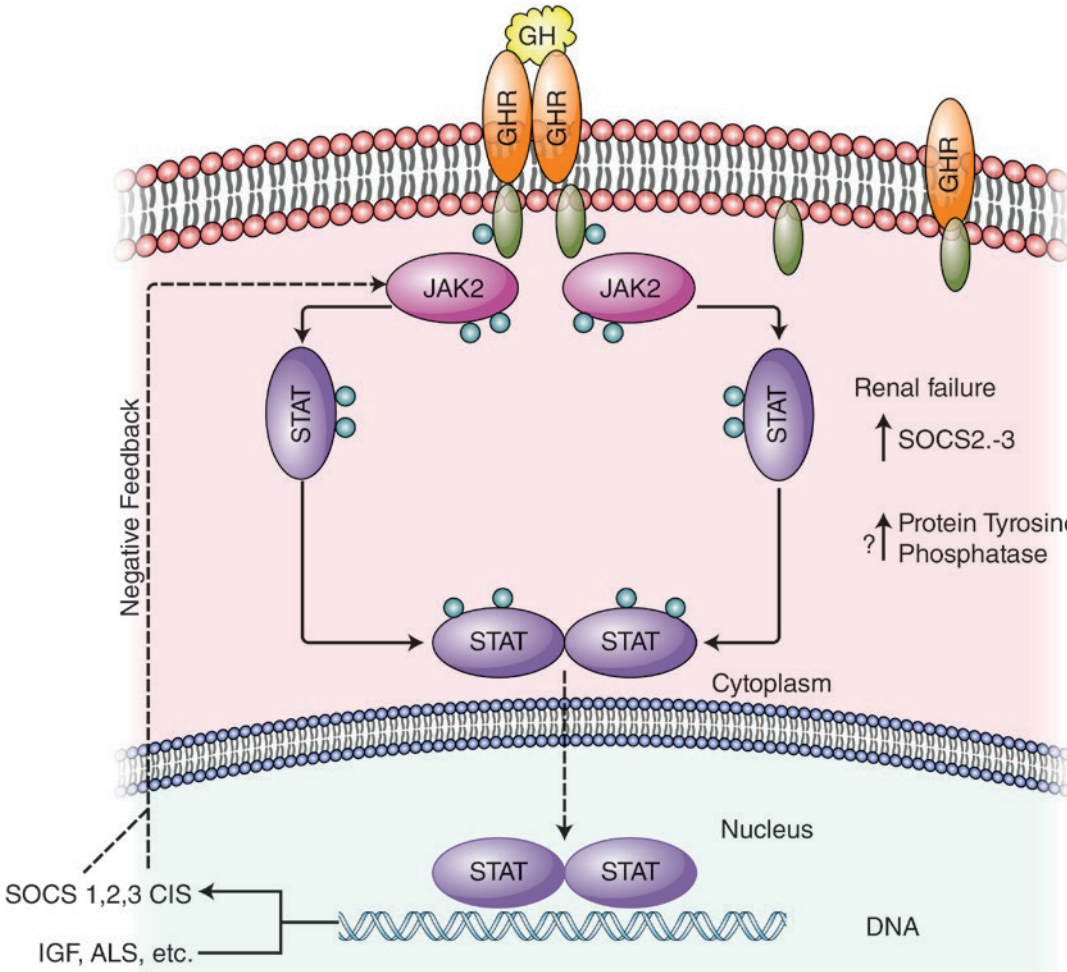


Fig. 28.8 Growth hormone (GH)-mediated JAK2/STAT signal transduction. GH activates several signaling pathways via Janus kinase2 (JAK2) including the JAK-STAT (signal transducer and activator of transcription) pathway. Binding of GH to its receptor (GH-R) activates JAK2, which then self-phosphorylates followed by phosphorylation of the GH-R and subsequently STAT 1a, 3, 5a, and 5b, members of a larger family of cytoplasmic transcription factors. These phosphorylated STATs form dimers that enter the nucleus where they bind to specific DNA sequences and activate their target genes including insulin-like growth factor-I (IGF-I) and some suppressors of cytokine signaling (SOCS). Deletion of STAT5 expression leads to retarded body growth, and STAT5b is required for GH-mediated IGF-1 gene expression. In renal failure, phosphorylation of JAK2 and the downstream signaling molecules STAT5, STAT3, and STAT1 are impaired, as are the nuclear levels of phosphorylated STAT proteins. This important cause of uremic GH insensitivity may result in part from the upregulation of SOCS2 and SOCS3 expression with suppressed GH signaling and also from increased protein tyrosine phosphatase activity, with enhanced dephosphorylation and deactivation of the signaling proteins. (Reproduced with permission of Ref. [179])

between GH-induced transcriptional activation of IGF-I and SOCS is shifted toward SOCS overstimulation. Current evidence suggests that the inflammatory state associated with uremia might also contribute to GH insensitivity, as SOCS are also induced by inflammatory cytokines [63, 64, 66, 109, 112, 113].

In humans, levels of circulating GH binding protein (GHBP), which in turn results from proteolytic cleavage of the extracellular receptor domain, are taken as a measure of GH receptor expression. In line with the above-described pathophysiologic mechanism, GHBP plasma levels were reduced in 77% of pediatric CKD patients compared to age- and gender-matched controls. The decrease of serum GHBP levels was significantly associated with the degree of renal impairment. In patients with eGFR < 35 ml/min/1.73 m^2, mean GHBP levels amounted to −1.04 SDS and in patients on dialysis to −2.25 SDS ($P < 0.001$) [114].

Insulin-Like Growth Factor Plasma Binding and Tissue Action

Apart from GH insensitivity, insensitivity to IGF-I is also associated with uremia [115–118]. While serum concentrations of IGF-I and IGF-II are usually within the normal range in children with CKD, IGF-I levels are slightly reduced, and those of IGF-II are mildly increased in dialyzed patients [119]. In contrast to the unchanged total amount of circulating immunoreactive IGF, somatomedin bio-availability is reduced in uremia pointing to the existence of circulating inhibitors [120]. A low-molecular-weight somatomedin inhibitor (~1 kDa) was detected in uremic serum in an early study [121], but this has not been characterized further. Later studies focused on the accumulation of specific high-affinity IGF-binding proteins (IGFBP1–6), which are normally cleared by the kidneys and are considered the main cause of diminished somatomedin bioactivity in uremia. In particular, the concentrations of IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, and IGFBP-6 increase as renal function declines, and IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6 have been shown to inhibit IGF-I bioactivity in vitro [116, 122–124]. In contrast, the serum concentrations of IGFBP-5 are normal, and IGFBP-5 proteins undergo intense proteolytic cleavage in chronic uremia [122]. Likewise, the elevated level of IGFBP-3 is primarily due to the accumulation of proteolytic fragments, whereas intact IGFBP-3 is markedly diminished [125]. The molar excess of IGFBPs over IGFs is approximately 150% in children with CKD and 200% in children on dialysis as compared to 25% in healthy children. An inverse correlation between growth retardation and IGFBP-1, IGFBP-2, and IGFBP-4 serum concentrations has been described [126]. Reduced IGF bioactivity can be returned to normal by removing unsaturated IGFBPs [120]. These data are in favor of the concept that serum IGFBPs increase with declining renal function in CKD patients and that the greater excess of IGFBPs in ESKD compared to pre-end-stage CKD patients contributes to the more severe growth failure and reduced response to rhGH therapy in children on dialysis. In addition, cellular IGF signaling is impaired in the uremic state. It remains to be elucidated whether a postreceptor mechanism similar to the one observed for GH signaling is responsible for this phenomenon [113].

In summary, markedly deficient IGF-I synthesis, modest elevations of GH levels due to decreased metabolic clearance, and the presence of increased IGF plasma binding capacity underscore the multi-level homeostatic failure of the GH-IGF-I system in uremia.

Treatment of Growth Failure in Chronic Kidney Disease and on Dialysis

General Measures

In infants and young children with CKD, the most important measure to avoid CKD-associated growth failure is the assurance of adequate caloric intake [60]. This often necessitates supplementary feeding via a nasogastric or gastrostomy tube [21]. In a retrospective analysis of growth in 101 infants and young children with severe CKD, persistent catch-up growth was achieved in the

majority of patients when measures such as tube feeding were commenced early as expected growth was not achieved (Fig. 28.4) [32].

The use of enteral feeding varies around the world, as has been clearly demonstrated by the IPPN report of 153 infants on PD: gastrostomy tubes are most commonly used in the USA, where 80% of infants on PD are gastrostomy fed; 20% of infants on PD have gastrostomies in Europe, but this practice is rare or absent in the rest of the world [72]. Nasogastric feeding is commonest in Europe and Latin America. Nevertheless, gastrostomy feeding, rather than demand or nasogastric tube feeding, has been associated with better preservation of linear growth in the infants in the IPPN database (Fig. 28.9). This may be related to the decreased vomiting that occurs with gastrostomy as compared to nasogastric tubes. In later childhood, enteral feeding improves nutritional status, although catch-up growth is rarely achieved by dietary manipulations alone [60].

In general, the targeted caloric intake should be between 80% and 100% of the recommended daily allowance (RDA) of healthy children [20]. The prescribed caloric intake should take into account growth failure and be related to "height age" rather than to chronological age. Protein intake should be 100% of RDA. In patients on peritoneal dialysis, a slightly higher dietary protein intake (+0.2 g/kg/day) is recommended to compensate for dialytic protein losses. A high-protein intake should be avoided since, despite many attempts, anabolizing or growth-promoting effects of high-protein diets have been demonstrated neither in animal models nor in children with CKD. On the contrary, high-protein diets may be detrimental by aggravating metabolic acidosis and augmenting dietary phosphorus load and CKD-MBD.

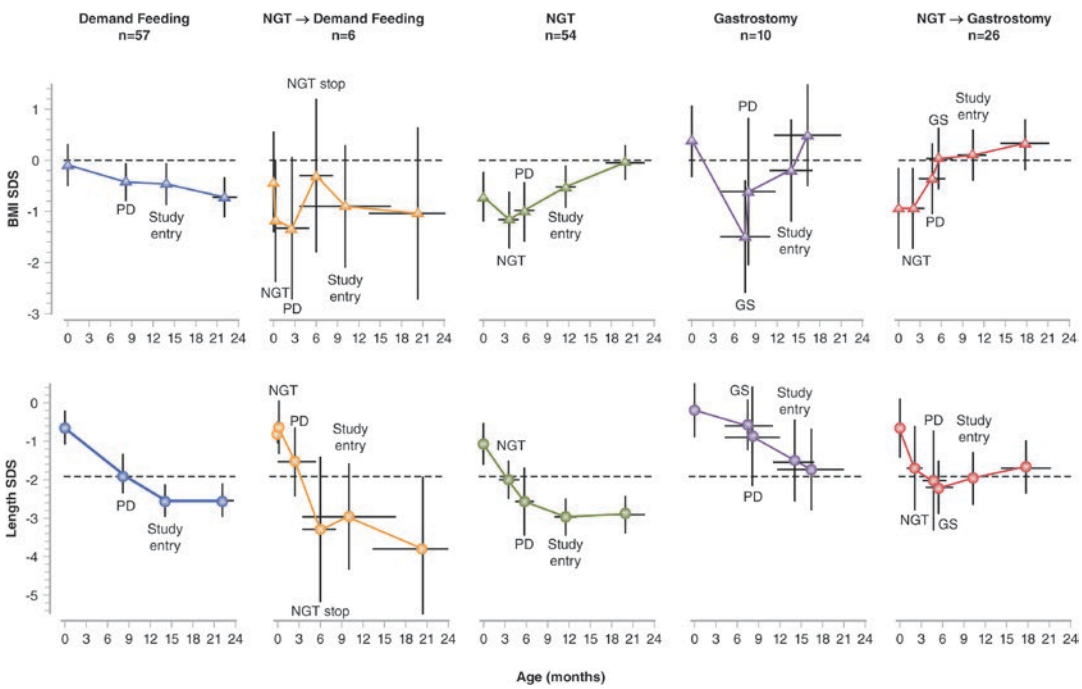


Fig. 28.9 Whereas both nasogastric tube (NGT) and gastrostomy (GS) feeding improve nutritional status, only GS feeding was associated with stabilized linear growth in young infants undergoing PD. The data points represent mean estimates at key time points of postnatal development (i.e., birth, commencement of PD, initiation and discontinuation of nasogastric tube or gastrostomy feeding, enrollment to IPPN (study entry), and last available observation). Two-dimensional error bars denote the 95% confidence intervals to mean age and SDS at the respective time point. (Reproduced with permission of Ref. [72])

Correction of Acid-Base/Electrolyte Abnormalities

Metabolic acidosis should be corrected to serum bicarbonate levels ≥22 mEq/l by administration of sodium bicarbonate and/or the use of HCO_3-based or lactate-based dialysis solutions in children on dialysis. In addition, supplementation of water and electrolytes is essential in patients presenting with polyuria and/or salt-losing nephropathies. Supplementation of sodium chloride is also important in young children on peritoneal dialysis, since significant amounts of sodium chloride (i.e., 2–5 mmol/kg body weight) may be eliminated via peritoneal ultrafiltration.

Dialysis and Intensified Dialysis

Although dialysis treatment attenuates the uremic state, longitudinal growth is usually not improved, and long-term PD or HD are associated with a gradual loss of standardized height in children and adolescents. In dialyzed infants, height losses of up to 1 SD per year have been reported, even with utilization of high-flux hemodialysis [127–129]. In fact, residual renal function appears to be a better predictor of longitudinal growth than dialytic clearance [130, 131]. However, a recent Italian study in infants on chronic PD reported catch-up growth in 50% of patients [132]. Longitudinal growth in this cohort was positively associated with both exchange volume and dialysis session length supporting the importance of dialysis adequacy in order to optimize growth in children on PD. Notably, high peritoneal transporter status, a condition associated with increased morbidity and mortality in adults, is associated with poor longitudinal growth in children on chronic PD [133]. This might be due to the putative association of high peritoneal transport with inflammation, which can suppress statural growth by interference with GH signaling (see above), or excessive losses of proteins and amino acids important to growth.

It has been suggested that intensified dialysis, achieved by either extended thrice-weekly nocturnal or short daily sessions, might be able to induce catch-up growth [134, 135]. According to a recent study, catch-up growth can be maximized when intensified hemodiafiltration (HDF; 3 hours, 6 times a week) and rhGH therapy are combined [136–139]. Using this approach in 15 mainly prepubertal children for an average observation time of 21 months, Fischbach et al. observed an average increase in growth velocity from 3.8 cm/year at baseline to 8.9 cm/year during the intervention. This resulted in a mean 1.7 SDS gain of standardized height, representing complete catch-up growth according to the attainment of the target height SDS. From a pathophysiological point of view, intensified HDF is a better substitute than conventional HD for physiological kidney function, and higher convection rates may result in substantially better clearance of uremic toxins [137]. As a result, inflammation and metabolic acidosis may be abolished, leading to an improved appetite and tissue anabolism. The improved removal of inflammatory cytokines and increased clearance of IGF-1-binding proteins might also reverse GH insensitivity and allow exploitation of the full therapeutic potential of exogenous rhGH therapy. However, the positive effects of this approach must be counterbalanced with the potential impact of intensified dialysis on psychosocial integration and augmented treatment costs.

Interestingly, a slight but significant increase in height SDS was also noticed in a recent observational study comparing growth in children on conventional HDF compared with patients on HD that was independent of rhGH therapy (Fig. 28.10) [140]. Interestingly, an inverse correlation between height SDS increase and beta 2-microglobulin was noted in the study from Shroff et al., suggesting that conventional HDF may also result in enhanced clearance of middle-molecular-weight compounds which, in turn, may partially alleviate rhGH therapy insensitivity in patients on dialysis. Prospective randomized trials will be required to provide definite proof regarding the impact of this therapy on the growth of children with CKD stage 5D.

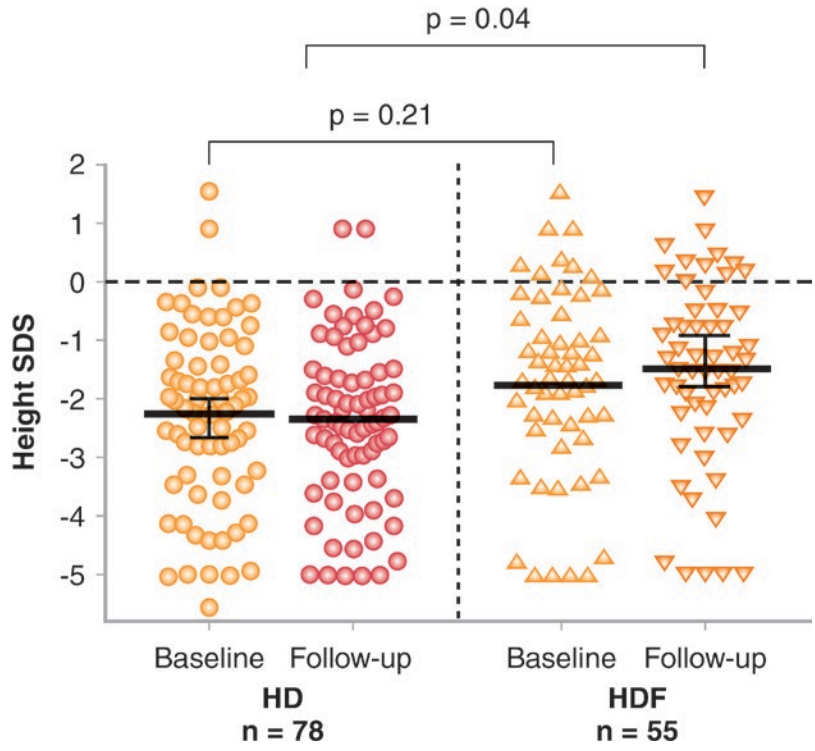


Fig. 28.10 Improved height SDS in children on hemodiafiltration (HDF) compared to hemodialysis (HD). The figure shows change in height SDS in the HD and HDF arms at baseline and 1-year follow-up. Data are shown as median and interquartile range. Within-group analyses performed by Wilcoxon matched-pairs signed-rank test and HD versus HDF cohorts compared by Mann-Whitney U test. At 12 months, the height SDS in the HDF group was higher than in the HD group ($P = 0.04$). (Reproduced with permission of Ref. [140])

Transplantation

Although many of the metabolic and endocrine disorders contributing to uremic growth failure are resolved by renal transplantation, post-transplant catch-up growth is usually restricted to young children and occurs far from regularly [141]. Beyond transplant function, age and extent of stunting at the time of transplantation, in addition to glucocorticoid dosage, are inversely associated with longitudinal growth. While complete steroid withdrawal as one means to enhance growth was associated with unacceptably high rejection rates in children who received azathioprine and/or cyclosporine A as maintenance immunosuppressive medication, withdrawal appears much safer with the currently preferred immunosuppressants [142]. In a randomized trial of late steroid withdrawal in patients on the combination of cyclosporine A and mycophenolate mofetil, steroid-free patients showed improved growth compared to controls (i.e., change in height SDS; 0.6 ± 0.1 versus −0.2 ± 0.1) within 27 months which was not associated with increased rejection rates [143]. However, catch-up growth in pubertal patients was rather limited compared to that in prepubertal patients.

It seems logical that if steroids are withdrawn at an early stage or even completely avoided, better growth outcomes will be observed. Indeed, a retrospective analysis of longitudinal growth in a cohort of 74 children who had been weaned off steroids within 6 months of transplantation showed remarkable results [8]. Mean adult height was −0.5 ± 1.1 SDS and −1.0 ± 1.3 SDS in prepubertal and pubertal patients and was within the normal range (>−2 SD) in 94% and 80% of patients, respectively. Likewise, early steroid withdrawal (<6 weeks) and complete steroid avoidance were shown to be safe and resulted in an improved standardized height by approximately 1.0 SDS within 3–5 years post-transplantation [144–147]. It is important to note that renal transplantation results in preferential stimulation of leg growth and thereby is able to completely normalize body proportions by adult age in children with ESKD, when the transplant is performed before pubertal age [4]. Thus,

efforts to avoid a substantial height deficit before transplantation, through the use of rhGH treatment, early (preemptive) renal transplantation, and immunosuppressive strategies characterized by the early withdrawal or even complete avoidance of steroids, can improve final height and normalize body proportions in children after successful transplantation.

Endocrine Therapies

Active Vitamin D

Calcitriol deficiency is a major cause of sHPT and renal osteodystrophy [79]. Although treatment with calcitriol reverses the biochemical, radiographic, and histological signs of high-turnover bone disease, neither experimental nor clinical studies provide evidence of consistent improvement of longitudinal height as a result of this therapy [82, 148, 149]. These conflicting results might be due to differences in the mode of administration and to the pleiotropic calcitriol-specific effects on growth plate chondrocytes. Minimal PTH suppressive calcitriol dosages should be used in order to keep PTH levels in the desired target range [150]. However, current pediatric consensus guidelines differ markedly with respect to the optimal PTH range. The European guidelines (EPDWG) recommend that the PTH should be maintained within the normal range in children with GFR < 30 ml/min/1.73 m^2 and within two to three times the ULN in CKD stage 5 [78, 90]. In contrast, the US-based K/DOQI guidelines recommend a target range of three to five times the ULN in stage 5 CKD [20]. The Global Outcome (KDIGO) guidelines recommend a PTH target range of two to nine times the ULN in stage 5 CKD, the higher end of the range rarely deemed acceptable in pediatric bone care [151]. However, most important is the recognition that none of these recommendations have been validated in a large pediatric stage 5 cohort. Most recently, data from the IPPN has suggested that an optimal PTH target range of 1.7–3 times ULN in pediatric PD patients is associated with lower CKD-MBD complications like growth failure [152].

Calcimimetics

Uncontrolled and controlled studies provide evidence that calcimimetics are an effective therapy of sHPT in pediatric dialysis patients [153–157]. Calcimimetics suppress PTH secretion by activating the calcium-sensing receptor (CaR). The CaR is expressed by epiphyseal chondrocytes; its stimulation stimulates chondrocytic proliferation and differentiation. Thus, calcimimetics may affect longitudinal growth in uremia as well. In fact, one calcimimetic (cinacalcet) has been shown to improve food efficiency and body weight gain in uremic rats, but no specific effects on growth plate morphology and/or longitudinal growth were seen [158]. Likewise, no beneficial or adverse effect on longitudinal growth was noted during calcimimetic treatment periods of up to 3 years in children on dialysis [153–155].

Growth Hormone

Pharmacological treatment of children with CKD and growth delay with rhGH actually predated understanding of the pathomechanisms that underlie chronic uremic alterations of the GH-IGF-I axis [109, 159, 160]. Administration of rhGH markedly stimulates IGF-I synthesis with only a modest effect on IGFBPs, thereby normalizing somatomedin bioactivity and promoting longitudinal growth [161]. The efficacy and safety of long-term treatment with rhGH in children with CKD before and after renal transplantation have been established, and clinical practice recommendations on this topic were recently published in 2019 [22].

Efficacy of rhGH in Prepubertal Children

In prepubertal children with pre-dialysis CKD, rhGH therapy typically doubles height velocity during the first treatment year [162]. Catch-up growth continues asymptotically during extended treatment [163–165]. In dialyzed children, the treatment response is significantly attenuated compared to children with pre-dialysis CKD (0.8 SD vs. 1.3 SD) [166]. RhGH responsiveness is similarly poor in children on

peritoneal dialysis and standard hemodialysis, but as noted previously, can be markedly improved when dialytic clearance is augmented by daily HDF [138].

Based on the current experience with rhGH in pediatric CKD patients, a model to predict growth response was developed [167]. The prediction model was developed using a cohort of 208 prepubertal children on conservative or dialysis treatment followed in a pharmaco-epidemiological survey (KIGS) and validated in an independent group of 67 CKD patients registered at the Dutch Growth Research Foundation. The height velocity during the first rhGH treatment year (PHV) was predicted by the following equation: PHV (centimeters per year) = 13.3 − [age (years) × 0.38 + (weight SDS × 0.39)] − [hereditary renal disorder (0 when absent or 1 when present) × 1.16] + [Ln rhGH dose (mg/kg/week) × 1.04] + [GFR (ml/min × 1.73 m^2) × 0.023]. This equation explains 37% of the overall variability of the growth response. The SE of the estimate or error SD of the prediction model was 1.6 cm, and non-responders in the validation group were correctly identified. This model may help in predicting non-responders and in tailoring treatment strategies for growth-retarded children with CKD.

Another useful method to assess adequacy of growth response to rhGH therapy in children with CKD comes from the Genentech National Cooperative Growth Study [168]. First-year growth response curves were constructed from actual data from 270 naive-to-rhGH, prepubertal children with CKD (186 males, 84 females). Data from both genders were combined because gender was not significantly related to height velocity. Age-specific height velocity (HV) in cm/year plots including mean, mean ± 1 SD, and mean − 2 SD during first year of rhGH treatment is available and can be used to assess a patient's first-year growth response. HV below the mean − 1 SD can be considered an inadequate response. These curves may help identify patients with a suboptimal growth response due to confounding medical factors and/or non-compliance.

Several RCTs have shown the benefit of GH therapy in short prepubertal renal transplant recipients. A meta-analysis of 5 prospective RCTs involving a total of 401 patients showed that patients receiving rhGH therapy had a significantly higher growth velocity 1 year after the initiation of therapy than the control group, with a mean height SDS difference of 0.68 (95% CI 0.25–1.11) [162]. The mean difference in height SDS change between the treated and the control group was 0.52 (95% CI 0.37–0.68).

Effects of rhGH on Pubertal Growth and Final Height

In a study following patients with CKD and ESKD from late prepubertal age to final height, the average height increment in rhGH-treated patients was twice that seen in a matched control group [12]. The main benefit for total growth and final height was achieved before the onset of the pubertal growth spurt, whereas no overall effect on pubertal height gain was observed (Fig. 28.11).

Data on adult height are available from 11 non-randomized trials in which rhGH was administered for at least 2 years, comprising a total of 836 patients on various modes of RRT which were summarized by Drube et al. [22]. In five studies, a matched historical control group was included. The median change in standardized height until attainment of adult height amounted to 1.1 SDS (range 0.2–1.6 SDS) in rhGH-treated patients ($P < 0.05$ for each final height measurement versus initial height measurement). This change corresponded to a median absolute increase in rhGH-treated patients of 7.4 cm (range 1.4–10.8 cm) in boys and 7.0 cm (range 1.3–10.1 cm) in girls, based on European reference values. However, this calculation may represent a poor estimate (likely an underestimate) of median absolute height increase, since adult height was significantly lower in non-rhGH-treated controls than initial standardized height indices in all except one study. Heights attained at the start of rhGH and throughout the duration

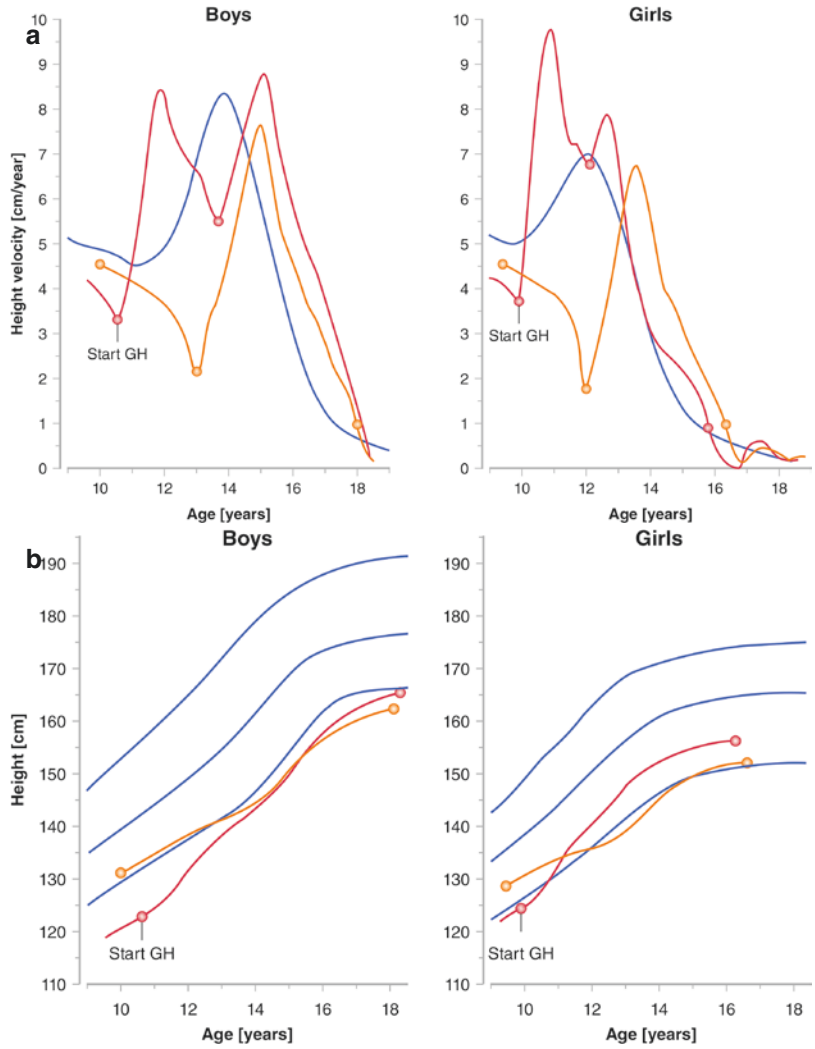


Fig. 28.11 (**a**) Synchronized mean height velocity curves of 32 boys (left panel) and 6 girls (right panel) with CKD during rhGH treatment (closed circles), as compared with 50 children with CKD not treated with rhGH (open circles) and 232 normal children (thin lines). The dots indicate the time of the first observation, which corresponds to the start of rhGH treatment in the growth hormone-treated children, minimal prespurt height velocity, and the time of the end of the pubertal growth spurt. (Reproduced with permission of Ref. [12]). (**b**) Synchronized mean height curves of 32 boys (left panel) and 6 girls (right panel) with CKD during rhGH treatment (closed circles), as compared with 50 children with CKD not treated with rhGH (open circles). Normal values are indicated by the 3rd, 50th, and 97th percentiles. The dots indicate the time of the first observation, which corresponds to the start of rhGH treatment in the growth hormone-treated children, and the time of the end of the pubertal growth spurt. (Reproduced with permission of Ref. [12])

of rhGH treatment were positively associated with final height, whereas time spent on dialysis, age at puberty onset, and age of start of rhGH were negatively associated with final height [12, 27]. Taken together, the available studies suggest that rhGH improves adult height in short prepubertal and pubertal CKD patients prior to and after renal transplantation.

Efficacy of rhGH in Infants

According to standard concepts of the pathophysiology of uremic growth failure, malnutrition and fluid and electrolyte imbalances have a much greater impact on infant growth than alterations of somatotropic hormones. Consequently, correction of the nutritional status has been considered the primary measure to restore normal growth in growth-retarded infants, postponing the option of endocrine therapeutic intervention to beyond the second year of life. This concept has been challenged by several reports of initiating rhGH in growth-retarded infants with CKD [169–172]. A randomized controlled study involving 30 growth-retarded infants (mean age: 16 months) with moderate CKD (mean GFR: 25 ml/min/1.73 m^2) revealed excellent catch-up growth from −3.0 to −1.1 SDS within 24 months of drug initiation, in contrast to no significant change in controls [172]. Likewise, Maxwell and Rees reported an increase in height SDS from −3.3 to −2.2 within 12 months in eight infants with a mean age of 22 months and CKD stage 3–4 [170]. Mencarelli et al. reported on a cohort of 27 infants with early-onset CKD receiving standard therapy with or without the addition of rhGH treatment [171]. Children treated with rhGH, but not patients undergoing close nutritional management only, showed significant increases in both weight and height SDS. Notably, two thirds of the patients receiving rhGH were on dialysis. Hence, the results of these studies lend further support to the previous observation that the relative efficacy and cost efficiency of rhGH are actually best when initiated at young age, i.e., during infancy and early childhood [22]. While the provision of adequate nutrition is certainly vital to growth and development of infants with CKD, some children show growth failure despite adequate nutrition. In these patients, any further increases of energy intake typically lead to fat deposition, but not catch-up growth. Early rhGH therapy appears to be an attractive option to accelerate length and weight gain in such infants. The fact that the enhanced growth also helps the infant achieve the body size required for renal transplantation more expeditiously is yet another benefit [22].

General rhGH Treatment Strategies

Children above 6 months of age with stage 3–5 CKD or on dialysis should be candidates for rhGH therapy if they have persistent growth failure, defined as a height below the 3rd percentile for age and sex and a height velocity below the 25th percentile, once other potentially treatable risk factors for growth failure have been adequately addressed, and provided the child has growth potential (open epiphysis on x-ray of the wrist) [22]. RhGH therapy should also be considered for children with stage 3–5 CKD or on dialysis aged above 6 months, who present with a height between the 3rd and 10th percentiles, but persistent low height velocity (<25th percentile), once other potentially treatable risk factors for growth failure have been adequately addressed. Such early, preventive therapy is probably more cost-effective than starting at a more advanced age when growth retardation has become more evident and higher absolute rhGH doses are required.

The growth response to rhGH treatment is positively associated with residual renal function, target height, initial target height deficit, and duration of rhGH treatment and inversely correlated with the age at the start of treatment [12, 27, 163, 166, 167]. Daily dosing is more effective than three doses per week, and the optimal dose is 0.045–0.05 mg/kg body weight per day by subcutaneous injections in the evening [22]. There has been a recent recommendation from patients/parents in Europe that parents and physicians should encourage children from about 8 to 10 years of age to do the rhGH injections on their own, if adequate training and adherence can be assured, because this may ultimately improve patient adherence and self-esteem [22]. Whereas discontinuation of rhGH results in catch-down growth in approximately 75% of CKD patients, this phenomenon is rarely observed when rhGH

treatment is discontinued after transplantation, highlighting the close relationship between renal function and growth [173]. Furthermore, although the absolute height gain achieved by rhGH is independent of age, the reference range increases with age. Thus, rhGH treatment should be started as early as growth retardation becomes evident (i.e., height below 3rd percentile) [22, 163]. If height velocity in the first year of rhGH treatment is less than 2 cm/year over baseline, it is recommended to assess patient adherence to rhGH therapy through the measurement of serum IGF-I levels, as well as ensuring the correct weight-adjusted rhGH dosage, and addressing any additional nutritional and metabolic issues [22].

The primary treatment target should be to return the child's height into her/his individual genetic percentile channel. Treatment may be suspended once this target is reached, but growth should be monitored closely as outlined above. In patients receiving rhGH while on conservative treatment, rhGH should be continued after the initiation of dialysis, but stopped at the time of renal transplantation. RhGH therapy should, however, subsequently also be considered for pediatric renal transplant recipients for whom expected catch-up growth cannot be achieved by steroid minimization or for patients in whom steroid withdrawal is not feasible due to high immunological risk, particularly in children with suboptimal graft function (eGFR <50 ml/min/1.73 m^2). Growth should be monitored for at least 1 year post-transplantation before rhGH therapy is considered, in order to allow for spontaneous catch-up growth without need for rhGH therapy [22].

Potential Adverse Events Associated with rhGH Therapy

The safety of long-term rhGH treatment in CKD has been evaluated in several clinical studies and registries which have been summarized by Drube et al. [22]. RhGH therapy in short children with CKD on conservative treatment, on dialysis, and after renal transplantation was not associated with an increased incidence of malignancy, slipped capital femoral epiphysis, avascular necrosis, glucose intolerance, pancreatitis, progressive deterioration of renal function, acute allograft rejection, or fluid retention. Intracranial hypertension (ICH) in 3 out of 1376 CKD patients was the only adverse event significantly associated with rhGH therapy [174]. However, in all three instances, ICH occurred after discontinuation of rhGH. Therefore, due to the potentially increased risk of ICH in CKD, baseline fundoscopy is recommended prior to therapy initiation [22]. Furthermore, hydration should be carefully monitored in CKD patients receiving rhGH since overhydration may be a predisposing factor for ICH. In the presence of symptoms like headache or vomiting, an immediate workup for ICH including fundoscopy should be performed.

Although insulin secretion increases during the first year of rhGH treatment and hyperinsulinemia persists during long-term therapy, normal glucose tolerance is preserved during up to 5 years of rhGH administration in CKD patients on conservative treatment, on dialysis, and after renal transplantation. Hyperinsulinemia is most pronounced in transplanted patients on concomitant glucocorticoid therapy. Hyperinsulinemia may, at least in theory, contribute to the development of atherosclerosis or induce diabetes mellitus by exhaustion of ß-cells. However, up to now, this has not been observed in CKD patients receiving rhGH [174].

Aggravation of secondary hyperparathyroidism has rarely been reported in CKD patients on rhGH treatment, and the underlying pathomechanisms remains to be elucidated [175]. RhGH might have a direct stimulatory effect on the parathyroid gland and/or might have subtle effects on calcium homeostasis which in turn stimulate PTH secretion. Finally, increased longitudinal bone growth by rhGH treatment may unmask preexisting renal osteodystrophy. Therefore, bone metabolism should be evaluated carefully in candidates for rhGH therapy, and severe hyperparathyroidism and renal osteodystrophy should be adequately treated before initiation of such therapy in CKD patients. Likewise, rhGH therapy should be stopped in patients with persistent severe secondary hyperparathyroidism

(PTH > 500 pg/ml). RhGH may be reinstituted when PTH levels return to the desired PTH target range [22].

Future Perspectives

Despite attention to nutrition and the availability of rhGH therapy, the problem of CKD-associated growth failure has not been resolved in the majority of dialysis patients. If early renal transplantation is not possible, the recently propagated concept of intensified hemodialysis (thrice-weekly nocturnal or short daily sessions) combined with rhGH may be a promising option for patients suffering from growth retardation and GH insensitivity on conventional dialysis therapy. If this is not feasible, conventional HDF should be pursued instead of HD in centers where HDF is available [137, 140].

Self-reported nonadherence to rhGH was associated with poorer growth velocity in children with CKD. Therefore, adherence to rhGH therapy may be an excellent opportunity for intervention and improved patient outcome [176]. Another avenue of promising clinical research may be related to the provision of recombinant IGF-I administered as monotherapy or in combination with rhGH and targeting of the SOCS2 signaling pathway [177].

A particular challenge is the management of severely diminished pubertal height gain seen in some adolescents with CKD. In such adolescents, pharmacological inhibition of epiphyseal closure may allow an extended duration of the remaining growth period. Since the closure of the epiphyseal growth plate is induced by local estrogen action, inhibition of estrogen synthesis is a principal therapeutic option. Whereas gonadotropin-releasing hormone analogues arrest pubertal progress, the potential growth benefit would come at the psychological disadvantage of delayed sexual maturation. In boys, aromatase inhibitors, which suppress local conversion of testosterone to estradiol, might extend the growth phase without affecting pubertal development and thereby increase the time window for the use of rhGH therapy. An initial proof of concept has been provided in short male adolescents treated with rhGH combined with the aromatase inhibitor anastrozole [178]. It would be fascinating to study its efficacy in adolescents on long-term dialysis. Nevertheless, successful early (preemptive) renal transplantation with minimal steroid exposure is ultimately the best current measure to improve growth and final height in children with CKD stage 5.

References

1. Haffner D, Zivicnjak M. Pubertal development in children with chronic kidney disease. Pediatr Nephrol. 2017;32(6):949–64.
2. Mehls O, Schaefer F. Endocrine, metabolic and growth disorders-patterns of growth and maturation in chronic renal failure-impact of developmental stage. In: Holliday MA, editor. Pediatr nephrology. 3rd ed. Baltimore: Williams & Wilkins; 1994. p. 1260–3.
3. Zivicnjak M, Franke D, Filler G, Haffner D, Froede K, Nissel R, et al. Growth impairment shows an age-dependent pattern in boys with chronic kidney disease. Pediatr Nephrol. 2007;22(3):420–9.
4. Franke D, Thomas L, Steffens R, Pavicic L, Gellermann J, Froede K, et al. Patterns of growth after kidney transplantation among children with ESRD. Clin J Am Soc Nephrol. 2015;10(1):127–34.
5. Harambat J, Bonthuis M, van Stralen KJ, Ariceta G, Battelino N, Bjerre A, et al. Adult height in patients with advanced CKD requiring renal replacement therapy during childhood. Clin J Am Soc Nephrol. 2014;9(1):92–9.
6. Gil S, Aziz M, Adragna M, Monteverde M, Belgorosky A. Near-adult height in male kidney transplant recipients started on growth hormone treatment in late puberty. Pediatr Nephrol. 2018;33(1):175–80.
7. Fine RN, Martz K, Stablein D. What have 20 years of data from the North American Pediatric Renal Transplant Cooperative Study taught us about growth following renal transplantation in infants, children, and adolescents with end-stage renal disease? Pediatr Nephrol. 2010;25(4):739–46.
8. Klare B, Montoya CR, Fischer DC, Stangl MJ, Haffner D. Normal adult height after steroid-withdrawal within 6 months of pediatric kidney transplantation: a 20 years single center experience. Transpl Int. 2012;25(3):276–82.
9. Franke D, Winkel S, Gellermann J, Querfeld U, Pape L, Ehrich JH, et al. Growth and maturation improvement in children on renal replacement therapy over the past 20 years. Pediatr Nephrol. 2013;28(10):2043–51.

10. Andre JL, Bourquard R, Guillemin F, Krier MJ, Briancon S. Final height in children with chronic renal failure who have not received growth hormone. Pediatr Nephrol. 2003;18(7):685–91.
11. Englund MS, Tyden G, Wikstad I, Berg UB. Growth impairment at renal transplantation – a determinant of growth and final height. Pediatr Transplant. 2003;7(3):192–9.
12. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. N Engl J Med. 2000;343(13):923–30.
13. Al-Uzri A, Matheson M, Gipson DS, Mendley SR, Hooper SR, Yadin O, et al. The impact of short stature on health-related quality of life in children with chronic kidney disease. J Pediatr. 2013;163(3):736–41.e1.
14. Wong CS, Gipson DS, Gillen DL, Emerson S, Koepsell T, Sherrard DJ, et al. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis. 2000;36(4):811–9.
15. Furth SL, Stablein D, Fine RN, Powe NR, Fivush BA. Adverse clinical outcomes associated with short stature at dialysis initiation: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics. 2002;109(5):909–13.
16. Ku E, Fine RN, Hsu CY, McCulloch C, Glidden DV, Grimes B, et al. Height at first RRT and mortality in children. Clin J Am Soc Nephrol. 2016;11(5):832–9.
17. Hartung EA, Furth SL. Growth in children on renal replacement therapy: a shrinking problem? Pediatr Nephrol. 2013;28(10):1905–8.
18. Schaefer F, Borzych-Duzalka D, Azocar M, Munarriz RL, Sever L, Aksu N, et al. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry. Perit Dial Int. 2012;32(4):399–409.
19. Akchurin OM, Kogon AJ, Kumar J, Sethna CB, Hammad HT, Christos PJ, et al. Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report. BMC Nephrol. 2017;18(1):181–017.
20. KDOQI Work Group. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53(3 Suppl 2):S11–104.
21. Mahan JD, Warady BA, Consensus Committee. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. Pediatr Nephrol. 2006;21(7):917–30.
22. Drube J, Wan M, Bonthuis M, Wuhl E, Bacchetta J, Santos F, et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. Nat Rev Nephrol. 2019;15(9):577–89.
23. Nissel R, Brazda I, Feneberg R, Wigger M, Greiner C, Querfeld U, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. Kidney Int. 2004;66(2):792–800.
24. Offner G, Latta K, Hoyer PF, Baum HJ, Ehrich JH, Pichlmayr R, et al. Kidney transplanted children come of age. Kidney Int. 1999;55(4):1509–17.
25. Ninik A, McTaggart SJ, Gulati S, Powell HR, Jones CL, Walker RG. Factors influencing growth and final height after renal transplantation. Pediatr Transplant. 2002;6(3):219–23.
26. Rees L, Shroff R, Hutchinson C, Fernando ON, Trompeter RS. Long-term outcome of paediatric renal transplantation: follow-up of 300 children from 1973 to 2000. Nephron Clin Pract. 2007;105(2):c68–76.
27. Nissel R, Lindberg A, Mehls O, Haffner D, Pfizer International Growth Database (KIGS) International Board. Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. J Clin Endocrinol Metab. 2008;93(4):1359–65.
28. Nissel R, Latta K, Gagnadoux MF, Kelly D, Hulton S, Kemper MJ, et al. Body growth after combined liver-kidney transplantation in children with primary hyperoxaluria type 1. Transplantation. 2006;82(1):48–54.
29. Schaefer F, Seidel C, Binding A, Gasser T, Largo RH, Prader A, et al. Pubertal growth in chronic renal failure. Pediatr Res. 1990;28(1):5–10.
30. Karlberg J, Schaefer F, Hennicke M, Wingen AM, Rigden S, Mehls O. Early age-dependent growth impairment in chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol. 1996;10(3):283–7.
31. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7.
32. Mekahli D, Shaw V, Ledermann SE, Rees L. Long-term outcome of infants with severe chronic kidney disease. Clin J Am Soc Nephrol. 2010;5(1):10–7.
33. Greenbaum LA, Munoz A, Schneider MF, Kaskel FJ, Askenazi DJ, Jenkins R, et al. The association between abnormal birth history and growth in children with CKD. Clin J Am Soc Nephrol. 2011;6(1):14–21.
34. Franke D, Volker S, Haase S, Pavicic L, Querfeld U, Ehrich JH, et al. Prematurity, small for gestational age and perinatal parameters in children with congenital, hereditary and acquired chronic kidney disease. Nephrol Dial Transplant. 2010;25(12):3918–24.
35. Kleinknecht C, Broyer M, Huot D, Marti-Henneberg C, Dartois AM. Growth and development of nondialyzed children with chronic renal failure. Kidney Int Suppl. 1983;15:S40–7.
36. Warady BA, Kriley M, Lovell H, Farrell SE, Hellerstein S. Growth and development of infants with end-stage renal disease receiving long-term peritoneal dialysis. J Pediatr. 1988;112(5):714–9.

37. Schaefer F, Wingen AM, Hennicke M, Rigden S, Mehls O. Growth charts for prepubertal children with chronic renal failure due to congenital renal disorders. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol. 1996;10(3):288–93.
38. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR. Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol. 2000;15(3–4):259–65.
39. Ku E, Kopple JD, McCulloch CE, Warady BA, Furth SL, Mak RH, et al. Associations between weight loss, kidney function decline, and risk of ESRD in the Chronic Kidney Disease in Children (CKiD) Cohort Study. Am J Kidney Dis. 2018;71(5):648–56.
40. Rodig NM, McDermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, et al. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. Pediatr Nephrol. 2014;29(10):1987–95.
41. Scharer K. Growth and development of children with chronic renal failure. Study Group on Pubertal Development in Chronic Renal Failure. Acta Paediatr Scand Suppl. 1990;366:90–2.
42. Burke BA, Lindgren B, Wick M, Holley K, Manivel C. Testicular germ cell loss in children with renal failure. Pediatr Pathol. 1989;9(4):433–44.
43. Tainio J, Qvist E, Vehmas R, Jahnukainen K, Holtta T, Valta H, et al. Pubertal development is normal in adolescents after renal transplantation in childhood. Transplantation. 2011;92(4):404–9.
44. Zivicnjak M, Franke D, Ehrich JH, Filler G. Does growth hormone therapy harmonize distorted morphology and body composition in chronic renal failure? Pediatr Nephrol. 2000;15(3–4):229–35.
45. Kinra S, Sarma KV, Hards M, Smith GD, Ben-Shlomo Y. Is relative leg length a biomarker of childhood nutrition? Long-term follow-up of the Hyderabad Nutrition Trial. Int J Epidemiol. 2011;40(4):1022–9.
46. Smith GD, Greenwood R, Gunnell D, Sweetnam P, Yarnell J, Elwood P. Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. J Epidemiol Community Health. 2001;55(12):867–72.
47. Gunnell D, Whitley E, Upton MN, McConnachie A, Smith GD, Watt GC. Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. J Epidemiol Community Health. 2003;57(2):141–6.
48. Franke D, Steffens R, Thomas L, Pavicic L, Ahlenstiel T, Pape L, et al. Kidney transplantation fails to provide adequate growth in children with chronic kidney disease born small for gestational age. Pediatr Nephrol. 2017;32(3):511–9.
49. Franke D, Alakan H, Pavicic L, Gellermann J, Muller D, Querfeld U, et al. Birth parameters and parental height predict growth outcome in children with chronic kidney disease. Pediatr Nephrol. 2013;28(12):2335–41.
50. Hiraoka M. Medical management of congenital anomalies of the kidney and urinary tract. Pediatr Int. 2003;45(5):624–33.
51. Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health. 2018;2(12):880–90.
52. Dufek S, Holtta T, Trautmann A, Ylinen E, Alpay H, Ariceta G, et al. Management of children with congenital nephrotic syndrome: challenging treatment paradigms. Nephrol Dial Transplant. 2019;34(8):1369–77.
53. Dufek S, Ylinen E, Trautmann A, Alpay H, Ariceta G, Aufricht C, et al. Infants with congenital nephrotic syndrome have comparable outcomes to infants with other renal diseases. Pediatr Nephrol. 2019;34(4):649–55.
54. Licht C, Eifinger F, Gharib M, Offner G, Michalk DV, Querfeld U. A stepwise approach to the treatment of early onset nephrotic syndrome. Pediatr Nephrol. 2000;14(12):1077–82.
55. Greco M, Brugnara M, Zaffanello M, Taranta A, Pastore A, Emma F. Long-term outcome of nephropathic cystinosis: a 20-year single-center experience. Pediatr Nephrol. 2010;25(12):2459–67.
56. Hohenfellner K, Rauch F, Ariceta G, Awan A, Bacchetta J, Bergmann C, et al. Management of bone disease in cystinosis: statement from an international conference. J Inherit Metab Dis. 2019;42(5):1019–29.
57. Gahl WA. Early oral cysteamine therapy for nephropathic cystinosis. Eur J Pediatr. 2003;162(Suppl 1):S38–41.
58. Van Stralen KJ, Emma F, Jager KJ, Verrina E, Schaefer F, Laube GF, et al. Improvement in the renal prognosis in nephropathic cystinosis. Clin J Am Soc Nephrol. 2011;6(10):2485–91.
59. Rumsby G, Cochat P. Primary hyperoxaluria. N Engl J Med. 2013;369(22):2163.
60. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. Pediatr Nephrol. 2013;28(4):527–36.
61. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. Pediatr Nephrol. 2012;27(2):173–81.
62. Rees L, Mak RH. Nutrition and growth in children with chronic kidney disease. Nat Rev Nephrol. 2011;7(11):615–23.
63. Chen Y, Biada J, Sood S, Rabkin R. Uremia attenuates growth hormone-stimulated insulin-like growth factor-1 expression, a process worsened by inflammation. Kidney Int. 2010;78(1):89–95.
64. Chen Y, Sood S, Krishnamurthy VM, Rotwein P, Rabkin R. Endotoxin-induced growth hormone resistance in skeletal muscle. Endocrinology. 2009;150(8):3620–6.
65. Zheng Z, Sun DF, Tummala P, Rabkin R. Cardiac resistance to growth hormone in uremia. Kidney Int. 2005;67(3):858–66.

66. Sun DF, Zheng Z, Tummala P, Oh J, Schaefer F, Rabkin R. Chronic uremia attenuates growth hormone-induced signal transduction in skeletal muscle. J Am Soc Nephrol. 2004;15(10):2630–6.
67. Mehls O, Ritz E, Gilli G, Bartholome K, Beissbarth H, Hohenegger M, et al. Nitrogen metabolism and growth in experimental uremia. Int J Pediatr Nephrol. 1980;1(1):34–41.
68. Arnold WC, Danford D, Holliday MA. Effects of caloric supplementation on growth in children with uremia. Kidney Int. 1983;24(2):205–9.
69. Coleman JE, Watson AR. Gastrostomy buttons for nutritional support in children with cystinosis. Pediatr Nephrol. 2000;14(8–9):833–6.
70. Ledermann SE, Shaw V, Trompeter RS. Long-term enteral nutrition in infants and young children with chronic renal failure. Pediatr Nephrol. 1999;13(9):870–5.
71. Bonthuis M, van Stralen KJ, Verrina E, Groothoff JW, Alonso Melgar A, Edefonti A, et al. Underweight, overweight and obesity in paediatric dialysis and renal transplant patients. Nephrol Dial Transplant. 2013;28(Suppl 4):iv195–204.
72. Rees L, Azocar M, Borzych D, Watson AR, Buscher A, Edefonti A, et al. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22(12):2303–12.
73. Bailey JL, Wang X, England BK, Price SR, Ding X, Mitch WE. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. J Clin Invest. 1996;97(6):1447–53.
74. Boirie Y, Broyer M, Gagnadoux MF, Niaudet P, Bresson JL. Alterations of protein metabolism by metabolic acidosis in children with chronic renal failure. Kidney Int. 2000;58(1):236–41.
75. Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: new cause of growth hormone insensitivity in humans. Kidney Int. 1997;51(1):216–21.
76. Challa A, Chan W, Krieg RJ, Thabet MA, Liu F, Hintz RL, et al. Effect of metabolic acidosis on the expression of insulin-like growth factor and growth hormone receptor. Kidney Int. 1993;44(6):1224–7.
77. Challa A, Krieg RJ, Thabet MA, Veldhuis JD, Chan JC. Metabolic acidosis inhibits growth hormone secretion in rats: mechanism of growth retardation. Am J Phys. 1993;265(4 Pt 1):E547–53.
78. Klaus G, Watson A, Edefonti A, Fischbach M, Ronnholm K, Schaefer F, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol. 2006;21(2):151–9.
79. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 2017;92(1):26–36.
80. Chesney RW, Hamstra A, Jax DK, Mazess RB, DeLuca HF. Influence of long-term oral 1,25-dihydroxyvitamin D in childhood renal osteodystrophy. Contrib Nephrol. 1980;18:55–71.
81. Kreusser W, Weinkauff R, Mehls O, Ritz E. Effect of parathyroid hormone, calcitonin and growth hormone on cAMP content of growth cartilage in experimental uraemia. Eur J Clin Investig. 1982;12(4):337–43.
82. Mehls O, Knoller N, Oh J, Wesch H, Wunsche B, Schmitt CP. Daily but not pulse calcitriol therapy improves growth in experimental uremia. Pediatr Nephrol. 2000;14(7):658–63.
83. Pereira RC, Salusky IB, Roschger P, Klaushofer K, Yadin O, Freymiller EG, et al. Impaired osteocyte maturation in the pathogenesis of renal osteodystrophy. Kidney Int. 2018;94(5):1002–12.
84. Klaus G, Jux C, Fernandez P, Rodriguez J, Himmele R, Mehls O. Suppression of growth plate chondrocyte proliferation by corticosteroids. Pediatr Nephrol. 2000;14(7):612–5.
85. Evenepoel P, Bover J, Torres PU. Parathyroid hormone metabolism and signaling in health and chronic kidney disease. Kidney Int. 2016;90(6):1184–90.
86. Kuizon BD, Goodman WG, Juppner H, Boechat I, Nelson P, Gales B, et al. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int. 1998;53(1):205–11.
87. Bakkaloglu SA, Wesseling-Perry K, Pereira RC, Gales B, Wang HJ, Elashoff RM, et al. Value of the new bone classification system in pediatric renal osteodystrophy. Clin J Am Soc Nephrol. 2010;5(10):1860–6.
88. Waller S, Shroff R, Freemont AJ, Rees L. Bone histomorphometry in children prior to commencing renal replacement therapy. Pediatr Nephrol. 2008;23(9):1523–9.
89. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, et al. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78(12):1295–304.
90. Morris KP, Sharp J, Watson S, Coulthard MG. Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia. Arch Dis Child. 1993;69(5):580–6.
91. Jabs K. The effects of recombinant human erythropoietin on growth and nutritional status. Pediatr Nephrol. 1996;10(3):324–7.
92. Doyon A, Fischer DC, Bayazit AK, Canpolat N, Duzova A, Sozeri B, et al. Markers of bone metabolism are affected by renal function and growth hormone therapy in children with chronic kidney disease. PLoS One. 2015;10(2):e0113482.
93. Troib A, Guterman M, Rabkin R, Landau D, Segev Y. Endurance exercise and growth hormone improve bone formation in young and growth-retarded chronic kidney disease rats. Nephrol Dial Transplant. 2016;31(8):1270–9.
94. Belgorosky A, Ferraris JR, Ramirez JA, Jasper H, Rivarola MA. Serum sex hormone-binding globulin

and serum nonsex hormone-binding globulin-bound testosterone fractions in prepubertal boys with chronic renal failure. J Clin Endocrinol Metab. 1991;73(1):107–10.
95. Van Kammen E, Thijssen JH, Schwarz F. Sex hormones in male patients with chronic renal failure. I. The production of testosterone and of androstenedione. Clin Endocrinol. 1978;8(1):7–14.
96. Oertel PJ, Lichtwald K, Hafner S, Rauh W, Schonberg D, Scharer K. Hypothalamo-pituitary-gonadal axis in children with chronic renal failure. Kidney Int Suppl. 1983;15:S34–9.
97. Mitchell R, Schaefer F, Morris ID, Scharer K, Sun JG, Robertson WR. Elevated serum immunoreactive inhibin levels in peripubertal boys with chronic renal failure. Cooperative Study Group on Pubertal Development in Chronic Renal Failure (CSPCRF). Clin Endocrinol. 1993;39(1):27–33.
98. Ferraris JR, Domene HM, Escobar ME, Caletti MG, Ramirez JA, Rivarola MA. Hormonal profile in pubertal females with chronic renal failure: before and under haemodialysis and after renal transplantation. Acta Endocrinol. 1987;115(3):289–96.
99. Schaefer F, Seidel C, Mitchell R, Scharer K, Robertson WR. Pulsatile immunoreactive and bioactive luteinizing hormone secretion in adolescents with chronic renal failure. The Cooperative Study Group on Pubertal Development in Chronic Renal Failure (CSPCRF). Pediatr Nephrol. 1991;5(4):566–71.
100. Schaefer F, Veldhuis JD, Robertson WR, Dunger D, Scharer K. Immunoreactive and bioactive luteinizing hormone in pubertal patients with chronic renal failure. Cooperative Study Group on Pubertal Development in Chronic Renal Failure. Kidney Int. 1994;45(5):1465–76.
101. Schaefer F, Daschner M, Veldhuis JD, Oh J, Qadri F, Scharer K. In vivo alterations in the gonadotropin-releasing hormone pulse generator and the secretion and clearance of luteinizing hormone in the uremic castrate rat. Neuroendocrinology. 1994;59(3):285–96.
102. Daschner M, Philippin B, Nguyen T, Wiesner RJ, Walz C, Oh J, et al. Circulating inhibitor of gonadotropin releasing hormone secretion by hypothalamic neurons in uremia. Kidney Int. 2002;62(5):1582–90.
103. Schaefer F, Vogel M, Kerkhoff G, Woitzik J, Daschner M, Mehls O. Experimental uremia affects hypothalamic amino acid neurotransmitter milieu. J Am Soc Nephrol. 2001;12(6):1218–27.
104. Mitchell R, Bauerfeld C, Schaefer F, Scharer K, Robertson WR. Less acidic forms of luteinizing hormone are associated with lower testosterone secretion in men on haemodialysis treatment. Clin Endocrinol. 1994;41(1):65–73.
105. Haffner D, Schaefer F, Girard J, Ritz E, Mehls O. Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. J Clin Invest. 1994;93(3):1163–71.
106. Schaefer F, Baumann G, Haffner D, Faunt LM, Johnson ML, Mercado M, et al. Multifactorial control of the elimination kinetics of unbound (free) growth hormone (GH) in the human: regulation by age, adiposity, renal function, and steady state concentrations of GH in plasma. J Clin Endocrinol Metab. 1996;81(1):22–31.
107. Tonshoff B, Veldhuis JD, Heinrich U, Mehls O. Deconvolution analysis of spontaneous nocturnal growth hormone secretion in prepubertal children with preterminal chronic renal failure and with end-stage renal disease. Pediatr Res. 1995;37(1):86–93.
108. Schaefer F, Veldhuis JD, Stanhope R, Jones J, Scharer K. Alterations in growth hormone secretion and clearance in peripubertal boys with chronic renal failure and after renal transplantation. Cooperative Study Group of Pubertal development in Chronic Renal Failure. J Clin Endocrinol Metab. 1994;78(6):1298–306.
109. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. J Clin Invest. 2001;108(3):467–75.
110. Troib A, Landau D, Kachko L, Rabkin R, Segev Y. Epiphyseal growth plate growth hormone receptor signaling is decreased in chronic kidney disease-related growth retardation. Kidney Int. 2013;84(5):940–9.
111. Edmondson SR, Baker NL, Oh J, Kovacs G, Werther GA, Mehls O. Growth hormone receptor abundance in tibial growth plates of uremic rats: GH/IGF-I treatment. Kidney Int. 2000;58(1):62–70.
112. Wiezel D, Assadi MH, Landau D, Troib A, Kachko L, Rabkin R, et al. Impaired renal growth hormone JAK/STAT5 signaling in chronic kidney disease. Nephrol Dial Transplant. 2014;29(4):791–9.
113. Tsao T, Fervenza F, Friedlaender M, Chen Y, Rabkin R. Effect of prolonged uremia on insulin-like growth factor-I receptor autophosphorylation and tyrosine kinase activity in kidney and muscle. Exp Nephrol. 2002;10(4):285–92.
114. Tonshoff B, Cronin MJ, Reichert M, Haffner D, Wingen AM, Blum WF, et al. Reduced concentration of serum growth hormone (GH)-binding protein in children with chronic renal failure: correlation with GH insensitivity. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. J Clin Endocrinol Metab. 1997;82(4):1007–13.
115. Fouque D. Insulin-like growth factor 1 resistance in chronic renal failure. Miner Electrolyte Metab. 1996;22(1–3):133–7.
116. Powell DR, Liu F, Baker BK, Hinzt RL, Kale A, Suwanichkul A, et al. Effect of chronic renal failure and growth hormone therapy on the insulin-like growth factors and their binding proteins. Pediatr Nephrol. 2000;14(7):579–83.
117. Powell DR, Liu F, Baker BK, Hintz RL, Lee PD, Durham SK, et al. Modulation of growth factors by growth hormone in children with chronic renal

failure. The Southwest Pediatric Nephrology Study Group. Kidney Int. 1997;51(6):1970–9.
118. Ding H, Gao XL, Hirschberg R, Vadgama JV, Kopple JD. Impaired actions of insulin-like growth factor 1 on protein synthesis and degradation in skeletal muscle of rats with chronic renal failure. Evidence for a postreceptor defect. J Clin Invest. 1996;97(4):1064–75.
119. Tonshoff B, Blum WF, Wingen AM, Mehls O. Serum insulin-like growth factors (IGFs) and IGF binding proteins 1, 2, and 3 in children with chronic renal failure: relationship to height and glomerular filtration rate. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. J Clin Endocrinol Metab. 1995;80(9):2684–91.
120. Blum WF, Ranke MB, Kietzmann K, Tonshoff B, Mehls O. Growth hormone resistance and inhibition of somatomedin activity by excess of insulin-like growth factor binding protein in uraemia. Pediatr Nephrol. 1991;5(4):539–44.
121. Phillips LS, Fusco AC, Unterman TG, del Greco F. Somatomedin inhibitor in uremia. J Clin Endocrinol Metab. 1984;59(4):764–72.
122. Ulinski T, Mohan S, Kiepe D, Blum WF, Wingen AM, Mehls O, et al. Serum insulin-like growth factor binding protein (IGFBP)-4 and IGFBP-5 in children with chronic renal failure: relationship to growth and glomerular filtration rate. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Pediatr Nephrol. 2000;14(7):589–97.
123. Kiepe D, Ulinski T, Powell DR, Durham SK, Mehls O, Tonshoff B. Differential effects of insulin-like growth factor binding proteins-1, -2, -3, and -6 on cultured growth plate chondrocytes. Kidney Int. 2002;62(5):1591–600.
124. Kiepe D, Andress DL, Mohan S, Standker L, Ulinski T, Himmele R, et al. Intact IGF-binding protein-4 and -5 and their respective fragments isolated from chronic renal failure serum differentially modulate IGF-I actions in cultured growth plate chondrocytes. J Am Soc Nephrol. 2001;12(11):2400–10.
125. Lee DY, Park SK, Yorgin PD, Cohen P, Oh Y, Rosenfeld RG. Alteration in insulin-like growth factor-binding proteins (IGFBPs) and IGFBP-3 protease activity in serum and urine from acute and chronic renal failure. J Clin Endocrinol Metab. 1994;79(5):1376–82.
126. Tonshoff B, Kiepe D, Ciarmatori S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. Pediatr Nephrol. 2005;20(3):279–89.
127. Neu AM, Bedinger M, Fivush BA, Warady BA, Watkins SL, Friedman AL, et al. Growth in adolescent hemodialysis patients: data from the Centers for Medicare & Medicaid Services ESRD Clinical Performance Measures Project. Pediatr Nephrol. 2005;20(8):1156–60.
128. Quinlan C, Bates M, Sheils A, Dolan N, Riordan M, Awan A. Chronic hemodialysis in children weighing less than 10 kg. Pediatr Nephrol. 2013;28(5):803–9.
129. Rees L, Schaefer F, Schmitt CP, Shroff R, Warady BA. Chronic dialysis in children and adolescents: challenges and outcomes. Lancet Child Adolesc Health. 2017;1(1):68–77.
130. Shroff R, Wright E, Ledermann S, Hutchinson C, Rees L. Chronic hemodialysis in infants and children under 2 years of age. Pediatr Nephrol. 2003;18(4):378–83.
131. Chadha V, Blowey DL, Warady BA. Is growth a valid outcome measure of dialysis clearance in children undergoing peritoneal dialysis? Perit Dial Int. 2001;21(Suppl 3):S179–84.
132. Vidal E, Edefonti A, Murer L, Gianoglio B, Maringhini S, Pecoraro C, et al. Peritoneal dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. Nephrol Dial Transplant. 2012;27(1):388–95.
133. Schaefer F, Klaus G, Mehls O. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. Mid-European Pediatric Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1999;10(8):1786–92.
134. Tom A, McCauley L, Bell L, Rodd C, Espinosa P, Yu G, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134(4):464–71.
135. Katz A, Bock GH, Mauer M. Improved growth velocity with intensive dialysis. Consequence or coincidence? Pediatr Nephrol. 2000;14(8–9):710–2.
136. Fischbach M, Zaloszyc A, Laetitia H, Menouer S, Terzic J. Why does three times per week hemodialysis provide inadequate dialysis for children? Hemodial Int. 2014;18(Suppl 1):S39–42.
137. Fischbach M, Fothergill H, Seuge L, Zaloszyc A. Dialysis strategies to improve growth in children with chronic kidney disease. J Ren Nutr. 2011;21(1):43–6.
138. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25(3):867–73.
139. Fischbach M, Terzic J, Menouer S, Dheu C, Soskin S, Helmstetter A, et al. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21(11):1746–52.
140. Shroff R, Smith C, Ranchin B, Bayazit AK, Stefanidis CJ, Askiti V, et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, heart and height study. J Am Soc Nephrol. 2019;30(4):678–91.
141. Laster ML, Fine RN. Growth following solid organ transplantation in childhood. Pediatr Transplant. 2014;18(2):134–41.
142. Grenda R. Steroid withdrawal in renal transplantation. Pediatr Nephrol. 2013;28(11):2107–12.
143. Hocker B, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, et al. Improved growth and

cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation. Nephrol Dial Transplant. 2010;25(2):617–24.
144. Sarwal MM, Ettenger RB, Dharnidharka V, Benfield M, Mathias R, Portale A, et al. Complete steroid avoidance is effective and safe in children with renal transplants: a multicenter randomized trial with three-year follow-up. Am J Transplant. 2012;12(10):2719–29.
145. Delucchi A, Valenzuela M, Lillo AM, Guerrero JL, Cano F, Azocar M, et al. Early steroid withdrawal in pediatric renal transplant: five years of follow-up. Pediatr Nephrol. 2011;26(12):2235–44.
146. Webb NJ, Douglas SE, Rajai A, Roberts SA, Grenda R, Marks SD, et al. Corticosteroid-free kidney transplantation improves growth: 2-year follow-up of the TWIST randomized controlled trial. Transplantation. 2015;99(6):1178–85.
147. Grenda R, Watson A, Trompeter R, Tonshoff B, Jaray J, Fitzpatrick M, et al. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. Am J Transplant. 2010;10(4):828–36.
148. Schmitt CP, Ardissino G, Testa S, Claris-Appiani A, Mehls O. Growth in children with chronic renal failure on intermittent versus daily calcitriol. Pediatr Nephrol. 2003;18(5):440–4.
149. Sanchez CP, He YZ. Bone growth during daily or intermittent calcitriol treatment during renal failure with advanced secondary hyperparathyroidism. Kidney Int. 2007;72(5):582–91.
150. Shroff R, Wan M, Nagler EV, Bakkaloglu S, Cozzolino M, Bacchetta J, et al. Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease stages 2-5 and on dialysis. Nephrol Dial Transplant. 2017;32(7):1114–27.
151. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;(113):S1–130. https://doi.org/10.1038/ki.2009.188.
152. Haffner D, Schaefer F. Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. Pediatr Nephrol. 2013;28(4):537–45.
153. Muscheites J, Wigger M, Drueckler E, Fischer DC, Kundt G, Haffner D. Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease. Pediatr Nephrol. 2008;23(10):1823–9.
154. Warady BA, Iles JN, Ariceta G, Dehmel B, Hidalgo G, Jiang X, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet in pediatric patients with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. Pediatr Nephrol. 2019;34(3):475–86.
155. Platt C, Inward C, McGraw M, Dudley J, Tizard J, Burren C, et al. Middle-term use of Cinacalcet in paediatric dialysis patients. Pediatr Nephrol. 2010;25(1):143–8.
156. Arenas Morales AJ, DeFreitas MJ, Katsoufis CP, Seeherunvong W, Chandar J, Zilleruelo G, et al. Cinacalcet as rescue therapy for refractory hyperparathyroidism in young children with advanced chronic kidney disease. Pediatr Nephrol. 2019;34(1):129–35.
157. Sohn WY, Portale AA, Salusky IB, Zhang H, Yan LL, Ertik B, et al. An open-label, single-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of cinacalcet in pediatric subjects aged 28 days to < 6 years with chronic kidney disease receiving dialysis. Pediatr Nephrol. 2019;34(1):145–54.
158. Nakagawa K, Perez EC, Oh J, Santos F, Geldyyev A, Gross ML, et al. Cinacalcet does not affect longitudinal growth but increases body weight gain in experimental uraemia. Nephrol Dial Transplant. 2008;23(9):2761–7.
159. Mehls O, Ritz E, Hunziker EB, Eggli P, Heinrich U, Zapf J. Improvement of growth and food utilization by human recombinant growth hormone in uremia. Kidney Int. 1988;33(1):45–52.
160. Kovacs G, Fine RN, Worgall S, Schaefer F, Hunziker EB, Skottner-Lindun A, et al. Growth hormone prevents steroid-induced growth depression in health and uremia. Kidney Int. 1991;40(6):1032–40.
161. Powell DR, Durham SK, Liu F, Baker BK, Lee PD, Watkins SL, et al. The insulin-like growth factor axis and growth in children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. J Clin Endocrinol Metab. 1998;83(5):1654–61.
162. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. Cochrane Database Syst Rev. 2012;2:CD003264.
163. Haffner D, Wuhl E, Schaefer F, Nissel R, Tonshoff B, Mehls O. Factors predictive of the short- and long-term efficacy of growth hormone treatment in prepubertal children with chronic renal failure. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. J Am Soc Nephrol. 1998;9(10):1899–907.
164. Fine RN, Kohaut E, Brown D, Kuntze J, Attie KM. Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. Kidney Int. 1996;49(3):781–5.
165. Hokken-Koelega A, Mulder P, De Jong R, Lilien M, Donckerwolcke R, Groothof J. Long-term effects of growth hormone treatment on growth and puberty in patients with chronic renal insufficiency. Pediatr Nephrol. 2000;14(7):701–6.
166. Wuhl E, Haffner D, Nissel R, Schaefer F, Mehls O. Short dialyzed children respond less to growth hormone than patients prior to dialysis. German

Study Group for Growth Hormone Treatment in Chronic Renal Failure. Pediatr Nephrol. 1996;10(3):294–8.
167. Mehls O, Lindberg A, Nissel R, Haffner D, Hokken-Koelega A, Ranke MB. Predicting the response to growth hormone treatment in short children with chronic kidney disease. J Clin Endocrinol Metab. 2010;95(2):686–92.
168. Mahan JD, Warady BA, Frane J, Rosenfeld RG, Swinford RD, Lippe B, et al. First-year response to rhGH therapy in children with CKD: a National Cooperative Growth Study Report. Pediatr Nephrol. 2010;25(6):1125–30.
169. Fine RN, Attie KM, Kuntze J, Brown DF, Kohaut EC. Recombinant human growth hormone in infants and young children with chronic renal insufficiency. Genentech Collaborative Study Group. Pediatr Nephrol. 1995;9(4):451–7.
170. Maxwell H, Rees L. Recombinant human growth hormone treatment in infants with chronic renal failure. Arch Dis Child. 1996;74(1):40–3.
171. Mencarelli F, Kiepe D, Leozappa G, Stringini G, Cappa M, Emma F. Growth hormone treatment started in the first year of life in infants with chronic renal failure. Pediatr Nephrol. 2009;24(5):1039–46.
172. Santos F, Moreno ML, Neto A, Ariceta G, Vara J, Alonso A, et al. Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. Clin J Am Soc Nephrol. 2010;5(7):1190–7.
173. Fine RN, Brown DF, Kuntze J, Wooster P, Kohaut EE. Growth after discontinuation of recombinant human growth hormone therapy in children with chronic renal insufficiency. The Genentech Cooperative Study Group. J Pediatr. 1996;129(6):883–91.
174. Fine RN, Ho M, Tejani A, Blethen S. Adverse events with rhGH treatment of patients with chronic renal insufficiency and end-stage renal disease. J Pediatr. 2003;142(5):539–45.
175. Picca S, Cappa M, Martinez C, Moges SI, Osborn J, Perfumo F, et al. Parathyroid hormone levels in pubertal uremic adolescents treated with growth hormone. Pediatr Nephrol. 2004;19(1):71–6.
176. Akchurin OM, Schneider MF, Mulqueen L, Brooks ER, Langman CB, Greenbaum LA, et al. Medication adherence and growth in children with CKD. Clin J Am Soc Nephrol. 2014;9(9):1519–25.
177. Kovacs GT, Oh J, Kovacs J, Tonshoff B, Hunziker EB, Zapf J, et al. Growth promoting effects of growth hormone and IGF-I are additive in experimental uremia. Kidney Int. 1996;49(5):1413–21.
178. Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, Rapaport R, Schwartz ID, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. J Clin Endocrinol Metab. 2008;93(3):823–31.
179. Rabkin R, Sun DF, Chen Y, Tan J, Schaefer F. Growth hormone resistance in uremia, a role for impaired JAK/STAT signaling. Pediatr Nephrol. 2005;20(3):313–8.

The Management of CKD-MBD in Pediatric Dialysis Patients

29

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Abbreviations

1,25D	1,25-Dihydroxyvitamin D
ADHR	Autosomal dominant hypophosphatemic rickets
ALP	Alkaline phosphatase
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease/mineral and bone disorders
CV	Cardiovascular
CVD	Cardiovascular disease
DXA	Dual X-ray absorptiometry
ESRD	End-stage renal disease
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
HR-pQCT	High-resolution peripheral quantitative computed tomography
PTH	Parathyroid hormone
ROD	Renal osteodystrophy

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Introduction

Children with chronic kidney disease (CKD), especially those on dialysis, have a tenfold increase of cardiovascular (CV) morbidity and mortality, due to a unique combination of traditional and uremia-related risk factors, especially disturbances of mineral and bone metabolism parameters [1]. Pediatric CKD patients usually do not present with the traditional risk factors for cardiovascular disease (CVD); however, despite our current therapies, CVD remains the leading cause of morbidity and mortality in this patient population [1]. The "tip of the iceberg" of these complications is multifactorial, and multiple factors have been identified such as abnormalities in bone and mineral metabolism, resistance to growth hormone (GH), modifications of the GH-insulin-like growth factor type 1 (IGF1) axis, hypogonadism, malnutrition, and drug toxicity (corticosteroids) [2]. Not only do these complications impact overall quality of life through their effects on both physical and mental well-being in children with CKD, but alterations in mineral metabolism and bone disease also contribute to a significant decrease in life expectancy.

Therefore, due to the complex interplay between bone disease, mineral metabolism, and cardiovascular disease in patients with CKD, a new definition of renal osteodystrophy (ROD) was proposed: indeed ROD is defined now as a systemic disorder of chronic kidney disease mineral and bone disorder (CKD-MBD) characterized by

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Table 29.1 The spectrum of renal osteodystrophy according to the TMV classification, adapted from [3]

	Turnover	Mineralization	Volume
Osteomalacia (OM)	Low	Abnormal	Low to normal
Adynamic bone (AD)	Low	Normal	Low to normal
Mild hyperparathyroid-related bone disease (HPT)	Mild	Normal	Normal to high
Mixed uremic osteodystrophy (MUO)	High	Abnormal	Normal
Osteitis fibrosa (OF)	High	Normal	High

one or a combination of the following abnormalities [3, 4]: (1) abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; (2) abnormalities in bone histology, linear growth, or strength; and (3) vascular or other soft tissue calcification. The term ROD refers only to the specific abnormalities of bone diagnosed by bone histomorphometry using three main criteria, turnover, mineralization, and volume (TMV classification), as illustrated in Table 29.1. The impact of CKD-MBD in children may occur early in the course of CKD and is characterized by hormonal (PTH, 1,25D, and fibroblast growth factor 23, FGF23) and biochemical (serum calcium and phosphorus levels) abnormalities, while delayed complications (e.g., growth retardation, bone deformities, fractures, vascular calcifications, increased morbidity and mortality) may also occur [3].The bone and growth long-term consequences of CKD have been highlighted in a cohort of 249 young Dutch adults with onset of end-stage renal failure before the age of 14 years: in this cohort, 61% of patients had severe growth retardation, 37% severe bone disease (as defined by at least one of the following conditions: deforming bone abnormalities, chronic pain related to the skeletal system, disabling bone abnormalities, aseptic bone necrosis, and low-trauma fractures), and 18% disabilities resulting from bone impairment [5]. More recently, a significantly increased risk of fractures was demonstrated in the pediatric North American CKiD cohort, evaluating 537 children with CKD at a median age at inclusion of 11 years. At baseline, 16% of them had a history of fractures, and after a median follow-up of 3.9 years, 43 boys and 24 girls experienced fractures, corresponding to a fracture risk two- to threefold higher than in general populations [6]. Moreover, risk factors were Tanner stage IV/V, decreased height Z-score, walking difficulty, and increased PTH levels. In contrast, the only protective factor was the use of phosphate binders, mainly calcium-based binders [6].

Evidence of vascular calcifications has been demonstrated in children and young adult dialysis patients with ESRD therapy initiated in childhood [7, 8]. Our understanding of the relationship between bone and vessels in CKD remains scarce. Associations between arterial lesions (atherosclerosis and arterial calcifications) and bone impairment (osteoporosis and abnormal bone activity) are described, usually following the rule "The better the bone, the better the vessels," at least in adults [9, 10]; however, things are not that clear in pediatric CKD, and using absorptiometry (DXA) and even high-resolution peripheral quantitative computed tomography (HR-pQCT), opposite results were reported [11, 12].The aim of this review is therefore to provide an overview of our current understanding of the abnormalities of bone and mineral metabolism associated with CKD in children undergoing maintenance dialysis, notably in terms of diagnosis and management.

Changes in Mineral Metabolism with Progressive CKD

CKD-MBD pathogenesis involves a complex interplay among the kidney, bone, and parathyroid glands. As functional nephrons are lost and GFR declines, a cascade of maladaptive events develops that result in bone disease, extra-skeletal calcification, and adverse cardiovascular outcomes. Different factors have been implicated in the pathogenesis of this maladaptive response, but the primary trigger remains to be defined. In the

early stages of CKD, FGF23 levels increase, while phosphate, calcium, and PTH levels remain within normal ranges [13]. With CKD progression, there are increase in phosphate levels, increased levels of FGF23 and PTH, progressive decline in 1,25D levels in order to lessen enteral phosphate absorption, and decreased ionized calcium levels via increased binding. Elevated FGF23 levels further decrease 1,25D levels via renal 1α-hydroxylase suppression and 24-hydroxylase induction. Decreased 1,25D levels reduce intestinal calcium absorption, and low 1,25D and low ionized calcium both further increase PTH levels, resulting in secondary hyperparathyroidism, as summarized in Fig. 29.1 [14].

Since bone consists primarily of calcium and phosphorus, in the form of hydroxyapatite, it is not surprising that alterations in mineral metabolism, as occur with progressive CKD, lead to bone disease. However, all these biochemical alterations do not completely explain CKD-MBD. In 2000, a novel hormone negatively regulating phosphate, 1,25D, and PTH has been identified, FGF23, completely modifying our view of CKD-MBD [15–17].

Indeed, the earliest biochemical abnormality in CKD is an increase in circulating FGF23 levels [13, 16]. FGF23, in conjunction with its co-receptor, Klotho, activates FGF receptor 1 (FGFR1) and acts on the kidney to induce renal phosphate wasting and to suppress renal 1α-hydroxylase activity [18–20]. FGF23 also acts on the parathyroid gland and may play a role in suppressing parathyroid hormone (PTH) levels [21]. FGF23 is stimulated by phosphate and $1,25(OH)_2$vitamin D, and, in both adults and children, FGF23 increases as GFR decreases, with elevations in circulating and bone levels occurring in very early stages of CKD, prior to any apparent alterations in circulating mineral content [22]. This increase could be explained by different factors, including a decreased renal

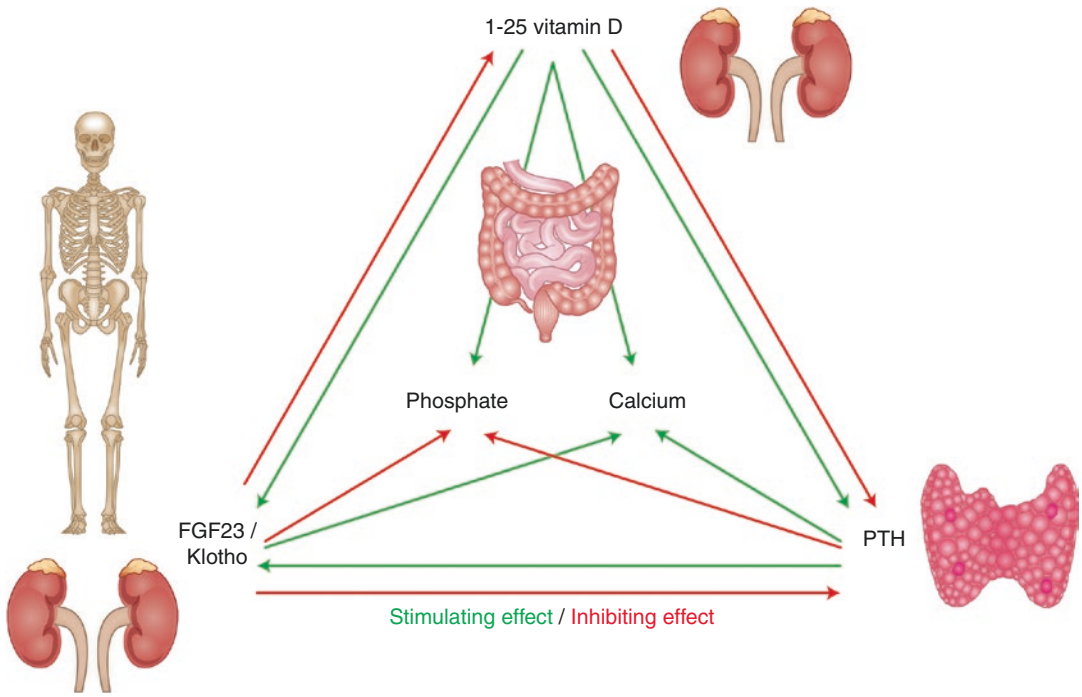

Fig. 29.1 Overview of normal phosphate/calcium metabolism. Phosphate and calcium are mainly stored in bone, but the gut and the kidneys have a key role in their homeostasis. Three hormones are crucial to maintain calcium and phosphate within the normal range: 1,25-dihydroxyvitamin D (1,25D), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Green lines correspond to a stimulating effect. Red lines correspond to an inhibitory effect

clearance of FGF23, a compensatory mechanism to excrete an increased phosphate load, a response to treatment with active vitamin D analogs, and/or a compensatory mechanism to the loss of the kidney-secreted Klotho protein. However, the initial factor that triggers FGF23 production remains to be defined. Data from CKiD nevertheless argue against the first hypothesis, since at the very early stages of pediatric CKD, circulation and bone FGF23 levels are already increased, whereas phosphate SDS are significantly decreased [13]. Although these increased circulating levels of FGF23 in CKD patients consist almost exclusively of the intact, active form of the molecule, it is not clear whether the biological effects of FGF23 are increased or decreased in the context of decreased kidney function. Indeed, decreased expression of FGFR1 and Klotho in parathyroid cells from dialysis patients and a resistance to the suppressive effects of FGF23 on PTH in uremic rats suggest that FGF23 signaling to the parathyroid glands is downregulated in CKD and may explain, at least in part, the refractory secondary hyperparathyroidism observed in CKD patients.

Over the last decade, the extra-skeletal and systemic effects of FGF23 have been well characterized in adults and children, highlighting a global "negative" role of FGF23 in global health [14], notably on the cardiovascular, immune, and central nervous systems, as illustrated in Fig. 29.2. The first "off-target" effect of FGF23 to be described was demonstrated on cardiomyocytes [23]. This seminal paper was a milestone in the understanding of FGF23 physiology since it was the first time that a Klotho-independent effect of FGF23 was demonstrated, with different downstream phosphorylation pathways, mainly the cal-

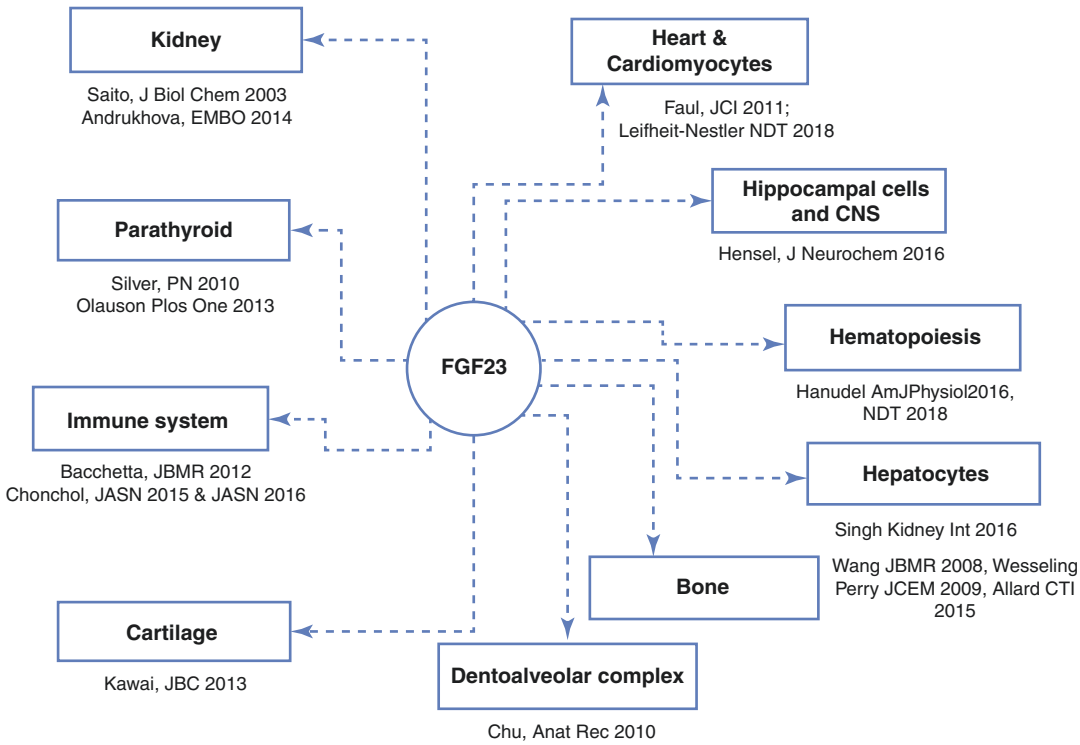

Fig. 29.2 Systemic effects of FGF23, adapted from [14]. Besides its "classical" effects on phosphate, calcium, PTH, and vitamin D metabolism, the knowledge in FGF23 physiology has dramatically improved recently. Complex regulations between FGF23 and all these systems have been described; the relevant papers are referenced on the figure, but this list is not exhaustive

cineurin/NFAT pathway. Faul et al. demonstrated that high FGF23 levels were associated with left ventricular hypertrophy (LVH) in cohorts of adult patients with chronic kidney disease (CKD), and they highlighted hypertrophic and pro-fibrotic effects of FGF23 in rat cardiomyocytes [23]. Since then, it has been demonstrated that the two MAPK and calcineurin/NFTA pathways may co-exist, for example, in the parathyroid glands: the MAPK pathway nevertheless remains the dominant pathway in this case [24]. FGF23 is also an inhibitor of monocytic 1α hydroxylase, with a concomitant suppression of the antibacterial cathelicidin [25]; in line with this, clinical studies in patients on hemodialysis have confirmed a higher risk of infection with increasing FGF23 levels [26]. In the renal tubule, FGF23 stimulates sodium reabsorption, thus increasing blood pressure [27]. In hippocampal cells, FGF23 enhances the number of primary neurites and the synaptic density in a FGFR-dependent manner, but it also decreases arborization, thus leading to a less complex morphology of neuron, possibly explaining, at least partly, the learning and memory deficits often observed in CKD patients [28]. FGF23 may also have a role in the growth hormone axis, since therapy with recombinant human growth hormone increases FGF23 levels in the long term, even after adjusting for age and phosphate levels [29]. Recently, novel endocrine loops have also been described, notably between FGF23 and adiponectin, with suppression of renal α-Klotho, decreased bone FGF23 release, and calcium renal loss by adiponectin both in mice and in CKD patients [30]. A link between iron metabolism and FGF23 has also been highlighted; systemic inflammation may have an impact on FGF23 levels; FGF23 levels are higher in patients with glomerular diseases when compared to CAKUT [31]. FGF23 directly targets hepatocytes to promote inflammation and C-reactive protein synthesis [32]. In a cohort of 700 patients with stable renal transplants, it was shown that C-terminal FGF23 levels were higher in iron-deficient patients [33]. The effects of iron infusions on FGF23/phosphate metabolism differ depending of the iron preparation. Specifically, ferric carboxymaltose, the currently preferred iv iron formulation, specifically induces transient hypophosphatemia via its carbohydrate moiety and not as a direct consequence of the iron infusion [34]. Older formulations such as iron sucrose avoid this specific effect. That being said, even though all these experimental findings demonstrate the role of FGF23 as a systemic (deleterious) hormone, their clinical relevance is not yet clear and will not change clinical management as long as prospective randomized trials are performed to assess the "off-target" effects of FGF23.

Subsequently, with CKD progression, abnormalities in other parameters of mineral metabolism appear. During mild CKD (stages 2 and 3), calcitriol levels decline in response to increased FGF23 concentrations. Since calcitriol suppresses PTH secretion, declining $1,25(OH)_2$vitamin D levels are followed, in moderate (stages 3 and 4) CKD, by increasing PTH concentrations and by loss of pulsatility in PTH secretion. Ultimately, in late stage 4 CKD, hypocalcemia and hyperphosphatemia develop in approximately 50–60% of patients in response to decreased intestinal calcium absorption (from critically low calcitriol concentrations) and decreased phosphate excretion (from critically low renal mass), respectively. Finally, 25(OH)vitamin D deficiency, which is prevalent worldwide, likely also contributes to the development of secondary hyperparathyroidism.

Patients with CKD are particularly prone to 25(OH)vitamin D deficiency (defined by values below 30 ng/mL or 75 nmol/L), due to several combined factors including decreased sunlight exposure, relative scarcity of vitamin D in occidental diets, lack of supplementation in vitamin D due to the current underestimation for recommended daily intake, and increased body fat mass in populations [35]. In addition to providing a substrate for the formation of calcitriol, thus indirectly suppressing PTH levels, Ritter et al. identified that 25(OH)vitamin D continues to directly suppress PTH synthesis even when parathyroid gland 1α-hydroxylase is inhibited, thus demonstrating a direct effect of 25(OH)vitamin D on PTH synthesis, independent of $1,25(OH)_2$vitamin D [36]. Moreover, a placebo-controlled randomized trial demonstrated that ergocalciferol was able to delay the onset of secondary hyperparathyroidism in pediatric patients with pre-dialysis

CKD [37]. 25(OH)vitamin D likely also has a direct effect on bone biology, independent of its effects on mineral metabolism; indeed, in a cohort of 675 deceased adults, mineralization defects were found when serum 25(OH)vitamin D level was below 30 ng/mL [38]. However, the skeletal mineralization defect observed across the spectrum of CKD was not associated with vitamin D deficiency. New roles of vitamin D in global health have also been highlighted: vitamin D may represent a protective factor against infections, auto-immune diseases, cardiovascular diseases, and cancer [39, 40].

Effects of Non-mineral Factors on CKD-MBD

Non-mineral metabolism factors such as iron status, erythropoietin, and inflammation also contribute to increased FGF23 production in CKD, and understanding the impact of each of them in the context of CKD may have potential effects on the pathophysiology and treatment of CKD-MBD. Inflammation increases bone and circulating FGF23 levels [41]. Iron deficiency, which is common in CKD, also increases FGF23 expression. Iron chelation increases FGF23 expression in vitro [42], and iron-deficient mice with normal and impaired kidney function have increased osteocytic FGF23 expression [43]. Hypoxia-inducible factor 1 alpha (HIF1α) protein may mediate the effects of iron deficiency on *FGF23* transcription [42]. In patients with congenital heart disease and normal kidney function, more severe chronic hypoxemia was associated with plasma FGF23 levels [44]. In murine models, both absolute iron deficiency, induced by low-iron diets, and "functional" iron deficiency, induced by inflammation or administration of exogenous hepcidin, increase bone FGF23 expression [41]. In a small study of iron-deficient dialysis patients, iron supplementation decreased circulating FGF23 levels [45]. In non-dialysis CKD patients, the use of ferric citrate both lowered serum phosphate levels and improved iron parameters, contributing to production in FGF23 concentrations [46].

Erythropoietin can also stimulate FGF23 production. Conversely FGF23 itself may have effects on erythropoiesis. Indeed, *FGF23* knockout mice have increased serum EPO levels and erythropoiesis and increased measures of erythropoiesis [47]. These data suggest that FGF23 may have negative regulatory effects on erythropoiesis. Consistent with these murine studies, in a large cohort of human CKD patients, elevated total FGF23 levels were independently associated with both prevalent and incident anemia [48]. These associations underscore the complex interrelationships among aspects of CKD-related anemia, CKD-MBD, and their respective treatment modalities that will have to be elucidated in order to define better strategic therapeutic approaches.

Assessment of CKD-MBD in Children Undergoing Maintenance Dialysis

When taking care of a child with ESRD, it is important to evaluate mineral metabolism, by assessing in parallel bone quality, growth, and cardiovascular status. In order to emphasize the complexity and interdependency of all CKD-MBD, the 2017 KDIGO CKD-MBD recommendations highlighted that treatments of CKD-MBD should be based on serial assessment of phosphate, calcium, and PTH levels and considered together for clinical decision-making [4].

The first step will consist of clinical evaluation with height, growth velocity, blood pressure, and a "bone-focused" examination, searching for bone pain, deformations, and/or fractures [49]. The second step will consist on the biological evaluation of CKD-MBD, mainly by assessing calcium, phosphate, PTH, and 25-D levels and alkaline phosphatase (ALP). However, the additional biomarkers such as FGF23, Klotho, 1,25D, DKK1, sclerostin, bone ALP, and sclerostin among others are currently utilized only for research purposes; neither are bone imaging techniques, such as DXA or pQCT/HR-pQCT, nor cardiovascular evaluation such as coronary calcification scores by computed tomography, carotid intima/media thickness, or pulse wave

Table 29.2 Reference values for phosphate and calcium metabolism in children, adapted from [53]

Age range	Normal range for calcium (mmol/L)	Normal range for ionized calcium (mmol/L)	Daily recommended intake for calcium (mg)	Normal range for phosphate (mmol/L)	Daily recommended intake for phosphate (mg)
Birth–5 months	2.18–2.83	1.22–1.40	210	1.50–2.40	100
6–12 months	2.18–2.75	1.20–1.40	270		275
1–5 years	2.35–2.70	1.22–1.32	500	1.50–2.10	460
6–12 years	2.35–2.58	1.15–1.32	800	1.20–1.90	500 until 8 years, 1250 after
13–20 years	2.20–2.55	1.12–1.30	1300	0.70–1.50	1250

For calcium, the conversion factor from mmol/L to mg/dL is to multiply by 4.0. The calculation formula for corrected calcium (CaC, mmol/L) using measured calcium (mmol/L) and albuminemia (g/L) is the following: CaC = Ca – 0.25 × (albuminemia − 40). If albuminemia is not available, CaC may be calculated with protidemia (g/L) with the following formula: CaC = Ca/(0.55 + P/160). For phosphate, the conversion factor from mmol/L to mg/dL is to multiply by 3.1

velocity. However, these latter techniques are crucial for research in the field [50, 51]. The 2017 KDIGO guidelines indicate to perform bone biopsies in patients with CKD3a-5D if knowledge of the type of renal osteodystrophy will impact treatment decisions.

Normal serum phosphate and calcium levels in children are age-dependent, and physicians must be aware of such values in order to adapt therapies accordingly [52, 53], as summarized in Table 29.2. The extracellular calcium fraction is tightly regulated and can be measured in serum, where approximately half is bound to negatively charged molecules such as albumin, serum proteins, and serum anions such as phosphate and citrate; the remainder corresponds to "free" or ionized calcium, this latter form being biologically active and responsible for most of its physiological functions notably muscular contraction, protein kinase activation, and enzyme phosphorylation [54, 55]. Indeed, only the ionized calcium is available to move into cells and activate cellular processes. It is not influenced by alterations in albumin, circulating levels of anions, and acid-base status that are rather frequent in end-stage renal disease [56]. The binding of calcium to albumin occurs in a pH-dependent manner, acidosis reducing the binding and thus increasing the ionized part. However, even though ionized calcium appears to be a more accurate measure of serum calcium rather than albumin-corrected calcium, in clinical practice, albumin-corrected calcium are usually used.

It is also important to keep in mind that PTH levels alone are not a good predictor of the underlying osteodystrophy; the combined use of total ALP and PTH levels may improve our ability to detect the underlying type of renal osteodystrophy [57]: in a cohort of 161 pediatric patients undergoing maintenance peritoneal dialysis, PTH levels below 400 pg/ml in combination with total ALP levels below 400 IU/L provided the highest correct prediction rate for patients with both normal bone turnover and normal mineralization. Levels of PTH were higher, and serum calcium levels were lower in patients with defective mineralization, irrespective of bone turnover [57]. In clinical practice, the treating physician should be aware of the different PTH assays, leading to discrepant results when using assays of different brands for second-generation assessment [58]; moreover, there are important differences between second- and third-generation assays. Third-generation PTH assays, also known as "whole PTH assays," use antibodies that exclusively recognize full-length 1–84 PTH. There is however limited evidence that the differentiation of 1–84 PTH from PTH fragments is of clinical use. Values obtained with third-generation assays are about 50–60% lower than those obtained with the second-generation assays with great inter-individual variation, and guidelines have been established with second-generation assays, as discussed below. In the future, the assessment of non-oxidized PTH may

reflect the biological activity of PTH more precisely, but their exact place in the clinical ward remains to be defined [59]. In those patients with elevated PTH levels and relatively low alkaline phosphate levels, a bone biopsy may be discussed in order to further define the appropriate therapy.

Which Targets for PTH in Pediatric Dialysis?

Uncontrolled SHPT in CKD is characterized by a sustained high PTH level in combination with a high or high-normal calcium level. SHPT gradually develops into tertiary HPT with important bone, cardiac, and vascular complications, such as *osteitis fibrosa* and calcium efflux from bone, potentially leading to vascular calcification [60].

As illustrated in Fig. 29.3, the management of patients differs considerably between countries [61], and this specific point should be taken into account when analyzing clinical research data in the field. Even though of low evidence from a strict methodological point of view, these data obtained in the International Pediatric Peritoneal Dialysis Network (IPPN) registry included 890 children and adolescents from 24 countries, therefore providing very interesting "bed-side" data for pediatric nephrologists: an optimal range of PTH between 1.7 and 3 times above the upper normal limit was suggested, namely, a target range between 100 and 200 pg/mL, as shown in Fig. 29.4. Indeed, greater PTH levels were associated with an increased frequency of patients presenting with alterations of bone and mineral metabolism, such as bone pains, limb deformities, extra-osseous calcifications, radiological osteomalacia, or osteopenia [61, 62]. However, as discussed above, there may be an important variability between PTH assays, and this is certainly one of the main limitations of these registry studies.

The optimal PTH levels for children treated with dialysis associated with clinical outcomes such as bone deformities, fractures, and growth retardation remain to be determined. There are currently two different recommendations related to target PTH levels in dialyzed children: (1) KDIGO 2017 and (2) European Paediatric Dialysis Working Group.

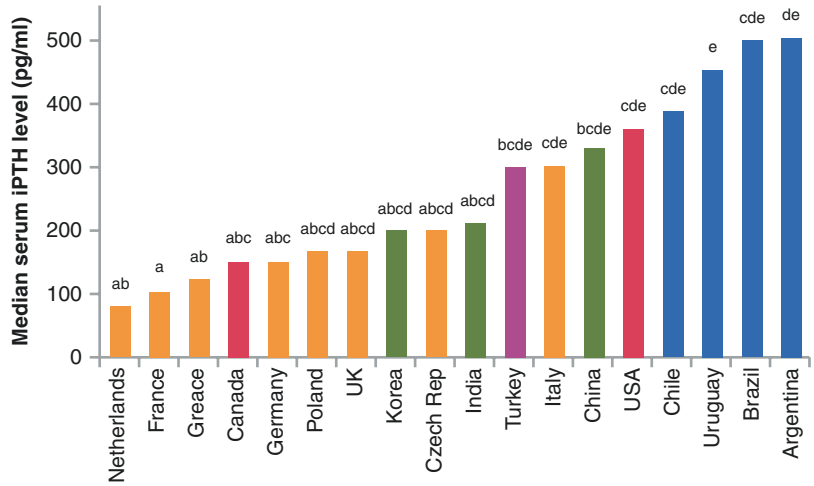

Fig. 29.3 PTH levels vary depending on the country of origin, data from the IPPN network, from [61]. Variation of intact parathyroid hormone (iPTH) levels by country. Only countries with ≥15 registered patients were considered. Bars denote medians of patient-specific time-averaged mean PTH levels. European countries light gray, Latin American countries dark gray, Turkey horizontally dashed, North America vertically dashed, and Asian countries diagonally dashed bars. Letters denote significances ($P < 0.05$) in Student-Newman-Keuls multiple comparison testing of log-transformed means; countries sharing same letters do not differ significantly. Data were obtained from 890 children and adolescents from 24 countries reported to the International Pediatric Peritoneal Dialysis Network (IPPN) registry. The main limitation of this study is the variability among PTH assays

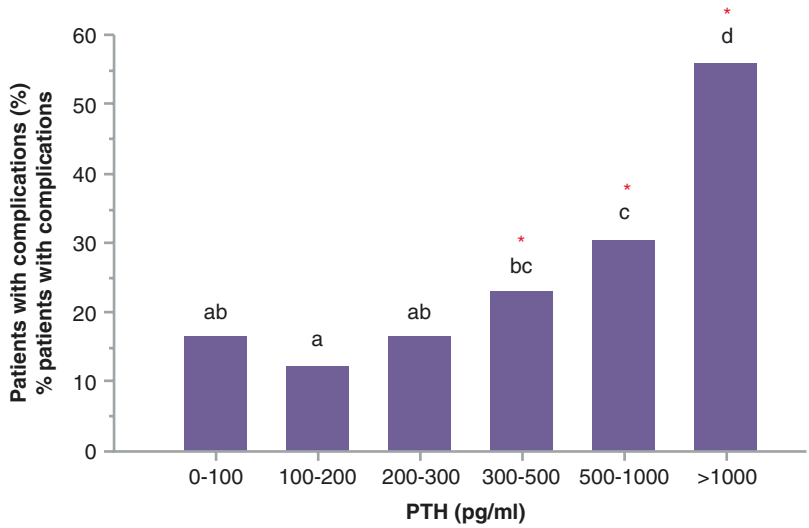

Fig. 29.4 PTH as a risk factor of bone and mineral complications in pediatric peritoneal dialysis, data from the IPPN network, from [61]. Percentage of patients with alterations of bone and mineral metabolism (bone pain, limb deformities, extra-osseous calcifications, radiological osteomalacia, and/or osteopenia) stratified by time-averaged mean PTH levels. Groups sharing same letters do not differ significantly. Data were obtained from 890 children and adolescents from 24 countries reported to the International Pediatric Peritoneal Dialysis Network (IPPN) registry

The KDIGO guidelines are based on bone histology data that demonstrated in the 1990s the development of more severe growth retardation in those patients with PTH <300 pg/ml [65] and from a prospective randomized trial that has compared two different vitamin D analogs and phosphate binders on the control of the skeletal lesions of secondary hyperparathyroidism in pediatric dialysis patients [63]. Thus, target PTH levels ranging from two to nine times the upper limit of normal in dialyzed children, thus corresponding to a target range of 120–540 pg/mL, have been recommended for adult and pediatric patients treated with dialysis [4, 64, 65]. Using the KDIGO target levels for the treatment of skeletal lesions of SHPT in pediatric dialysis patients, normal rates of bone turnover were observed in the majority of pediatric dialysis patients treated with intermittent calcitriol or doxercalciferol regardless of the type of phosphate binder [63]. However, other groups have challenged this observation, showing that high bone turnover lesions can occur at lower PTH levels than "current" guidelines would suggest in children beginning renal replacement therapy [67]. In a cross-sectional cohort of 161 pediatric patients undergoing maintenance peritoneal dialysis, PTH levels below 400 pg/ml in combination with total ALP levels below 400 IU/L provided the highest correct prediction rate for patients with both normal bone turnover and normal mineralization [57].

The 2006 recommendations of the European Paediatric Dialysis Working Group suggested keeping PTH levels up to two to three times the upper limit of normal in dialyzed children, thus corresponding to a target range of 120–180 pg/mL for iPTH, in accordance with the observations of the IPPN registry. Thus, there is presently limited information on the association of recommended PTH levels with clinical outcomes such as bone deformities and fractures, and such studies are critically needed.

Thus, existing guidelines for PTH targets are conflicting and based on limited clinical outcomes and old data. More than a specific target "number," the philosophy of PTH levels in pediatric dialysis should be balanced by the trend: "not too low, not too high, and keep phosphate and calcium concentrations within age-appropriate levels."

Management of CKD-MBD in Children Undergoing Maintenance Dialysis

Figure 29.5 summarizes the cornerstones of daily management of pediatric CKD-MBD in dialysis patients. The standard of care of CKD-MBD in pediatrics relies on a combination of the following variables.

First, all metabolic and clinical abnormalities that can worsen both bone and growth such as metabolic acidosis, anemia, and malnutrition should be corrected [65]. To optimize growth, recombinant human growth hormone therapy can also be proposed except in those patients with severe SHPT; recent guidelines from the European Society of Paediatric Nephrology have been proposed on the topic (European guidelines Epub 2019) [66].

Second, native vitamin D deficiency should be treated, with a target of circulating 25-D levels ranging between 75 and 120 nmol/L (20–30 ng/ml), as recently recommend by the European guidelines [68] and also discussed in the 2017 KDIGO [4].

Third, in addition to nutritional control of phosphate intake and dialysis intensification, calcium-based and non-calcium-/non-aluminum-based phosphate binders can be used, however without using aluminum binders. Sevelamer carbonate and hydrochloride have been found to be effective phosphate binder agents in dialyzed children; however, sevelamer HCL was associated with the development of metabolic acidosis [69]. Lanthanum carbonate has been shown to be an effective phosphate binder in adults, but it has not been evaluated in children. In addition, lanthanum was shown to accumulate in bone tissue in adult dialysis patients with no data on a potential accumulation in the growth plate, and there are concerns on potential neurological side effects for a developing brain, at least theoretically [70].

Calcium-based phosphate binders, including calcium carbonate and calcium acetate (containing 40% and 25% of elemental calcium, respec-

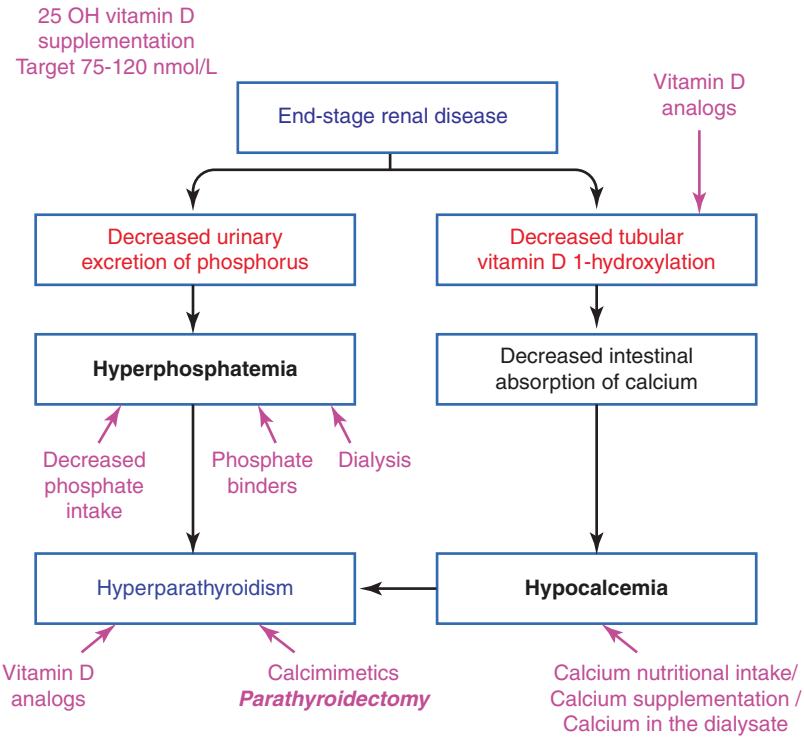

Fig. 29.5 The cornerstones of daily CKD-MBD management in pediatric dialysis

tively), are widely prescribed and are effective in lowering serum phosphate levels. However, the benefit of such binders especially when used concurrently with active vitamin D sterols must be weighed against the possible adverse effects of hypercalcemia and/or extra-skeletal and vascular calcifications [7].

More recently, the iron-based compounds sucroferric oxyhydroxide and ferric citrate (FC) have been found to be effective phosphate binders in adults treated with dialysis. Both compounds are intriguing given their theoretical ability to both bind enteral phosphorus and deliver iron. However, hematological indices only improved with ferric citrate in adults with CKD and those treated with dialysis (XX). In a small cohort of dialyzed children, FC was well tolerated, reduced serum phosphate levels, and improved iron parameters [71]. Thus, given the recent evidence that iron deficiency increases FGF23 production, the use of FC especially in iron-deficient CKD patients may affect FGF23 levels by both limiting phosphate absorption and delivering iron. Further studies are needed in order to confirm such hypothesis. FC may have added value especially for pediatric CKD patients prior to dialysis because iron deficiency and elevated FGF23 levels are highly prevalent.

Fourth, a nutritional management aiming at providing age-appropriate calcium intake with controlled phosphorus intake should be proposed; indeed, the 2008 nutrition guidelines in pediatric CKD suggested that the total oral and/or enteral calcium intake from nutritional sources and medications be in the range of 100–200% of the daily recommended intake (DRI) for calcium for age [53]. The calcium DRI are 210 mg between birth and 5 months, 270 mg between 6 and 12 months, 500 mg between 1 and 5 years, 800 mg between 6 and 12 years, and 1300 mg between 13 and 20 years [53]. Nutritional intake of phosphate and calcium is indeed very important data to monitor mainly during the first few years of life; calcium intake may come from diet, but also from medications (direct calcium intake through calcium supplementation or calcium-based phosphate binders, indirect increased intestinal calcium absorption with active vitamin D analogs) and dialysate.

Indeed, not providing age-appropriate calcium intake may have negative consequences on the growing skeleton. In pediatric CKD, low calcium levels have been associated with impaired bone parameters. In a histomorphometry study, lower serum calcium levels were associated with defective skeletal mineralization [22]. In a prospective pQCT study in 171 pediatric patients with CKD stage 2-5D, lower calcium levels were independently associated with baseline and progressive cortical deficits, and lower cortical bone mineral density was associated with increased fracture risk [50]. A greater improvement in osteoid volume was observed in pediatric patients treated with calcium carbonate (CaCO3), regardless of vitamin D sterol, than in patients treated with sevelamer [43]. Moreover, in children on peritoneal dialysis, serum calcium concentrations were inversely related to mineralization (osteoid volume) but did not relate to bone turnover. For any given level of bone turnover, levels of PTH were higher, and serum calcium values were lower in patients with a concomitant mineralization defect [57]. Recent data from the CKiD cohort highlighted the need of calcium supplements for adequate skeletal development in pediatric CKD: While children with CKD exhibit a two- to threefold increased fracture risk compared to healthy children, phosphate binder treatment (predominantly calcium-based) was associated with a significant lower fracture risk [6]. All these data provide a strong rationale for providing age-appropriate calcium supplementation in pediatric CKD, at least for bone quality and quantity.

Conversely, higher doses of calcium-based binders were associated with greater degrees of vascular calcifications in adult and pediatric dialysis patients [7]. Medial arteriosclerosis is a multifactorial process creating a permissive environment for the nucleation of Ca-P crystals: diffuse mineral deposition in the tunica media of the arterial wall (as a result of high calcium-phosphate product), suppression of natural crystallization inhibitors, and vascular smooth muscle cell phenotypic changes leading to osteoblastic differentiation [73–75]. Other calcification risk

factors are the cumulative doses of Ca-containing phosphate binders and vitamin D analogs. Medial arteriosclerosis induces vascular stiffness and contributes to arterial hypertension, increased pulse pressure, and LVH [75].

The challenge for pediatric nephrologists is therefore to balance between a positive calcium balance required for bone accrual and quality and the potential risk of vascular calcifications. The mean daily calcium accretion rate in healthy pubertal boys and girls peaks at 359 and 284 mg, respectively [76]; physicians may keep in mind these higher calcium requirements for a growing skeleton. Calcium deficiency in pediatric CKD may further worsen SHPT and induce mineralization abnormalities and secondary rickets; in this regard, the 2017 KDIGO guidelines suggest to maintain serum calcium in the age-appropriate normal range in dialysis children [4]. Similarly, the 2017 KDIGO recommendations ruled out the use of calcium-based phosphate binders in adults but stated that they could be used in children, provided normal circulating calcium levels for age [4]. The recent Cochrane update on the management of metabolic bone disease in pediatric CKD did not rule out the use of calcium-based phosphate binders: although fewer episodes of hypercalcemia occurred with the non-calcium-containing phosphate binder sevelamer, as compared to calcium-containing binders, there were no other significant differences [77]. Although the optimal calcium intake for children treated with dialysis has not been defined, the KDOQI guidelines recommend not to exceed 1500 mg/day. Such requirements may be different during the first few years of life. Thus, there is an urgent need to perform calcium balance studies in pediatric dialysis patients in order to define the optimal calcium intake which is critically important during the first years of life.

In the case of SHPT, therapy with active vitamin D analogs should be initiated [78], and dialysis may be intensified; parathyroidectomy should be indicated to patients with refractory SHPT. The follow-up of such management obviously relies on regular biological evaluation, using biomarkers that should always be interpreted depending on age, notably for calcium and phosphate. It is of utmost importance that therapeutic decisions are based on trends rather than on a single laboratory value, taking into account all available CKD-MBD measurements, including calcium, phosphate, PTH, and 25-D [4].

The 2017 KDIGO guidelines suggest that adult dialysis patients can receive cinacalcet as a first- or second-line therapy in combination with vitamin D analogs [4], but there is currently no evidence that cinacalcet can be given as first-line therapy in pediatric patients undergoing chronic dialysis. The calcimimetic cinacalcet is an allosteric modulator of the calcium-sensing receptor (CaSR). It has proven to be effective and safe in adults to suppress PTH, but data on its use in children are limited: to date, studies in children only comprise two RCTs, nine uncontrolled interventional or observational studies, and several case reports [79–85]. In 2017, the European Medicines Agency nevertheless approved the use of cinacalcet for the treatment of SHPT in children on dialysis, in whom SHPT is not adequately controlled with standard therapy. Notably, based on the same data, US regulatory authorities did not approve cinacalcet for this indication in children [86]. European guidelines have just been published to define the practical approach to cinacalcet in a child receiving maintenance dialysis with severe SHPT above 3 years of age [87]; one key message is the security warning concerning the risk of hypocalcemia with cinacalcet: as such, cinacalcet should not be started in the case of albumin-corrected calcium levels below 2.40 mmol/L and should be decreased or withdrawn if calcium levels fall below 2.2 mmol/L and immediately withdrawn in the case of symptomatic hypocalcemia or if calcium levels fall below 2.0 mmol/L. A prolonged QT interval and history of seizures, cardiac arrhythmia, significant liver disease, and/or concomitant medications that prolong the QTc interval or that interact with cinacalcet are essential issues to check before prescribing (or ruling out) cinacalcet.

Lastly, all these drugs can modify mineral metabolism. Considering the stimulating effects of active vitamin D analogs on FGF23 [88], the inhibitory effect of cinacalcet on FGF23 levels [89], and the differential effects of phosphate binders on FGF23 levels [45, 90, 91], the clinical picture transforms into a very complex cascade in

which each therapeutic intervention may have direct consequences on FGF23 levels.

Effects of Primary Kidney Diseases Inducing a Specific Bone Impairment in Addition to CKD-MBD

It has been known for decades that primary hyperoxaluria (PH) has a direct deleterious effect on bone [92]. Indeed, deposition of calcium oxalate crystals in the kidney and bone is a hallmark of primary hyperoxaluria. Since the bone compartment can store massive amounts of oxalate, patients present with recurrent low-trauma fractures, bone deformations, severe bone pain, and specific oxalate osteopathy on X-ray. Calcium oxalate (whewellite) deposits are located in the bone marrow space with a granulomatous reaction, but not in the bone matrix. In such a case, bone mineralization is not modified by the presence of calcium oxalate. However, bone quality reveals a harder bone than normal, possibly related to decreased carbonate content of the mineral. This increase in bone hardness may explain a more "brittle" bone [93]. In clinical practice, dialysis is a period during which patients dramatically worsen their bone lesions since the epuration of oxalate by dialysis (even using intensive regimens) is far less effective than endogenous production. This very specific feature explains the specific post-transplant management in PH, requiring optimal hyperhydration and alkalinization [94].

More recently, other rare inherited renal diseases have been shown to induce specific mineral and bone abnormalities: for example, patients with autosomal dominant polycystic kidney disease present with significant hypophosphatemia even at pediatric age [95] and increased FGF23 levels [96]. However, the clinical relevance of such biological abnormalities remains to be fully determined, even though a specific bone phenotype has recently been described in adults with ADPKD, with low bone turnover and low ALP levels [97].

The concept of "cystinosis metabolic bone disease" is currently emerging, with the description in vivo of bone fragility and symptoms [98, 99] and in vitro of the underlying mechanisms, with a functional deficit both in osteoblasts and in osteoclasts [100, 101]. Indeed, nephropathic cystinosis is a rare autosomal recessive lysosomal storage disease characterized by a deficiency of the cystine lysosomal transport protein (i.e., cystinosin encoded by the *CTNS* gene), resulting in systemic accumulation of cystine crystals and thus leading to tissue damage. Patients suffer from complete proximal tubulopathy early during infancy; the natural evolution is a progressive chronic interstitial nephritis leading to end-stage renal disease (ESRD) within the first decade of life [102]. The use of cysteamine therapy since the 1980s has postponed ESRD and extra-renal morbidities to the second or third decade of life [103]. As patients receive cysteamine and as global survival improves [102], bone impairment occurring during teenage or early adulthood was recently described as a "novel" complication of NC [104, 105]. Even though the exact underlying pathophysiology remains unclear, six hypotheses are currently discussed: copper deficiency [106], long-term consequences of hypophosphatemic rickets together with iatrogenic effects of its supportive management, cysteamine toxicity [105], abnormal thyroid metabolism, chronic hypoparathyroidism, and/or direct bone effect of the *CTNS* mutation [100, 101]. International guidelines have been recently published to guide the management of these very specific patients, keeping in mind that some other factors may worsen bone disease, such as malnutrition and myopathy [107].

Last, and more anecdotally, patients with Pierson syndrome may present with skeletal deformations, maybe due to the absence of laminin-β2 in bone [108].

In the future, understanding the impact of the different genetic defects on the growing skeleton will lead to targeted therapeutic strategies.

Conclusion and Perspectives

Since growth failure during CKD has been well demonstrated to be associated with increased hospitalization rates and increased morbidity/

mortality, and since bone status probably represents only the tip of the iceberg of cardiovascular health and vascular calcifications, large prospective multicenter trials are urgently required in this specific pediatric population to evaluate the impact current therapies not only on final adult height but also on bone status, fracture risk, and global cardiovascular status. In this setting, bone histomorphometry remains an important component of well-designed clinical studies, but the role of new non-invasive imaging techniques should also be evaluated.

The evaluation of growth and bone status remains challenging in CKD children even though the recent description of the FGF23 bone/kidney/parathyroid axis highlights new promising and exciting hypotheses to improve diagnosis and clinical management of CKD-MBD. Therefore, at the current time, the daily clinical management of CKD-MBD in children should still focus on three main objectives: (1) to provide an optimal nutritional support to maximize the final height and avoid bone deformations, (2) to equilibrate calcium-phosphate metabolism so as to provide acceptable bone quality and cardiovascular status, and (3) to correct all metabolic and clinical abnormalities that can worsen both bone and growth (mainly metabolic acidosis, anemia, malnutrition, and 25(OH) vitamin D deficiency).

References

1. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol JASN. 2012;23(4):578–85.
2. Bacchetta J, Harambat J, Cochat P, Salusky IB, Wesseling-Perry K. The consequences of chronic kidney disease on bone metabolism and growth in children. Nephrol Dial Transplant. 2012;27(8):3063–71.
3. Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945–53.
4. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int. 2017;92(1):26–36.
5. Groothoff JW, Offringa M, Van Eck-Smit BLF, Gruppen MP, Van De Kar NJ, Wolff ED, et al. Severe bone disease and low bone mineral density after juvenile renal failure. Kidney Int. 2003;63(1):266–75.
6. Denburg MR, Kumar J, Jemielita T, Brooks ER, Skversky A, Portale AA, et al. Fracture burden and risk factors in childhood CKD: results from the CKiD cohort study. J Am Soc Nephrol JASN. 2016;27(2):543–50.
7. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
8. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation. 2002;106(1):100–5.
9. Cejka D, Weber M, Diarra D, Reiter T, Kainberger F, Haas M. Inverse association between bone microarchitecture assessed by HR-pQCT and coronary artery calcification in patients with end-stage renal disease. Bone. 2014;64:33–8.
10. Malluche HH, Blomquist G, Monier-Faugere M-C, Cantor TL, Davenport DL. High parathyroid hormone level and osteoporosis predict progression of coronary artery calcification in patients on dialysis. J Am Soc Nephrol JASN. 2015;26(10):2534–44.
11. Ziolkowska H, Brzewski M, Roszkowska-Blaim M. Determinants of the intima-media thickness in children and adolescents with chronic kidney disease. Pediatr Nephrol Berl Ger. 2008;23(5):805–11.
12. Preka E, Ranchin B, Doyon A, Vierge M, Ginhoux T, Kassai B, et al. The interplay between bone and vessels in pediatric CKD: lessons from a single-center study. Pediatr Nephrol Berl Ger. 2018;33(9):1565–75.
13. Portale AA, Wolf MS, Messinger S, Perwad F, Jüppner H, Warady BA, et al. Fibroblast growth factor 23 and risk of CKD progression in children. Clin J Am Soc Nephrol CJASN. 2016;11(11):1989–98.
14. Bacchetta J, Bardet C, Prié D. Physiology of FGF23 and overview of genetic diseases associated with renal phosphate wasting. Metabolism. 2020;103S:153865.
15. ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet. 2000;26(3):345–8.
16. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int. 2011;79(12):1370–8.
17. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92.
18. Kurosu H, Kuro-O M. The Klotho gene family as a regulator of endocrine fibroblast growth factors. Mol Cell Endocrinol. 2009;299(1):72–8.
19. Yamazaki Y, Tamada T, Kasai N, Urakawa I, Aono Y, Hasegawa H, et al. Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23. J Bone Miner Res. 2008;23(9):1509–18.

20. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113(4):561–8.
21. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, et al. The parathyroid is a target organ for FGF23 in rats. J Clin Invest. 2007;117(12):4003–8.
22. Wesseling-Perry K, Pereira RC, Tseng C-H, Elashoff R, Zaritsky JJ, Yadin O, et al. Early skeletal and biochemical alterations in pediatric chronic kidney disease. Clin J Am Soc Nephrol CJASN. 2012;7(1):146–52.
23. Faul C, Amaral AP, Oskouei B, Hu M-C, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011;121(11):4393–408.
24. Olauson H, Lindberg K, Amin R, Sato T, Jia T, Goetz R, et al. Parathyroid-specific deletion of Klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulates PTH secretion. PLoS Genet. 2013;9(12):e1003975.
25. Bacchetta J, Sea JL, Chun RF, Lisse TS, Wesseling-Perry K, Gales B, et al. Fibroblast growth factor 23 inhibits extrarenal synthesis of 1,25-dihydroxyvitamin D in human monocytes. J Bone Miner Res. 2013;28(1):46–55.
26. Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK. Low vitamin D and high fibroblast growth factor 23 serum levels associate with infectious and cardiac deaths in the HEMO study. J Am Soc Nephrol JASN. 2016;27(1):227–37.
27. Andrukhova O, Slavic S, Smorodchenko A, Zeitz U, Shalhoub V, Lanske B, et al. FGF23 regulates renal sodium handling and blood pressure. EMBO Mol Med. 2014;6(6):744–59.
28. Hensel N, Schön A, Konen T, Lübben V, Förthmann B, Baron O, et al. Fibroblast growth factor 23 signaling in hippocampal cells: impact on neuronal morphology and synaptic density. J Neurochem. 2016;137(5):756–69.
29. Gardner J, Ashraf A, You Z, McCormick K. Changes in plasma FGF23 in growth hormone deficient children during rhGH therapy. J Pediatr Endocrinol Metab JPEM. 2011;24(9–10):645–50.
30. Rutkowski JM, Pastor J, Sun K, Park SK, Bobulescu IA, Chen CT, et al. Adiponectin alters renal calcium and phosphate excretion through regulation of klotho expression. Kidney Int. 2017;91(2):324–37.
31. Denburg MR, Kalkwarf HJ, de Boer IH, Hewison M, Shults J, Zemel BS, et al. Vitamin D bioavailability and catabolism in pediatric chronic kidney disease. Pediatr Nephrol Berl Ger. 2013;28(9):1843–53.
32. Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, et al. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. Kidney Int. 2016;90(5):985–96.
33. Eisenga MF, van Londen M, Leaf DE, Nolte IM, Navis G, Bakker SJL, et al. C-terminal fibroblast growth factor 23, iron deficiency, and mortality in renal transplant recipients. J Am Soc Nephrol JASN. 2017;28(12):3639–46.
34. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. J Bone Miner Res. 2013;28(8):1793–803.
35. Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis. 2012;60(1):139–56.
36. Ritter CS, Armbrecht HJ, Slatopolsky E, Brown AJ. 25-Hydroxyvitamin D(3) suppresses PTH synthesis and secretion by bovine parathyroid cells. Kidney Int. 2006;70(4):654–9.
37. Shroff R, Wan M, Gullett A, Ledermann S, Shute R, Knott C, et al. Ergocalciferol supplementation in children with CKD delays the onset of secondary hyperparathyroidism: a randomized trial. Clin J Am Soc Nephrol CJASN. 2012;7(2):216–23.
38. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res. 2010;25(2):305–12.
39. Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. 2010;95(2):471–8.
40. Bacchetta J, Salusky IB, Hewison M. Beyond mineral metabolism, is there an interplay between FGF23 and vitamin D in innate immunity? Pediatr Nephrol Berl Ger. 2013;28(4):577–82.
41. David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int. 2016;89(1):135–46.
42. Farrow EG, Yu X, Summers LJ, Davis SI, Fleet JC, Allen MR, et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. Proc Natl Acad Sci U S A. 2011;108(46):E1146–55.
43. Hanudel MR, Chua K, Rappaport M, Gabayan V, Valore E, Goltzman D, et al. Effects of dietary iron intake and chronic kidney disease on fibroblast growth factor 23 metabolism in wild-type and hepcidin knockout mice. Am J Physiol Renal Physiol. 2016;311(6):F1369–77.
44. Hanudel MR, Wesseling-Perry K, Gales B, Ramos G, Campbell V, Ethridge K, et al. Effects of acute kidney injury and chronic hypoxemia on fibroblast growth factor 23 levels in pediatric cardiac surgery patients. Pediatr Nephrol Berl Ger. 2016;31(4):661–9.
45. Iguchi A, Kazama JJ, Yamamoto S, Yoshita K, Watanabe Y, Iino N, et al. Administration of ferric citrate hydrate decreases circulating FGF23 levels independently of serum phosphate levels in hemodialysis patients with Iron deficiency. Nephron. 2015;131(3):161–6.
46. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and

iron deficiency anemia. J Am Soc Nephrol JASN. 2017;28(6):1851–8.
47. Coe LM, Madathil SV, Casu C, Lanske B, Rivella S, Sitara D. FGF-23 is a negative regulator of prenatal and postnatal erythropoiesis. J Biol Chem. 2014;289(14):9795–810.
48. Mehta R, Cai X, Hodakowski A, Lee J, Leonard M, Ricardo A, et al. Fibroblast growth factor 23 and anemia in the chronic renal insufficiency cohort study. Clin J Am Soc Nephrol CJASN. 2017;12(11):1795–803.
49. Bakkaloglu SA, Bacchetta J, Lalayiannis AD, Leifheit-Nestler M, Stabouli S, Haarhaus M, Reusz G, Groothoff J, Schmitt CP, Evenepoel P, Shroff R, Haffner D, European Society for Paediatric Nephrology (ESPN) Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) and Dialysis Working Groups and CKD-MBD Working Group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Bone evaluation in paediatric chronic kidney disease: clinical practice points from the European Society for Paediatric Nephrology CKD-MBD and Dialysis working groups and CKD-MBD working group of the ERA-EDTA. Nephrol Dial Transplant. 2020 Nov 2:gfaa210. https://doi.org/10.1093/ndt/gfaa210. Online ahead of print. PMID: 33245331.
50. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, et al. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. J Clin Endocrinol Metab. 2013;98(5):1930–8.
51. Querfeld U, Anarat A, Bayazit AK, Bakkaloglu AS, Bilginer Y, Caliskan S, et al. The cardiovascular comorbidity in children with chronic kidney disease (4C) study: objectives, design, and methodology. Clin J Am Soc Nephrol CJASN. 2010;5(9):1642–8.
52. Ardeshirpour L, Cole DEC, Carpenter TO. Evaluation of bone and mineral disorders. Pediatr Endocrinol Rev PER. 2007;5 Suppl 1:584–98.
53. KDOQI Work Group. KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 update. Executive summary. Am J Kidney Dis. 2009;53(3 Suppl 2):S11–104.
54. Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? Chest. 2016;149(3):846–55.
55. Yu E, Sharma S. Physiology, Calcium. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 [cité 17 déc 2018]. Disponible sur: http://www.ncbi.nlm.nih.gov/books/NBK482128/
56. Sakaguchi Y, Hamano T, Kubota K, Oka T, Yamaguchi S, Matsumoto A, et al. Anion gap as a determinant of ionized fraction of divalent cations in hemodialysis patients. Clin J Am Soc Nephrol CJASN. 2018;13(2):274–81.
57. Bakkaloglu SA, Wesseling-Perry K, Pereira RC, Gales B, Wang H-J, Elashoff RM, et al. Value of the new bone classification system in pediatric renal osteodystrophy. Clin J Am Soc Nephrol CJASN. 2010;5(10):1860–6.
58. Souberbielle J-C, Boutten A, Carlier M-C, Chevenne D, Coumaros G, Lawson-Body E, et al. Inter-method variability in PTH measurement: implication for the care of CKD patients. Kidney Int. 2006;70(2):345–50.
59. Hocher B, Oberthür D, Slowinski T, Querfeld U, Schaefer F, Doyon A, et al. Modeling of oxidized PTH (oxPTH) and non-oxidized PTH (n-oxPTH) receptor binding and relationship of oxidized to non-oxidized PTH in children with chronic renal failure, adult patients on hemodialysis and kidney transplant recipients. Kidney Blood Press Res. 2013;37(4–5):240–51.
60. Rees L, Shroff R. The demise of calcium-based phosphate binders-is this appropriate for children? Pediatr Nephrol Berl Ger. 2015;30(12):2061–71.
61. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, et al. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78(12):1295–304.
62. Haffner D, Schaefer F. Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. Pediatr Nephrol Berl Ger. 2013;28(4):537–45.
63. Wesseling-Perry K, Pereira RC, Sahney S, Gales B, Wang H-J, Elashoff R, et al. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. Kidney Int. 2011;79(1):112–9.
64. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;113:S1–130.
65. Klaus G, Watson A, Edefonti A, Fischbach M, Rönnholm K, Schaefer F, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol Berl Ger. 2006;21(2):151–9.
66. Drube J, et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. Nat Rev Nephrol. 2019;15(9):577–89. PMID: 31197263.
67. Waller S, Shroff R, Freemont AJ, Rees L. Bone histomorphometry in children prior to commencing renal replacement therapy. Pediatr Nephrol Berl Ger. 2008;23(9):1523–9.
68. Shroff R, Wan M, Nagler EV, Bakkaloglu S, Fischer D-C, Bishop N, et al. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease Stages 2–5 and on dialysis. Nephrol Dial Transplant. 2017;32(7):1098–113.
69. Gonzalez E, Schomberg J, Amin N, Salusky IB, Zaritsky J. Sevelamer carbonate increases serum bicarbonate in pediatric dialysis patients. Pediatr Nephrol Berl Ger. 2010;25(2):373–5.
70. Jin C, Gao L, Li Y, Wu S, Lu X, Yang J, et al. Lanthanum damages learning and memory and suppresses astrocyte-neuron lactate shuttle in rat hippocampus. Exp Brain Res. 2017;235(12):3817–32.

71. Hanudel MR, Laster M, Ramos G, Gales B, Salusky IB. Clinical experience with the use of ferric citrate as a phosphate binder in pediatric dialysis patients. Pediatr Nephrol Berl Ger. 2018;33(11):2137–42.
72. Kalantar-Zadeh K, Parameswaran V, Ficociello LH, Anderson L, Ofsthun NJ, Kwoh C, et al. Real-world scenario improvements in serum phosphorus levels and pill burden in peritoneal dialysis patients treated with sucroferric oxyhydroxide. Am J Nephrol. 2018;47(3):153–61.
73. Shroff R. Phosphate is a vascular toxin. Pediatr Nephrol Berl Ger. 2013;28(4):583–93.
74. Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. J Am Soc Nephrol JASN. 2013;24(2):179–89.
75. Rinat C, Becker-Cohen R, Nir A, Feinstein S, Shemesh D, Algur N, et al. A comprehensive study of cardiovascular risk factors, cardiac function and vascular disease in children with chronic renal failure. Nephrol Dial Transplant. 2010;25(3):785–93.
76. Bailey DA, Martin AD, McKay HA, Whiting S, Mirwald R. Calcium accretion in girls and boys during puberty: a longitudinal analysis. J Bone Miner Res. 2000;15(11):2245–50.
77. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2015;(11):CD008327.
78. Shroff R, Wan M, Nagler EV, Bakkaloglu S, Cozzolino M, Bacchetta J, et al. Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease Stages 2–5 and on dialysis. Nephrol Dial Transplant. 2017;32(7):1114–27.
79. Warady BA, Iles JN, Ariceta G, Dehmel B, Hidalgo G, Jiang X, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet in pediatric patients with chronic kidney disease and secondary hyperparathyroidism receiving dialysis. Pediatr Nephrol Berl Ger. 2019;34(3):475–86.
80. Sohn WY, Portale AA, Salusky IB, Zhang H, Yan LL, Ertik B, et al. An open-label, single-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of cinacalcet in pediatric subjects aged 28 days to <6 years with chronic kidney disease receiving dialysis. Pediatr Nephrol Berl Ger. 2019;34(1):145–54.
81. Muscheites J, Wigger M, Drueckler E, Fischer D-C, Kundt G, Haffner D. Cinacalcet for secondary hyperparathyroidism in children with end-stage renal disease. Pediatr Nephrol Berl Ger. 2008;23(10):1823–9.
82. Silverstein DM, Kher KK, Moudgil A, Khurana M, Wilcox J, Moylan K. Cinacalcet is efficacious in pediatric dialysis patients. Pediatr Nephrol Berl Ger. 2008;23(10):1817–22.
83. Padhi D, Langman CB, Fathallah-Shaykh S, Warady BA, Salusky IB, Lee E, et al. An open-label study to evaluate a single-dose of cinacalcet in pediatric dialysis subjects. Pediatr Nephrol Berl Ger. 2012;27(10):1953–9.
84. Platt C, Inward C, McGraw M, Dudley J, Tizard J, Burren C, et al. Middle-term use of Cinacalcet in paediatric dialysis patients. Pediatr Nephrol Berl Ger. 2010;25(1):143–8.
85. Arenas Morales AJ, DeFreitas MJ, Katsoufis CP, Seeherunvong W, Chandar J, Zilleruelo G, et al. Cinacalcet as rescue therapy for refractory hyperparathyroidism in young children with advanced chronic kidney disease. Pediatr Nephrol Berl Ger. 2019;34(1):129–35.
86. Kim J, Ross JS, Kapczynski A. Pediatric exclusivity and regulatory authority: implications of amgen v HHS. JAMA. 2018;319(1):21–2.
87. Bacchetta J, Schmitt CP, Ariceta G, Bakkaloglu S, Groothoof J, Wan M, Vervloet M, Shroff R, Haffner D, on behalf of the ESPN and the CKD-MBD working groups of the ERA-EDTA J. Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA. Nephrol Dial Transpl. 2020;35(1):47–64. https://doi.org/10.1093/ndt/gfz159.
88. Pereira RC, Jüppner H, Gales B, Salusky IB, Wesseling-Perry K. Osteocytic protein expression response to doxercalciferol therapy in pediatric dialysis patients. PLoS One. 2015;10(3):e0120856.
89. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, et al. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Circulation. 2015;132(1):27–39.
90. Oliveira RB, Cancela ALE, Graciolli FG, Dos Reis LM, Draibe SA, Cuppari L, et al. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin J Am Soc Nephrol CJASN. 2010;5(2):286–91.
91. Liabeuf S, Ryckelynck J-P, El Esper N, Ureña P, Combe C, Dussol B, et al. Randomized clinical trial of sevelamer carbonate on serum klotho and fibroblast growth factor 23 in CKD. Clin J Am Soc Nephrol CJASN. 2017;12(12):1930–40.
92. Bacchetta J, Boivin G, Cochat P. Bone impairment in primary hyperoxaluria: a review. Pediatr Nephrol Berl Ger. 2016;31(1):1–6.
93. Bacchetta J, Farlay D, Abelin-Genevois K, Lebourg L, Cochat P, Boivin G. Bone impairment in oxalosis: an ultrastructural bone analysis. Bone. 2015;81:161–7.
94. Duclaux-Loras R, Bacchetta J, Berthiller J, Rivet C, Demède D, Javouhey E, et al. Pediatric combined liver-kidney transplantation: a single-center experience of 18 cases. Pediatr Nephrol Berl Ger. 2016;31(9):1517–29.
95. De Rechter S, Bacchetta J, Godefroid N, Dubourg L, Cochat P, Maquet J, et al. Evidence for bone and mineral metabolism alterations in children with autosomal dominant polycystic kidney disease. J Clin Endocrinol Metab. 2017;102(11):4210–7.

96. Chonchol M, Gitomer B, Isakova T, Cai X, Salusky I, Pereira R, et al. Fibroblast Growth Factor 23 and Kidney Disease Progression in Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol CJASN. 2017;12(9):1461–9.
97. Evenepoel P, Claes K, Cavalier E, Meijers B, Stenvinkel P, Behets G, et al. A distinct bone phenotype in ADPKD patients with end-stage renal disease. Kidney Int. 2019;95(2):412–9.
98. Bertholet-Thomas A, Claramunt-Taberner D, Gaillard S, Deschênes G, Sornay-Rendu E, Szulc P, et al. Teenagers and young adults with nephropathic cystinosis display significant bone disease and cortical impairment. Pediatr Nephrol Berl Ger. 2018;33(7):1165–72.
99. Florenzano P, Ferreira C, Nesterova G, Roberts MS, Tella SH, de Castro LF, et al. Skeletal consequences of Nephropathic Cystinosis. J Bone Miner Res. 2018;33(10):1870–80.
100. Conforti A, Taranta A, Biagini S, Starc N, Pitisci A, Bellomo F, et al. Cysteamine treatment restores the in vitro ability to differentiate along the osteoblastic lineage of mesenchymal stromal cells isolated from bone marrow of a cystinotic patient. J Transl Med. 2015;13:143.
101. Claramunt-Taberner D, Flammier S, Gaillard S, Cochat P, Peyruchaud O, Machuca-Gayet I, et al. Bone disease in nephropathic cystinosis is related to cystinosin-induced osteoclastic dysfunction. Nephrol Dial Transpl. 2018;33(9):1525–32. https://doi.org/10.1093/ndt/gfx362.
102. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. Pediatr Nephrol Berl Ger. 2013;28(1):51–9.
103. Bertholet-Thomas A, Bacchetta J, Tasic V, Cochat P. Nephropathic cystinosis–a gap between developing and developed nations. N Engl J Med. 2014;370(14):1366–7.
104. Langman CB. Bone complications of Cystinosis. J Pediatr. 2017;183S:S2–4.
105. Besouw MTP, Bowker R, Dutertre J-P, Emma F, Gahl WA, Greco M, et al. Cysteamine toxicity in patients with cystinosis. J Pediatr. 2011;159(6):1004–11.
106. Besouw MTP, Schneider J, Janssen MC, Greco M, Emma F, Cornelissen EA, et al. Copper deficiency in patients with cystinosis with cysteamine toxicity. J Pediatr. 2013;163(3):754–60.
107. Hohenfellner K, Rauch F, Ariceta G, Awan A, Bacchetta J, Bergmann C, et al. Management of bone disease in cystinosis: statement from an international conference. J Inherit Metab Dis. 2019;42(5):1019–29.
108. Beaufils C, Farlay D, Machuca-Gayet I, Fassier A, Zenker M, Freychet C, et al. Skeletal impairment in Pierson syndrome: is there a role for lamininβ2 in bone physiology? Bone. 2018;106:187–93.

30 The Cardiovascular Status of Pediatric Dialysis Patients

Rukshana Shroff and Mark M. Mitsnefes

Epidemiology of CVD in CKD Patients

A seminal paper by Foley et al. drew the attention of the medical community to the very high rate of cardiovascular deaths in patients on dialysis [1]. This epidemiological study compared the mortality of maintenance dialysis patients with that of age, gender, and race-matched healthy controls, and showed that the mortality of young adults (25–34 years old) on dialysis was approximately 700-fold higher than age-related mortality and comparable to that of an 80-year-old.

CVD is not only the leading cause of death in young adults with childhood-onset end-stage renal disease (ESRD) [2, 3], but it also occurs in children with CKD. The United States Renal Data System's (USRDS) initial analysis published in 2002 showed that the mortality from CVD was 1000 times more common in children on dialysis than in the general pediatric population [4]. This study analyzed 1380 deaths over a 5-year period among patients who had started renal replacement therapy as children and died before 30 years of age [4]. Twenty-three percent of all deaths were from cardiovascular causes, and deaths on hemodialysis (HD) were approximately twice as common as on peritoneal dialysis (PD) [49% vs. 22% respectively] and 78% higher than that in transplant recipients [4].

Subsequently, several large national registries have published similar findings for pediatric dialysis recipients. The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry has shown that 45% of all deaths were due to CVD, with 57% of deaths on HD and 43% of deaths on PD from cardiovascular causes [5]. Chavers et al. have used the large USRDS database to examine the incidence and extent of CVD in incident pediatric (0–19 years) dialysis patients from 1991 to 1996 [6]. Of the 1454 children studied, 31% developed a cardiac-related event. Arrhythmia was the most common (20%), followed by valvular heart disease (12%), cardiomyopathy (9%), and cardiac arrest (3%). Thirty-eight percent of the deaths during the study period were cardiac deaths. The incidence of valvular heart disease and arrhythmias was highest among the teenagers [6].

A more recent USRDS analysis of more than 20,000 patients initiating dialysis therapy during childhood demonstrated that mortality rates improved between 1990 and 2010 [7]. Although improvements were observed across all ages, the gains in survival were greater for children initiating dialysis care at <5 years of age. Despite some improvement in survival, the lifespan of a

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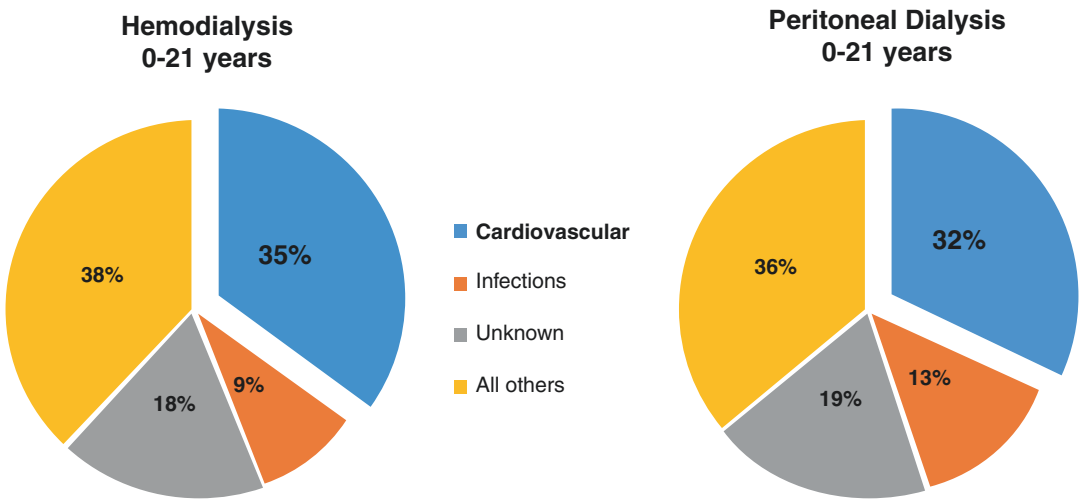

Fig. 30.1 Leading causes of death (2014–2016 combined) in children on dialysis. USRDS 2018 Annual Report [8]

pediatric patient on dialysis is still shortened by 30–40 years compared with control individuals matched for age and ethnicity with CVD remaining the most common cause of death (Fig. 30.1).

Cardiovascular Disease Begins Early in the Course of CKD

Studies over last two decades have shown disturbing evidence of the development of CVD even in the very early stages of CKD [9]. The National Kidney Foundation's task force on CVD in CKD has concluded that in terms of risk stratification, individuals with CKD should be considered to be at very high risk for CVD [10]. In a population-based study of over one million adults who were followed up for over 4 years, both the risk of death and the risk of cardiovascular events increased as the estimated GFR dropped below 60 mL/min/1.73 m^2 [11]. This independent and graded association between renal function and CVD and death highlights the importance of recognizing and controlling modifiable risk factors from the earliest stages of CKD.

In children, our current knowledge and understanding of the early development of CVD comes largely from the Pathological Determinants of Atherosclerosis in Youth (PDAY) study [12] and the Bogalusa Heart Study [13]. These studies have demonstrated pathological evidence of early atherosclerosis in relatively unbiased "healthy" individuals. The PDAY study showed that fatty streaks and raised lesions increase rapidly in prevalence and extent during the 15–34-year age span. In this study, early atherosclerotic lesions were reported in association with hypertension, dyslipidemia, cigarette smoking, and increased body mass index [12, 14]. The PDAY study also showed that the association of lipoprotein risk factors with intermediate type atherosclerotic lesions becomes evident in subjects in their late teens, whereas associations with raised lesions become evident in subjects greater than 25 years of age, consistent with a transitional role of intermediate lesions in the formation of advanced plaques [15]. As in the PDAY study, the Bogalusa autopsy study [13] showed that CVD is present in children and young adults and is associated with traditional risk factors such as systolic and diastolic hypertension, hyperlipidemia, and smoking.

Children with CKD amplify their CVD risk due to uremia-related risk factors such as abnormal mineral metabolism, anemia, chronic inflammation, hyperhomocysteinemia, malnutrition, oxidative stress, and fluid overload. More importantly, these "CKD-related" risk factors are central in the development of arteriosclerosis, arterial stiffening, and vascular calcification, findings

that present early in the course of childhood CKD. It is not surprising that the American Heart Association guidelines for cardiovascular risk reduction in high-risk pediatric patients [16] declared that pediatric CKD patients should be stratified in the "high risk" category for the development of CVD, with associated "pathological and/or clinical evidence for manifest coronary disease before 30 years of age."

Cross-sectional association studies have uniformly shown an increase in surrogate parameters with advancing stages of CKD, suggesting that CVD comorbidity already starts at an early stage of CKD and that the progression of CVD parallels the loss of renal function. However, the effect of risk factors on the progression of CVD can only be answered by prospective cohort studies. Two large prospective cohort studies have studied children in pre-dialysis CKD stages and comprehensively described CVD-related risk factors as they advance through successive stages of CKD. A prospective observational study including >700 European children with CKD, the Cardiovascular Comorbidity in Children with CKD (4C) study, showed that at baseline (eGFR 10–60 ml/min per 1.73 m2), left ventricular hypertrophy (LVH) was present in 33%, cIMT was elevated in 42%, and PWV was increased in 20% of patients [17]. Thus, preclinical changes of CVD with myocardial and vascular remodeling and stiffening are prevalent in many children with pre-dialysis CKD. Similar results were found in the CKiD (Chronic Kidney Disease in Children) Study, a prospective study with an initial cohort of 586 US children aged 1–16 years, but with relatively better preserved renal function at baseline (eGFR 30–90 ml/min per 1.73 m^2) [18].

Risk Factors for the Development of CVD in CKD

CKD patients have a higher prevalence of both the "traditional" Framingham risk factors and nontraditional risk factors that increase their cardiovascular risk (Table 30.1).

Table 30.1 Cardiovascular risk factors in chronic kidney disease

Traditional risk factors	CKD-specific risk factors
Old age	Abnormal Ca and PO_4 levels
Male gender	Abnormal PTH levels
Hypertension	Vitamin D deficiency
Diabetes	Anemia
Higher total cholesterol	Extracellular fluid overload
Higher LDL cholesterol	Inflammation
Lower HDL cholesterol	Oxidative stress
Family history of cardiovascular disease	Perturbation in the circulating calcification inhibitors
Lipoprotein (a)	Albuminuria
Smoking	Hyperhomocysteinemia
Physical inactivity	Abnormal fibroblast growth factor 23 (FGF-23) Malnutrition and hypoalbuminemia Altered nitric oxide/endothelin balance

"Traditional" Risk Factors

Over half of all children even in early CKD have *hypertension*, increasing to 50–75% in CKD stage 5, and 50–87% in transplant recipients [19–22]. In children, hypertension is the single most prevalent and significant "traditional" risk factor for left ventricular hypertrophy (LVH) [23, 24] as well as for vascular damage and remodeling [25]. Despite wide availability of multiple antihypertensive agents, BP is difficult control in children on dialysis. A recent study from Poland looked at the efficacy of antihypertensive drugs used for the treatment of hypertension in pediatric dialyzed patients in 2013 in comparison with data collected in 2003/2004 [26]. In 61% of the patients, hypertension was treated inadequately, which is similar to the results obtained in 2003/2004 (65%). The level of underdiagnosed hypertension also remained the same. Data from the ESPN/ERA-EDTA, the IPPN (since 2007), the Japanese Registry, or the Australian and New Zealand Dialysis and Transplant (ANZDATA)

Registry demonstrated that among children requiring renal replacement therapy (RRT) during the neonatal period, hypertension (57%) was still a major problem after 2 years of dialysis [27]. The use of a 24-hour ABPM can provide additional information on BP control in dialyzed children. For example, in one small study, the authors determined that about one half of children had an abnormally high mean ambulatory BP and up to three quarters had an abnormal BP load or dipping status [28].

Multiple factors contribute to the high prevalence of hypertension in this population. Sympathetic overactivity is one of the key players of CKD, which appears to occur very early in the course of the disease. Activation of the renin–angiotensin system, sodium and fluid overload, and functional nitric oxide (NO) deficiency due to the accumulation of the circulating nitric oxide synthase (NOS) inhibitor asymmetric dimethylarginine (L-ADMA) also contribute to hypertension in patients with ESRD.

Fluid overload (see also Chap. 21) among patients on maintenance dialysis is a frequent problem and is a primary mechanism for the development and persistence of hypertension, particularly in patients treated with intermittent HD rather than PD. Vandevoorde et al. demonstrated that in pediatric HD patients, hypertensive subjects had significantly higher excess weight post dialysis and increased normalized intradialytic weight gain than did non-hypertensive subjects, with volume overload identified as the main cause of hypertension [29]. Furthermore, chronic volume overload in children is associated with higher rates of early cardiac structural and functional abnormalities that will be discussed later in this chapter [30–32]. A recent study has suggested that serum B-type natriuretic peptide (BNP) could serve as a biomarker of fluid retention in hypertensive children on peritoneal dialysis [33].

Dyslipidemia is an independent risk factor for CVD in CKD patients. Renal disease is often associated with dyslipidemia, and some evidence exists that dyslipidemia is an independent risk factor not only for the progression of CVD, but also for progressive CKD [34]. The degree of dyslipidemia parallels the degree of renal impairment [35]. Underlying mechanisms of uremic dyslipidemia include insulin resistance [36], hyperparathyroidism [37], malnutrition, acidosis [38], and impaired catabolism of triglyceride-rich lipoproteins by decreased activity of lipoprotein lipase and hepatic triglyceride lipase [39, 40], whereas lipoprotein synthesis appears to be unaltered. Lipoprotein (a) (Lp(a)), which exerts a pro-atherosclerotic and pro-thrombotic effect, is also increased in ESRD. In line with findings in adults, in children with CKD, serum triglycerides are elevated whereas total cholesterol is close to normal. Hemodialysis does not seem to alter the pattern of dyslipidemia associated with CKD, whereas PD may contribute to an elevation of total cholesterol with a further increase in hypertriglyceridemia [41]. This is probably due to further aggravation of insulin resistance secondary to continuous glucose absorption from the dialysis fluid.

Obesity, another traditional risk factor, plays a subordinate role in pediatric dialysis patients. However it might be present in children with syndrome-associated CKD, like Bardet–Biedl syndrome, or occasionally in children on PD. An increased susceptibility to obesity in some PD patients may be due to the increased calorie supply by dialysate glucose administration in combination with a polymorphism in the UCP2 gene, the latter regulating adipose tissue accumulation [42].

The "traditional" risk factors may have a qualitatively and quantitatively different risk relationship in CKD compared to the general population; a phenomenon of reverse epidemiology or risk factor reversal has been reported between body mass index, blood pressure, cholesterol levels [43], and the hazard ratio for morbidity or mortality. One of the major causes for this risk factor reversal may be the confounding effects of protein energy malnutrition and inflammatory disorders that are prevalent in maintenance dialysis patients [44].

Uremia-Related Risk Factors

Nontraditional risk factors, such as anemia, chronic inflammation, oxidative stress, malnutrition,

hyperhomocysteinemia, or dysregulation of the Ca–phosphate–PTH axis, are risk factors primarily present in CKD patients. Furthermore, there are a number of potential iatrogenic or treatment-related risk factors such as exposure to a high Ca load from dialysate, calcium-based phosphate binders, and vitamin D therapy; advanced glycation end-products, metabolic acidosis, and warfarin therapy can all contribute to the pro-calcific uremic milieu. The key factors are described in detail below.

Dysregulations in the Ca–P–PTH axis (see also Chap. 29) are central to the vascular damage and calcification in CKD patients. Phosphate has probably the best described spectrum of toxicity of all molecules that circulate in excess in CKD. Decreased renal P excretion plays a major role in the onset of hyperparathyroidism. Furthermore, plasma P levels are positively and independently correlated with an increasing risk of death from CVD [45]. Phosphate is filtered at the glomerulus and reabsorbed in the proximal tubules, with approximately 85% of the filtered phosphate reabsorbed via the sodium-phosphate co-transporter IIa located in the proximal tubular brush border membranes. It would be expected, therefore, that CKD would result in hyperphosphatemia. However, we now know that compensatory mechanisms in the form of increased fibroblast growth factor-23 (FGF-23) levels act to preserve a normal plasma P in early CKD [46]. FGF-23 is a hormone produced by the osteocyte, and together with its obligate co-receptor, Klotho, results in a negative phosphate balance, by decreasing renal tubular phosphate reabsorption and suppressing renal 1-α hydroxylase, thereby reducing the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) [46]. However, as CKD progresses, there is increasing FGF-23 resistance and P retention occurs, stimulating PTH secretion.

Studies in adult patients have conclusively identified that plasma phosphate is an independent predictor of mortality in CKD. This link was first demonstrated in adult HD patients: as serum phosphate levels increased above 5.6 mg/dL (= 1.8 mmol/L), the hazards ratio for mortality increased by 6% for every 1 mg/dL (= 0.3 mmol/L) increase in serum phosphate [45]. Hyperphosphatemia has also been shown to be an independent risk factor for death in the predialysis population [47, 48]. Data from >26,000 adult dialysis patients have shown that in over 80% of patients, at least one biochemical variable was uncontrolled. Pediatric studies have similarly shown that plasma phosphate adversely affects cIMT, coronary calcification, and left ventricular mass, and these studies are discussed in detail below. Several in vitro studies using vascular smooth muscle cell (VSMC) cultures and intact human vessels have shown the direct causal role of P in inducing and promoting vascular calcification [49, 50], and are discussed below.

CKD patients are thought to be in a net positive Ca balance as a result of iatrogenic Ca loading from Ca-based phosphate binders, vitamin D therapy, dialysate Ca, and reduced or absent Ca removal via the kidneys. In the above study by Block et al., patients with high calcium levels and PTH > 300 pg/dl were consistently associated with a higher risk of death or cardiac dysfunction [51]. Current guidelines state that hypercalcemia may be harmful in all GFR categories of CKD and call for restriction in the use of calcium-containing phosphate binders [52]. Current K/DOQI guidelines recommend a maximum elemental calcium load of 2000 mg/day, including calcium-containing medication (maximum 1500 mg/day) and a maximum dialysate calcium concentration of 1.25 mmol/L (to avoid intradialytic Ca loading) [53]. Ca balance studies during HD have shown that the majority of HD patients are continually experiencing Ca overload. Also, the amount of Ca removed during dialysis was independent of the exogenous Ca load from diet or binders [54]. These transient increases in Ca that inevitably occur in clinical practice may go unrecorded, but can impact on ectopic calcification, particularly in the setting of high P conditions. Clinical studies have reported that the extent of arterial calcification was directly related to the number of episodes of hypercalcemia during the preceding 6 months [55] and in the "Treat-to-Goal" study, the Ca-treated group had significantly more hypercalcemic episodes than the sevelamer group [56].

Oxidative stress is a major contributor to increased atherosclerosis and cardiovascular

morbidity and mortality in CKD. Malnutrition and hypoalbuminemia reduce the antioxidant defense and increase vulnerability to oxidant injury. Retained uremic solutes, such as the advanced glycation end-products (AGE) that are substrates of oxidized dialysate components, homocysteine, cysteine, and ß2-microglobulin, further contribute to the pro-atherogenic milieu in uremia. Although dialysis treatment reduces the concentration of oxidized substrates, ameliorating the oxidant–antioxidant balance, dialysis-associated factors such as vascular catheters, dialysis membranes, and exposure to dialysate or oxidants in HD water, can also induce further pro-atherogenic insults [57].

ESRD can be considered a low-grade *inflammatory state*. Oxidative and carbonyl stress may stimulate cells and the endothelium to release IL-6 and other pro-inflammatory cytokines that are directly linked with the initiation and progression of atherosclerosis in HD and PD patients [58–60]. The inflammatory state is often associated with malnutrition, and the combination is directly linked with a high risk of atherosclerosis [61], often known as the malnutrition-inflammation-atherosclerosis (MIA) complex. The presence of MIA in a CKD patient is associated with a significantly higher mortality rate [62]. The physiological calcification inhibitor, fetuin-A, is a negative acute phase reactant and its production is downregulated in an inflammatory milieu [63]; fetuin-A may be the missing link between inflammation and atherosclerosis [64]. Recent studies have shown that vitamin D has a cardioprotective effect, and one of its several beneficial effects on the heart and vasculature may be mediated by its anti-inflammatory effects [65, 66].

Hyperhomocysteinemia is a significant risk factor for atherosclerosis [67, 68] and has been associated with increased carotid artery intima-medial thickness (cIMT) and LVH in children [60, 69]. Folic acid and B vitamins, required for remethylation of homocysteine to methionine, are the most important dietary determinants of homocysteine, and daily supplementation typically lowers plasma homocysteine levels, but it is unclear whether the decreased plasma levels of homocysteine through diet or drugs may be paralleled by a reduction in cardiovascular risk. It is presumed that homocysteine exerts a direct toxic effect on the vessel wall, and one small study in children has shown that folic acid supplementation may improve endothelial function with an increased resistance of LDL to oxidation [70]. However, several randomized controlled studies in adults have failed to show a beneficial effect of folic acid supplementation, and very high doses of folic acid have recently been linked with an increased risk of malignancies [71].

Anemia (see also Chap. 27) is a major uremia-related cardiovascular risk factor that is highly prevalent in children and adolescents with advanced CKD. Unlike the other major uremia-related risk factors, it appears relatively early in the course of CKD. Despite the introduction and wide use of recombinant erythropoeisis stimulating agents (ESAs), anemia remains common. Data from the CKiD cohort have demonstrated that below a measured GFR of 43 mL/min/1.73 m^2, the hemoglobin decreased by 0.3 g/dL for every 5 mL/min/1.73 m^2 decrement in GFR [72]. Data from the NAPRTCS registry support the finding that anemia is common in pediatric CKD patients (increasing from 18.5% in stage 2 CKD to 68% in stage 5 pre-dialysis patients); furthermore, patients with anemia were 55% more likely to be hospitalized than those with a normal hemoglobin level [73]. Anemia remains a significant risk for both morbidity and mortality [74, 75]. Data from IPPN demonstrated that 25% of patients had hemoglobin levels below target, and low hemoglobin levels were associated with low urine output, low serum albumin, high parathyroid hormone, high ferritin, and the use of biocompatible PD fluid [76]. In this study, anemia and high ESA dose requirements (likely secondary to ESA resistance due to inflammation) independently predict mortality. Until recently, posttransplant anemia has also been underappreciated. However, with introduction of more potent immunosuppression therapy, recently reported anemia prevalence rates have ranged from 61% to 86% [75, 77].

Dialysis vintage (the time on dialysis) has been implicated as a predictor of coronary artery

calcification in children and young adults (Table 30.2). Coronary calcification can be seen as early as the first decade of life in children on dialysis. Dialysis vintage was associated with the presence of calcifications, even in patients who had undergone transplantation (dialysis vintage was calculated as cumulative time on dialysis) [78].This suggests that calcification develops in a time-dependent manner on dialysis, and suggests that there is little or no regression associated with a functioning transplant. A recent review article has suggested that there is a strong, albeit insignificant linear association between dialysis vintage and coronary artery calcification (CAC) score across all published studies of CAC in young patients with childhood-onset ESRD, suggesting an exponential effect of dialysis vintage on the development of CAC [79].

Surrogate Measures of Cardiovascular Risk in CKD Patients

Unlike studies in adult CKD patients where "hard" end points such as death or cardiovascular events are used, pediatric studies must rely on surrogate measures of cardiovascular damage. These include cardiac and vascular measures of structure and function, and biomarkers from blood and urine. Echocardiography is a gold standard to assess for the presence of LVH or systolic and diastolic dysfunction. Measures of structural changes in the vessels include the cIMT (measured by high-resolution ultrasound scan of the common carotid arteries) and direct evidence of CAC on multi-slice CT scan. Functional changes in the vasculature can be determined by the pulse wave velocity (PWV) that determines stiffness or loss of compliance in the vessel and distensibility of the common carotid artery measured by ultrasound (Fig. 30.2). Although cIMT, PWV, and CAC have been extensively used in many studies of vascular outcome, there is recent evidence to show that they are not sensitive markers of early vascular damage and must be interpreted with caution [76]. In addition, numerous biomarkers of vascular damage and future cardiovascular events have been described and some validated against "hard endpoints." In our current state of knowledge, these can best serve as corroborative evidence of vascular injury or predictors of future cardiovascular events, but cannot replace the established vascular measures described above. Some of the better defined biomarkers are vitamin D levels (25-hydroxyvitaminDand1,25-dihydroxyvitamin D) [80–82] and FGF-23 [83], the physiological calcification inhibitors (fetuin-A, matrix Gla-protein, and osteoprotegerin) [84], endothelial microparticles, and cardiac troponin levels [85].

Left Ventricular Structure and Function

As in adults, a number of studies have shown that LVH develops relatively early in the course of CKD in children, and becomes more common as renal function declines. Although some small retrospective studies demonstrate regression of LVH with better blood pressure and volume control while on dialysis, others have demonstrated worsening of LVH. Left ventricular hypertrophy is also commonly seen after renal transplantation in children. Considering all of the available data, approximately one third of children with CKD stages 2–4 [23, 86, 87] and up to 50–80% of pediatric dialysis patients have LVH [24]. The prevalence of LVH has remained stable and quite high over last two decades. Data from the Turkish registry of children on maintenance dialysis collected from 2008 to 2013 showed the prevalence of LVH to be 59% [88]. Data from IPPN demonstrated the overall LVH prevalence to be 48%. In the IPPN prospective analysis, the incidence of LVH developing de novo in patients with normal baseline LV mass was 29%, and the incidence of regression from LVH to normal LV mass was 40% per year [89]. Beyond childhood, in the follow-up of 140 adults who developed ESRD before the age of 14 years, the Dutch Late Effects of Renal Insufficiency in Children (LERIC) study has also demonstrated that LVH is common (47% of male and 39% of female patients), as is diastolic dysfunction (13%) [3].

Table 30.2 Vascular measures and their correlations in pediatric and young adult dialysis patients (in chronological order of publication date)

No.	Author, journal, year	No. of patients	Mean age (years)	Duration of dialysis (years)	Vascular measures	Clinical and biochemical correlations	Key message
1.	Goodman et al., NEJM, 2000	39	19 ± 7 (range 7–30)	7 ± 6 (range 0.3–21)	CAC	Presence of CAC correlated with Age Dialysis duration Mean serum PO_4 and Ca × PO_4 Ca intake from binders	No CAC in any patients <20 years age, but 14/16 patients >20 years had CAC CAC doubled on follow-up scan at 20 months
2.	Eifinger et al., NDT, 2000 [105]	16	26.5 (range 14–39)	RRT for 2.5–21 years	CAC	None found	CAC in 6/16 (37%) patients All children asymptomatic despite high CAC burden
3.	Oh et al., Circulation, 2002	39	27.3 (range 19–39) (young adults with childhood onset ESRD)	5.0 (range 0–22)	CAC + cIMT	CAC and cIMT correlated with ESRD duration Dialysis duration Mean serum Ca × PO_4 CAC correlated with PTH levels Hs-CRP Homocysteine levels	50% of deaths are due to cardiovascular or cerebrovascular causes High prevalence of arteriopathy in young adult survivors of CKD Vascular damage correlates with Ca–PO_4 load, hyperparathyroidism, and microinflammation, but not "traditional" risk factors
4.	Groothoff et al., JASN, 2002 [106]	130 29 dialysis	29 (range 20.7–40.6) (young adults with childhood onset ESRD)	RRT – 18 years Dialysis – 4.5 years Tx (n = 101) – 13.5 years	cIMT, stiffness measures	Hypertension main determinant of abnormal arterial wall properties No biochemical data available	No increase in cIMT compared with controls, but reduced distensibility and increased vascular stiffness parameter in all CKD groups No difference in cIMT or arterial wall stiffness between dialysis and transplant groups
5.	Litwin et al., JASN, 2005	55– CKD 2–4 37 – dialysis 34 – transplant	Range 10–20 years	Pre-dialysis CKD – 7.1 ± 5.1 years Dialysis – 2.2 ± 2.9 years Transplant-2.8 ± 3.2 years	Carotid and femoral IMT, wall and lumen cross-sectional areas	cIMT correlated with Dialysis duration Mean serum Ca × PO_4 Ca intake from binders Mean calcitriol dose	Increased cIMT in all CKD groups – significantly greater in dialysis compared with transplant patients. Suggest partial reversibility post-Tx Carotid lumen increased post-Tx – possibly as a result of higher BP post-Tx
6.	Mitsnefes et al., JASN, 2005	44– CKD 2–4 16 – dialysis		Pre-dialysis CKD –? Dialysis – 1.2 ± 1.3 years (range 0.3–3.7 years)	IMT, distensibility, and stiffness of carotid artery and ECHO	cIMT correlated with Dialysis duration Mean serum Ca × PO_4 Ca intake from binders Mean calcitriol dose Stiffness correlated with Mean serum Ca × PO_4 Mean PTH levels	Increased cIMT in dialysis compared with pre-dialysis patients No change in vessel stiffness pre-dialysis, but increased carotid artery stiffness noted in the dialysis group, suggesting that structural changes precede functional abnormalities

7.	Covic et al., NDT, 2006	14	14.1 ± 2.6 years	1 month to 6 years (all HD)	cIMT, PWV, and aortic augmentation index	PWV correlated with Mean PO_4 levels Mean serum Ca × PO_4 Age was the only significant predictor of aortic augmentation index	PWV and aortic augmentation index significantly higher in patients than controls, and comparable with adult values No reversibility after a dialysis session, suggesting that structural changes underlie the loss of function
8.	Briese et al., NDT, 2006	40	23.6 years (young adults who developed ESRD at ~11 years age)	9-dialysis – 2.9 ± 3.5 years 31 – transplant 9.2 ± 4.3 years	cIMT, ECHO, and CAC	Patients with calcification were Older Longer dialysis duration Increased cIMT Higher mean serum Ca × PO_4 Increased Ca intake from binders Increased mean calcitriol dose	No difference in cIMT between dialysis patients, transplant recipients, and controls 10% had moderate to severe CAC, and 9% had mild CAC cIMT was higher in patients with calcification
9.	Civilibal et al., Ped Nephrol, 2006	53	15.7 years (range 6.9–22.7 years)	39-dialysis – 4.9 ± 2.7 years 14 – transplant 3.4 ± 2.7 years	CAC	Presence of CAC correlated with Longer dialysis duration Higher mean serum PO_4 and Ca × PO_4 Higher mean PTH levels Higher Ca intake from binders Higher mean calcitriol dose	CAC was present in 8 of 53 (15%) – 6 currently on dialysis and 2 transplanted
10.	Shroff et al., JASN, 2007	85	5–18 years	Minimum 6 months; mean 2.2 ± 1.8 years	cIMT PWV CAC	cIMT and CAC correlated with Higher mean PTH levels Higher mean calcitriol dose Mean time-averaged Ca x P	When mean PTH levels > twofold upper limit of normal increased risk of vascular damage and calcification as compared to those with PTH levels < twofold upper limit of normal
11.	Civilibal et al., Ped Nephrol, 2007	39	14.8 ± 3.8 years	4.8 ± 2.6 years	cIMT, endothelium-dependent dilatation, and ECHO	cIMT correlated with Diastolic BP Higher mean serum Ca × PO_4 Higher total and LDL cholesterol Higher homocysteine levels Higher mean calcitriol dose	Increased cIMT, hs-CRP, and homocysteine levels in patients compared with controls, but no difference in endothelium-dependent dilatation between the groups Endothelium-dependent dilatation correlated with cIMT
12.	Poyrazoglu et al., Ped Nephrol, 2007 [111]	34	18.0 ± 4.3 years	4.6 ± 2.9 years	cIMT and ECHO	cIMT correlated with Mean BP Left ventricular mass index Inversely with PTH (negative correlation) (No data available for phosphate binder or calcitriol dosage)	Increased cIMT, left ventricular hypertrophy, and higher left ventricular mass index in the dialysis as compared to control groups Significant negative correlation between cIMT and PTH

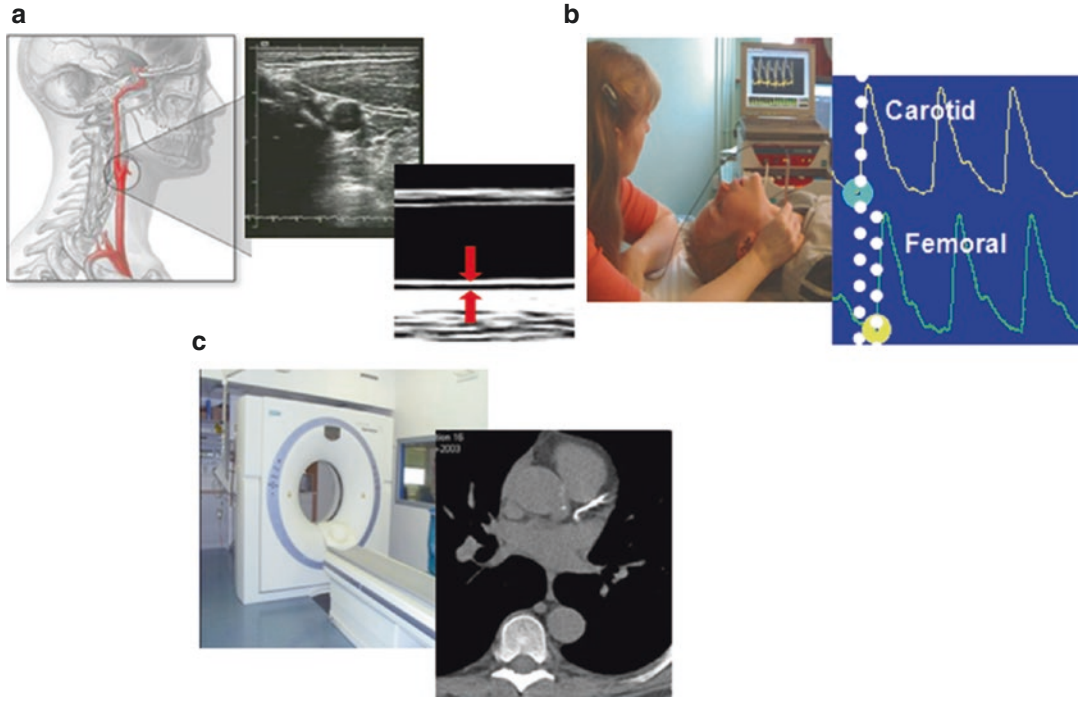

Fig. 30.2 Surrogate measures of cardiovascular risk in CKD patients. (**a**) High-resolution ultrasound of the common carotid artery to measure the carotid artery intima-media thickness (cIMT). (**b**) Tonometry to measure the pulse wave velocity. Inset shows carotid and femoral waveforms. (**c**) Multislice CT scan showing coronary artery calcification (*inset*)

Diastolic dysfunction is thought to be the initial functional LV abnormality evident in children with CKD. Historically, the most widely used method of assessment of impaired LV relaxation has been the use of Doppler measurement of the mitral inflow velocity (with E/A ratio <1.0 defined as abnormal relaxation). By this method, a number of studies have demonstrated reduced and/or frankly abnormal E/A ratios in patients with CKD, and after renal transplantation [86, 90, 91]. Given that many patients with advanced CKD are chronically hypervolemic, the E/A ratio may not be the ideal means of assessing diastolic function in this group. More recently, tissue Doppler imaging (TDI) was introduced as a less load-dependent and therefore more accurate means of evaluating diastolic function in CKD. A number of recent studies have documented the presence of diastolic dysfunction by TDI [92–94], thus confirming the findings of earlier studies. Overall, children on maintenance dialysis (irrespective of modality) have worse diastolic function than those with either CKD stages 2–4 or functioning renal transplants. In terms of functional consequences, diastolic dysfunction was recently demonstrated to be independently associated with reduced maximal aerobic capacity (VO_2max) in patients with stages 2–4 CKD, ESRD, and renal transplants [95]. There are no longitudinal studies of whether abnormal diastolic function predicts the development of frank systolic dysfunction and congestive heart failure in this patient group, although that has been clearly documented in adult survivors of myocardial infarction.

Normal systolic function has classically been thought to be relatively well preserved in children with CKD. While that still appears to be true in terms of overt systolic function abnormalities as assessed by LV contractility or endocardial shortening fraction (eSF), recent studies have demonstrated that subclinical systolic dysfunc-

tion is common in children with CKD, affecting up to 40% of pediatric HD patients. Using measurements of midwall shortening fraction (mwSF), similar systolic function abnormalities also have been identified in early CKD, albeit at lower frequency [96]. The mwSF is thought to be a more accurate marker of systolic function than eSF, particularly in those patients with LVH, as eSF tends to overestimate systolic function in this group. One of relatively new markers of subclinical myocardial dysfunction is abnormal LV systolic strain [97]. It is considered to be an early predictor of LV dysfunction [98]. In the 4C study of children with advanced CKD in Europe, LV strain was assessed by echocardiography [99]. While there was no difference in LV ejection fraction (EF) between CKD patients and healthy controls, children with CKD were found to have a higher prevalence of reduced global circumferential strain components [99]. Rumman et al. using echocardiography, also showed global longitudinal strain (GLS) to be lower in dialysis patients compared to CKD patients [100]. These patients were followed longitudinally and found to have improvement of their GLS to their predialysis CKD levels [101].

Cardiac MRI has recently been utilized in the assessment of CV structure and function in children with CKD. Malatesta-Muncher et al. showed that children on maintenance dialysis had significantly lower circumferential strain than in children after transplantation; strain was inversely correlated with LVMI [102]. Hothi et al. assessed myocardial stunning in children during hemodialysis treatment [103]. In their study, 11 of 12 patients developed myocardial stunning while maintaining LV EF throughout hemodialysis.

Vascular Structure, Function, and Coronary Artery Calcification (CAC)

A number of cross-sectional observational studies in pediatric dialysis patients or young adult survivors of pediatric dialysis programs have described surrogate measures of vascular damage and sought to identify associated risk factors. Children provide a good opportunity to study uremic influences on the vasculature as they have fewer confounding pro-atherosclerotic risk factors such as diabetes and dyslipidemia that are major confounders in similar adult studies. Since the initial study of CAC in pediatric patients on dialysis published in 2000 by Goodman et al. [104], virtually all studies conducted in children on maintenance dialysis consistently have shown increased carotid artery IMT and increased arterial stiffness (e.g., increased PWV). Many of these studies also detected CAC. Key pediatric studies are shown in Table 30.2.

Although all of the available pediatric studies are small, often single-center and cross-sectional, they show remarkably similar risk factors associated with cardiovascular damage. A key risk factor highlighted by virtually all of the studies is the strong linear association between deteriorating vascular measures and time spent on dialysis [2, 25, 104, 107, 110, 113]. Prolonged exposure to the uremic milieu with high, and often worsening Ca–P–PTH control, exposure to pro-inflammatory agents such as advanced glycation end-products and oxidative stress, and reduced levels of the circulating calcification inhibitors all contribute toward deleterious structural and functional changes in the vasculature. To support this, vascular measures have consistently and significantly correlated with Ca, P [2, 25, 69, 78, 104, 107–110], and PTH levels [2, 78, 107, 110]. The vascular changes have also correlated with medication dosages of calcium-based P binders and vitamin D compounds, suggesting that dysregulated mineral metabolism is central to the vasculopathy of CKD, and that these modifiable risk factors require careful monitoring and strict control from the earliest stages of CKD.

An increase in cIMT and PWV have been shown to begin even in the first decade of life in children on dialysis [78] and in pre-dialysis CKD stages 2–4 as well [25, 107, 114]. The 4C study [17] determined the vascular phenotype in 737 children with advanced CKD: cIMT was elevated in 41.6%, with only 10.8% of patients displaying measurements below the 50th percentile; PWV was increased in 20.1%. The office systolic BP was the single independent factor significantly associ-

ated with all surrogate markers of cardiovascular disease. Importantly, although structural vascular changes are found in pre-dialysis patients, the vessel retains its normal compliance and distensibility properties as compared to controls [107]. However, with progressive duration and severity of uremic damage as found in dialysis patients, a further deterioration in cIMT coupled with increased vascular stiffness occurs. Interestingly, an increase in the vessel wall thickness or cIMT is coupled with a remodeling of the vessel such that an increase in the carotid artery lumen occurs, possibly to counter the stiffness or loss of compliance of the vessel [25]. It may be this compensatory remodeling in the early stages of CKD and the more plastic vessels of children that protect them against the deleterious consequences of vascular damage.

Direct evidence of calcification in the coronary vessels has been shown in 15–20% of pediatric chronic dialysis patients [78, 110, 112, 115, 116] and correlates with many of the above listed risk factors. However, despite the presence of these risk factors and of CAC, none of the patients in these studies had overt CVD.

None of the studies in children with CKD have reported the presence of intimal plaques in the cardiac or carotid arteries, and although ultrasound is not an accurate means of assessing intimal versus medial changes in the vessel wall, it appears that uremic vasculopathy, at least in children, is a predominantly medial process.

Progression of Vascular Calcification Through Different Stages of CKD

Despite a plethora of observational cross-sectional studies, there are very few longitudinal studies that have followed children through pre-dialysis–dialysis–transplantation phases and described changes in vascular markers at different stages of uremia. Calcification progresses rapidly in patients on dialysis as shown in a systematic follow-up study by Goodman et al. [78, 104]. When a repeat CT scan was performed after a mean interval of 20 months, the calcification score almost doubled in the 10 patients who had evidence of initial calcification [78, 104]. Calcification progression on CT scan has also been shown by Civilibal et al., with the time-averaged serum Ca × P product and serum albumin levels predicting the final CAC score and change in CAC score, respectively [69]. This suggests that in the pro-calcific and pro-inflammatory uremic milieu "calcium begets calcium," so our efforts must be directed at the prevention of calcification starting in the earliest stages CKD. It is fascinating that in all studies, patients who did not have baseline calcification continued to remain free of calcification despite exposure to similar uremic conditions. Importantly, the presence of CAC is strongly predictive of myocardial infarction, heart failure and stroke in adult pre-dialysis CKD patients [117], and it is an independent predictor of all-cause mortality, cardiovascular events, and cardiovascular mortality in adult dialysis patients [118].

By ameliorating the uremic milieu, renal transplantation might intuitively be thought of as a procedure that might lead to a reversal of some of the cardiovascular damage from dialysis. However, there is increasing evidence from adult studies to show that CVD remains a significant problem posttransplantation, a problem that may be driven by hypertension, obesity, and related risk factors and possibly by immunosuppressive agents. Krmar et al. have shown that there is no increase in cIMT following renal transplantation when there is good blood pressure control [119]. As cIMT progressively increases with age, this can be interpreted as a regression in cIMT when hypertension is ameliorated after transplantation [120]. Litwin et al. have shown that cIMT thickening and remodeling of the vessel wall begins early in CKD and progress rapidly on dialysis, correlating with the blood pressure and mean serum phosphorus levels. Successful transplantation can improve the cIMT toward pre-dialysis values, but cannot normalize it [113].

Physiological Inhibitors of Calcification

Vascular calcification occurs in the majority of patients with CKD, but as noted above, a subset of patients do not develop calcification despite expo-

sure to a similar uremic environment [63]. There is now a growing body of evidence showing that calcification is a highly regulated cell-mediated process, involving a complex interplay of promoters and inhibitors of calcification. Animal knockout models and human single-gene defects have confirmed the role of physiological inhibitors in regulating vascular calcification [121].

Fetuin-A (α_2-Heremans–Schmid protein) is a key circulating calcification inhibitor that contributes to ~50% of the calcification inhibitory capacity of human plasma and walls off the nidus of calcification, thereby preventing further crystal growth. Fetuin-A is a negative acute phase reactant, and in the pro-inflammatory dialysis milieu its production may be reduced [63]. Several studies have reported that adults on dialysis have significantly lower fetuin-A levels than controls. Interestingly, whereas a protective upregulation of fetuin-A has been reported in pediatric dialysis patients, with increasing dialysis vintage and in the associated pro-calcific and pro-inflammatory uremic milieu, fetuin-A levels are decreased [84]. At the VSMC level, fetuin-A can inhibit apoptosis, enhance phagocytosis, and protect the smooth muscle cell from calcifying [84, 122]. Another group has reported lower fetuin-A levels in pediatric transplant recipients, but did not find an association with vascular measures [123].

An important local inhibitor of calcification, matrix Gla [γ-carboxyglutamic acid] protein (MGP), is expressed in the media of arteries where it acts as an inhibitor of Ca–P precipitation [97, 124]. The γ-carboxylation of MGP is vitamin K dependent, and drugs such as warfarin may inhibit this process, resulting in the accumulation of inactive under-carboxylated MGP and ectopic calcification [84, 124]. Osteoprotegerin and pyrophosphate are other potent calcification inhibitors that are shown to be perturbed in children with CKD [84]. The importance of circulating calcification inhibitors was recently confirmed by studies using an in vitro test (T50 test) for the determination of calcification propensity in blood. The T50 test quantifies the calcification inhibition of serum by treatment with supersaturated calcium and phosphate solutions, which results in the formation of primary calciprotein particles that mainly contain fetuin [125]. Calcification propensity was significantly associated with cardiovascular events in pre-dialysis CKD and hemodialysis patients [125, 126]. In incident adult dialysis patients, OPG and fetuin-A were significantly associated with all-cause and cardiovascular mortality during follow-up [127]. While further longitudinal studies are required to fully characterize these circulating biomarkers in children, they may prove to be a useful and convenient measure of an individual patient's susceptibility to vascular calcification.

The Role of Vitamin D in Cardiovascular Health in CKD

Virtually all studies in dialysis patients have reported the prevalence of 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] deficiency to be on the order of 50–90% [128, 129], and have shown that deficiency begins early in the course of renal decline [129]. CKD patients can have low 25(OH)D levels for several reasons: they may have less sunlight exposure, the endogenous synthesis of vitamin D in the skin is reduced in CKD, ingestion of foods that are natural sources of vitamin D may be diminished, and proteinuria may be accompanied by high urinary losses of vitamin D-binding protein [129]. In addition, when the GFR falls to <50 mL/min/1.73 m^2, the kidney cannot convert "nutritional" 25(OH)D to the biologically active $1,25(OH)_2D$ [130]. The synthesis, metabolism, and interactions of vitamin D in the Ca–P–PTH axis are shown in Fig. 30.3. A recent report of nearly 700 children with CKD across Europe has shown that disease-related factors and vitamin D supplementation are the main correlates of vitamin D status in children with CKD, whereas variations in the vitamin D-binding protein showed only a weak association with the vitamin D status [131]. A core working group of the European Society for Paediatric Nephrology has developed recommendations for the evaluation, treatment, and prevention of native vitamin D deficiency and active

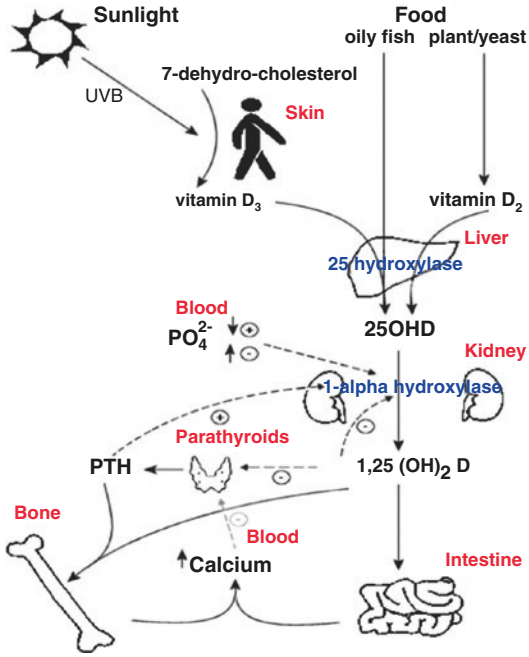

Fig. 30.3 The synthesis, metabolism, and interactions of vitamin D in the Ca–P–PTH axis

vitamin D analog therapy in children with CKD stages 2 to 5 and on dialysis [132, 133].

Most tissues and cells in the body have a vitamin D receptor and also have the enzymatic machinery to convert 25(OH)D to the active form $1,25(OH)_2D$ [128]. In the cardiovascular system, vitamin D acts as a negative endocrine regulator of the renin–angiotensin system [134], inhibits atrial natriuretic peptide [135], increases myocardial contractility, and reduces cardiomyocyte hypertrophy [136]. Several large epidemiological studies have consistently shown that hemodialyzed patients receiving any activated vitamin D treatment have a significant survival advantage on the order of 20–25% as compared to untreated patients [80–82].

Clinical studies in children have examined the effects of vitamin D therapy on vascular measures and calcification (Table 30.2) and shown that both CAC and cIMT correlated with a higher calcitriol dosage [25, 66, 78, 107]. However, the association of vitamin D levels with vascular measures is more interesting. In a recent study of children on maintenance dialysis, Shroff et al. have shown that there is a bimodal association of vitamin D levels with vascular measures such that both low and high levels of vitamin D are associated with abnormal cIMT and CAC [66]. These effects may be determined by the effects of vitamin D on Ca–P homeostasis, as well as its pro-inflammatory effect [66].

The Vascular Biology of Calcification

In recent years, converging evidence from in vitro studies, molecular genetic techniques, and human single-gene defects has shown that vascular calcification is an active, highly regulated process and not merely a passive deposition of Ca and P in dead or dying cells [50]. In response to raised extracellular Ca and P levels, vascular smooth muscle cells (VSMCs) undergo specific phenotypic changes including apoptosis, osteo-/chondrocytic differentiation, and the release of small membrane-bound bodies called vesicles that form a nidus for the deposition of basic Ca–P in the form of hydroxyapatite [50]. Transformation of VSMC to an osteo-/chondrocytic phenotype is characterized by the upregulation of bone-specific transcription factors and matrix proteins, including Runx2/Cbfa1, osterix, and alkaline phosphatase, that in turn lead to accelerated calcification. Raised serum P has been shown to be a key factor that triggers osteoblastic differentiation of the VSMC [49, 50, 137]. A schematic diagram depicting key events in the calcification process is shown in Fig. 30.4.

Using intact arteries from children, Shroff et al. have shown that calcification in the vessel wall begins in pre-dialysis CKD stages 4 and 5, but is significantly greater in dialysis patients [121]. The calcium load in the vessel wall increases linearly with time on dialysis and is strongly correlated with the mean time-averaged serum Ca x P product. Dialysis vessels showed VSMC apoptosis with significantly fewer VSMCs as compared to pre-dialysis or healthy control vessels, and this may be a key event that triggers accelerated calcification in dialysis patients. Importantly, the vessel Ca load did not result in an increase in cIMT and only the

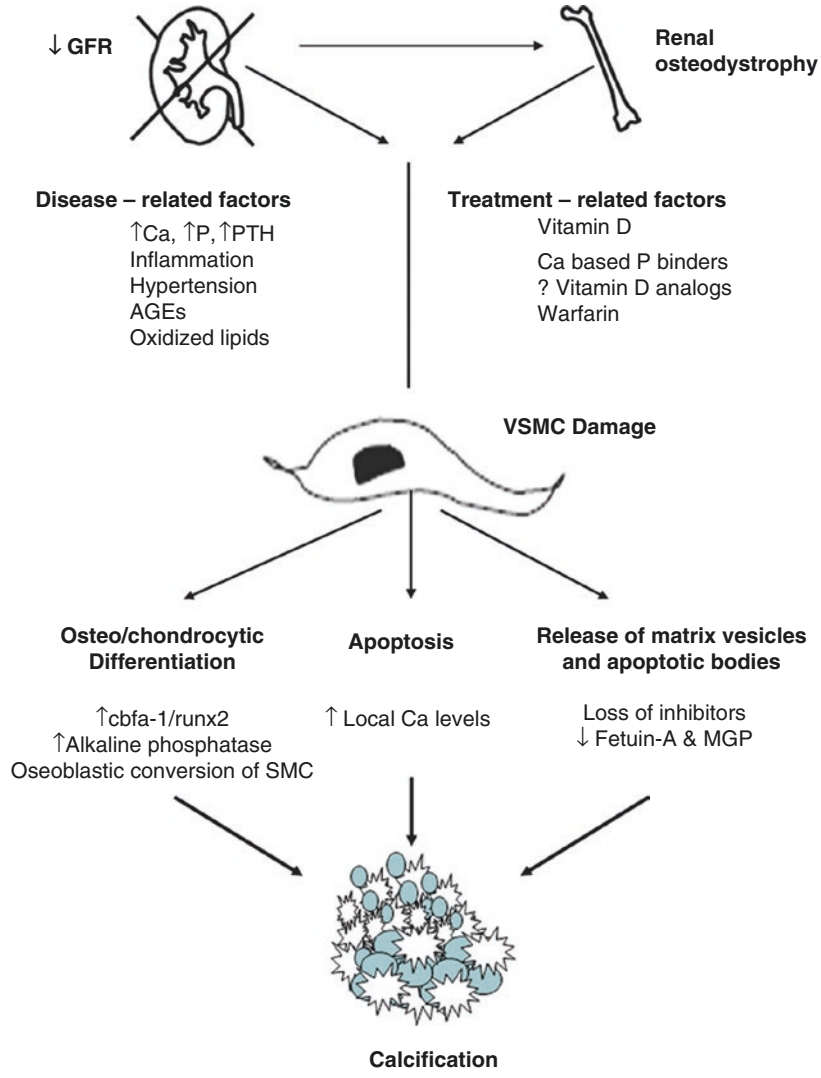

Fig. 30.4 A schematic diagram showing disease-related and treatment-related risk factors that lead to vascular smooth muscle cell (VSMC) damage and the mechanisms that drive accelerated calcification

most severely affected patients had coronary calcification on CT scan, implying that the currently available vascular measures are not sensitive enough to detect early calcification. Shroff et al. cultured vessel rings from healthy subjects and pre-dialysis and dialysis patients in graded concentrations of Ca and P and showed that normal and pre-dialysis vessels were resistant to calcification, while dialysis vessels showed accelerated calcification in high Ca and P media [138]. This suggests that dialysis vessels have lost protective mechanisms; exposure to the uremic milieu has "primed" them to calcify. In the presence of a high P, even a small increase in Ca in the culture medium significantly increased calcification, implying that Ca may be a key mediator of VSMC damage and calcification [138], and careful attention must be paid to even transient increases in calcium levels such as are seen after HD, or with the use of calcium-containing phosphate binders and vitamin D analogs.

Recent research suggests that premature aging in dialysis vessels may drive the process of accelerated calcification. Accumulation of the aging biomarker prelamin A has been shown in the calcified arteries of children on dialysis [139]. Prelamin A interferes with DNA damage repair leading to accelerated VSMC senescence [140].

This toxic nuclear protein also accumulates in the calcified vasculature of aged adults and is causal in the induction of accelerated vascular calcification and stiffening in children with the premature aging disorder Hutchinson–Gilford progeria syndrome [141]. In a recent study, Shanahan et al. have shown that vessels from children with CKD undergo oxidative DNA damage and have elevated senescence markers that may drive osteogenic differentiation and calcification [142].

The Bone-Vascular Link

There is a growing awareness that mineral dysregulation in CKD is closely linked to abnormal bone pathology, and that this in turn leads to extraskeletal calcification. Hormones such as PTH and vitamin D that closely regulate calcium–phosphate metabolism affect skeletal mineralization and can lead to ectopic soft-tissue calcification. Key factors produced by osteocytes (e.g., FGF-23), osteoblasts (e.g., alkaline phosphatase), and osteoclasts (e.g., osteoprotegerin) also influence vascular calcification [49].

It is a matter of debate whether vascular calcification and bone loss are simultaneously occurring but largely independent processes, or whether poor bone health predisposes to vascular calcification, especially in patients with kidney disease. In a prospective study in 213 adult HD patients, bone mineral density of the spine was inversely related to the coronary artery calcification score, and CAC progression was associated with the severity of osteoporosis [143]. A further study in adults on HD has shown that low trabecular bone volume and decreased cortical bone density are associated with coronary artery calcification [144].

The K/DIGO (Kidney Disease Improving Global Outcomes) working group has proposed a broader and more encompassing term to describe this clinical disorder: CKD-mineral and bone disorder (CKD-MBD) [145]. They proposed three primary components of CKD-MBD: (1) biochemical abnormalities in calcium, phosphorus, PTH, or vitamin D metabolism; (2) changes in bone histology (bone turnover or mineralization), linear growth, and fractures; and (3) vascular or other soft-tissue calcification. The broader definition of CKD-MBD is an improvement on historical practice in which renal ostedystrophy and its management was thought only to affect skeletal health and growth. Recognition of the importance of the full spectrum of CKD-MBD also highlights the need for more cautious use of calcium-containing P binders and vitamin D analogs to minimize the risk of vascular disease, as will be discussed in detail below.

Evaluation and Management of CV Risks in CKD

Primary among all management strategies in childhood CKD/ESRD is the avoidance of long-term dialysis, with preference given to preemptive transplantation when feasible, as the strongest evidence for cardiovascular risk reduction is that associated with avoiding dialysis [5]. Although far from perfect with regard to cardiovascular risk, successful transplantation can eliminate or significantly improve uremia-related risk factors and increase predicted life expectancy by 20–30 years when compared to long-term dialysis. Otherwise, management strategies should be specific to the stage of CKD (pre-dialysis, dialysis, or transplant) as each has a unique subset of common risk factors. For those patients who must have long-term dialysis, the strategy is directly linked to the achievement of adequate dialysis outcomes, which include aggressive monitoring and management of hypertension, dyslipidemia, calcium–phosphorus metabolism, anemia, nutrition, systemic inflammation, and other dialysis complications. Current recommendations for the management of the most common individual risk factors are summarized below.

The Need for More Frequent Dialysis

Although mostly anecdotal in nature, an increasing body of pediatric literature supports using intensified hemodialysis programs to improve patient outcome [30, 146–148]. Intensified hemodialysis includes different forms of frequent dialysis (such as short daily dialysis) or longer hours on dialysis (such as nocturnal dialysis at home or in center) in different combinations, as well as hemodiafiltration (HDF). The adult literature also supports the potential for improved outcomes with more frequent and intensified dialysis [149, 150]. These outcomes include improvements in the following metrics: patient quality of life, phosphate balance, blood pressure, anemia, nutrition and growth, and cardiac indices as measured by echocardiography. More frequent dialysis has the potential to result in decreased hospital admissions, increased patient adherence, and a decrease in vascular access complications. Patients receiving more frequent home dialysis also have lower health-care costs [151, 152], but not all patients are willing or able to perform home-based therapy [153].

HDF is a newer technique of dialysis that utilizes a combination of diffusive and convective solute transport through a highly permeable membrane [154–156], thereby achieving clearance of middle and large molecular weight solutes unlike conventional HD. In recent years, randomized trials in adults have shown that HDF is associated with improved cardiovascular and all-cause mortality compared to HD. A pooled analysis of four randomized trials in adult patients comparing HDF with conventional HD demonstrated a reduction in all-cause and cardiovascular mortality risk [157–159]. In children, a short daily dialysis program combining in-center high-efficiency online hemodiafiltration (HDF) with growth hormone therapy has reported impressive catch up growth [30]. Small observational studies also suggest that HDF improves cardiovascular function and inflammatory status [160, 161]. In a substudy of the ongoing Hemodiafiltration, Heart and Height (3H) study [162], a switch from conventional HD to HDF resulted in significant improvement in inflammation, antioxidant capacity, and endothelial risk profile within just 3 months [163], and keeping all other dialysis-related parameters constant. The 3H study has shown that on fully adjusted analyses, the annualized changes in both cIMT-SDS and MAP-SDS were significantly lower in HDF compared to HD patients, largely due to improved fluid removal as well as clearance of middle molecular weight uremic toxins by HDF.

Patients on longer or more frequent HD programs have less stringent fluid or dietary restrictions, and a reduced medication burden [164], with some patients even requiring phosphate supplementation [165]. BP control improves and EPO doses are often reduced [164]. A nocturnal home hemodialysis program has been shown to improve the child's quality of life, school attendance [153], and growth [166]. In a crossover study of in-center nocturnal HD and HDF, further improvement of dialysis efficacy with HDF compared to HD was reported [167]. Despite the many advantages of frequent / nocturnal HD, its use is limited to few pediatric patients and centers. A recent online survey among pediatric nephrologists identified lack of adequate funding, shortage of staff, and to a lesser degree, lack of expertise and motivation as barriers [168].

Management of Key Modifiable Risk Factors That Contribute to the Development and Progression of CVD in CKD

Fluid overload with associated hypertension (see also Chap. 31) and chronic mineral dysregulation are likely the key drivers of CVD in childhood CKD. The management of these and other important modifiable risk factors is discussed below.

Prevention and Treatment of Hypertension and LVH

In the child on dialysis, the presence of hypertension, as discussed above, is primarily related to fluid overload. Attainment of dry weight will

result in lowering (but not necessarily normalization) of blood pressure in the majority of patients. Dry weight and dialysis prescription need to be frequently adapted to avoid fluid overload induced hypertension. Bioelectrical impedance analysis [169] or assessment of the inferior vena cava diameter [170] may be helpful tools for the assessment of dry weight in combination with standard clinical measures. Supportive measures aiming for a low extracellular volume, such as dietary salt restriction, low dialysate sodium content, restriction of fluid intake, and prolonged dialysis time have been shown to maintain normotension in 98% of adult patients [171]. More frequent [30] or nocturnal dialysis [167, 172, 173] might also be helpful to maintain dry weight and normal blood pressure. An appropriate target for clinical use may be an interdialytic blood pressure below the 90th percentile. Long-term data on the effects of strict blood pressure control (e.g., ESCAPE trial target of 24-hour MAP <50th percentile) on CVD in the pediatric dialysis population are lacking.

Only when hypertension cannot be controlled by adequate volume control should pharmacological antihypertensive treatment be considered. Angiotensin-converting enzyme inhibitors (ACEi), Ca-channel blockers, and ß-blockers, alone or in combination with other drugs, are the most widely used antihypertensive agents in children on dialysis. Pharmacological treatment is usually tolerated well; however, dose modifications for reduced renal function might be required. Drug resistance is most often a problem in the setting of persistent hypervolemia; a paradoxical blood pressure increase during dialysis might be due to an inadequate response of the renin–angiotensin system to ultrafiltration (see also Chap. 21).

There is no consensus on how frequent echocardiographic monitoring for LVH should be performed in pediatric CKD patients. The K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients [174] recommend screening echocardiography within 3 months of beginning maintenance dialysis, with follow-up examinations every 6 months for those with abnormal studies or annually for those with normal cardiac structure and function. There is also no consensus on the definition of LVH in children. Published pediatric age- and gender-specific reference values for LVM index have been widely used over last decade [175]. On the other hand, Foster et al. demonstrated that LVM index varies not only according to age, but also according to absolute height, with higher values in children with shorter height [176]. Given that children with CKD have a significantly reduced height relative to age, normative values according to age should take into account the patient's height, especially in those with height <130 cm. Borzych et al. suggested the use of height-age instead of chronological age to assess LVM, assuming that the body composition, cardiac mass, and cardiac output of a child should match that of a child with the same height who is at the 50th percentile for age [177]. The 2017 Clinical Practice Guidelines on Management of BP in Children defines LVH as a LVM index value above 51 g/$m^{2.7}$ or LV mass >115 g per body surface area (BSA) for boys and LV mass >95 g/BSA for girls [178]. Chinali at al. recently developed a simplified method to identify the presence of LVH in pediatric populations: a value of 45 g/$m^{2.16}$ was defined as the upper normal limit for LVM index [179]. A utility of this index in children with CKD still needs to be determined.

Ca–P–PTH and Vitamin D Management

While most physicians now accept that high P levels have deleterious cardiovascular effects, there is much controversy over what "optimal" PTH levels should be. "Optimal" PTH levels may be defined as levels that maintain normal bone turnover without increasing the risk of ectopic calcification. Guidelines on the optimal levels of Ca, PO_4, and PTH levels and all aspects of their control have been proposed by the K/DOQI and the European Paediatric Dialysis Working Group [180, 181]. The European recommendations are more conservative and advise keeping PTH levels in the normal range until CKD stage 5, when two to three times the upper limit of normal is

recommended. K/DOQI has set higher allowable targets of up to twice the upper limit of normal in CKD stage 3 and three to five times the upper limit of normal in patients on dialysis. The recently published KDIGO (Kidney Disease Improving Global Outcome) guidelines that are more rigorously evidence-based, suggest maintaining PTH levels at two to nine times the upper limit of normal, reflecting the lack of good clinical studies to inform an evidence base [145].

Although dietary management may be adequate to control plasma phosphate in its early stages, most patients develop hyperphosphatasemia by CKD stages 3–4 and require the addition of a phosphate binder. One interesting study has demonstrated that the use of any type of phosphate binder, even with phosphate levels in the normal range and therefore below levels currently recommended for phosphate binder use, is associated with decreased mortality in patients on HD [182].

A normal diet contains around 800–1500 mg of phosphate, of which 50–70% is absorbed, depending on serum phosphate and vitamin D levels. In the first instance in early CKD, dietary restriction may be sufficient to control plasma phosphate levels. Dietary phosphate is principally found in protein-containing foods, dairy products in particular. However, foods high in phosphate are also usually high in calcium and vitamin D, so that nutritional 25-hydroxyvitamin D [25(OH)D] and calcium deficiency are common in patients with CKD who maintain a phosphorus-restricted diet.

Phosphate control is a particular problem for patients on conventional thrice weekly HD because it is poorly removed by the dialysis process: most is removed in the first hour, and as the rate of movement out of cells is slow, little is removed when the normal range for phosphate is reached. By 12 h post HD, levels are 80% of predialysis values. PD is equally inadequate at phosphate removal: ~800 mg of phosphate is removed in a standard adult HD session (i.e., 2400 mg per week) and 300 mg per day in adults on PD (i.e., 2100 mg/week). In a diet containing ~1000 mg of phosphate each day, ~600 mg would be absorbed (and 400 mg would be excreted in the stool), requiring this amount to be bound or cleared by dialysis. Therefore, the absorption of around 300 mg of phosphate per day needs to be managed [183]. Patients on dialysis are the group in whom calcium-containing phosphate binders can cause the most problems with hypercalcemia, because of the reduced ability to excrete calcium in the urine. Use of calcium neutral dialysate (1.25 mmol/L) allows for prescription of larger doses of calcium. Short daily or slow nocturnal HD is most effective for removing phosphate, to the point that some patients need phosphate supplementation [153].

Phosphate binders are usually divided into calcium containing and non-calcium containing [183, 184]. Calcium-containing preparations have been used the longest, but they have fallen out of favor because of their theoretical link with soft-tissue calcification [185]. The fear of ectopic calcification with excess calcium intake has led to a switch to newer non-calcium-containing drugs. Phosphate binders must be given with food and must not be given at the same time as iron preparations as they form insoluble compounds in the gut. Dissociation of calcium carbonate is maximal below a pH of 5, and is therefore not as effective when given with H2-blockers or proton pump inhibitors. Calcium acetate, however, has better solubility over a wider range of pH and has a greater binding capacity for the same elemental calcium content so that less calcium is absorbed. Calcium absorption will also vary with plasma $1,25(OH)_2D$ levels, being as low as 3% in deficiency to presumably higher than the expected normal range in patients who are prescribed activated vitamin D, when hypercalcemia may occur [183].

Several new non-calcium-containing phosphate binders: magnesium carbonate, sevelamer hydrochloride, and lanthanum carbonate are now available [183, 184]. Sevelamer, the most widely used in children, is a nonabsorbable polymer of allyamine hydrochloride that acts like an exchange resin [139]. In addition to phosphate, sevelamer also binds bile salts, thereby exerting a beneficial effect on plasma total and low-density cholesterol, while at the same time binding fat-soluble vitamins. The first report of the use of sevelamer in children appeared in 2003 [186].

Only two randomized controlled trials have examined phosphate-lowering therapy in children with CKD or on dialysis. The first RCT examined biochemical end-points only and showed equivalent phosphate control with calcium acetate and sevelamer hydrochloride in an 8-week cross-over trial; phosphate control was similar but with fewer episodes of hypercalcemia in the sevelamer group, although acidosis was more common [187]. In the second, 29 children were randomized to different combinations of phosphate binders and vitamin D analogs: bone biopsies suggested that the sevelamer group had reduced bone formation at 8-month follow-up, but patient numbers were too small for comparison. Biochemical and histological abnormalities improved in both groups, but serum calcium levels were at the lower limit of the normal range in the sevelamer group. Sevelamer may, in turn, increase the safety of treatment with activated vitamin D in patients with secondary hyperparathyroidism [188, 189]. On the other hand, 20% of the sevelamer treated group needed calcium supplements [188], and the development of hypocalcaemia is as high as 24% in adult studies [190]. Sevelamer carbonate (as opposed to sevelamer hydrochloride) does not cause metabolic acidosis; safety and efficacy were recently confirmed in a first multicenter study of hyperphosphatemic pediatric patients with CKD [191]. Since hypercalcemia is frequent with calcium-containing binders, more studies in pediatric patients are needed to evaluate calcium-free preparations. A recent study from CKiD in 537 children with predialysis CKD reported that phosphate binder treatment (calcium based in 82%) was associated with decreased risk of incident fractures (HR 0.37, 95% CI 0.15–0.941), independent of age, sex, eGFR, and PTH levels [192].

It has also been suggested that sevelamer can attenuate the progress of coronary and aortic calcification when compared to calcium-based phosphate binders [46]. A recent review of 23 randomized trials in adults patients comparing sevelamer with calcium-based binders concluded that sevelamer attenuated the progression of coronary and aortic calcification, but was not associated with a significant difference in all-cause or cardiovascular mortality [193]. Several other calcium-free phosphate binders have been used in adult patients; however, a recent meta-analysis evaluating all currently available phosphate binders found no evidence that phosphate binder treatment reduces all-cause mortality compared to placebo in adults with CKD [194]. However, a study of progression of CAC in 48 children over 2 years with CKD stage 5 was not able to demonstrate an association between the type of phosphate binder and CAC [195]. Likewise, the Dialysis Clinical Outcomes Revisited trial found no difference in the mortality rate at 2 years in just over 2000 adult HD patients randomized to either sevelamer or calcium-based binders, being 26% and 27%, respectively, despite the additional lipid-lowering benefits of sevelamer [196].

Sevelamer is of potential benefit in patients who have a high dietary calcium intake. However, children on a low-phosphate diet who are not receiving a calcium-containing phosphate binder probably do not have a positive calcium balance when they are on maintenance dialysis. Indeed, KDOQI recommends that in children exclusively on sevelamer, a higher dialysate calcium concentration and/or calcium supplementation with a calcium-containing phosphate binder should be considered [180].

An interesting new approach to phosphorus management is the use of chewing gum to remove salivary phosphate between meals: Chitosan is a natural polymer that binds phosphate [197]. Salivary phosphate levels may be as much as five times higher than plasma levels, and, in adults, there is between 350 and 400 mg of phosphate in saliva available to be bound [197].

Treatment of CKD-MBD is especially difficult in the pediatric population due to the demands of a growing skeleton. Undertreatment with vitamin D preparations carries the risk of rickets, diminished growth, uncontrolled hyperparathyroidism and high-turnover bone disease, while oversuppression of PTH may result in adynamic bone disease and – especially in combination with calcium-containing phosphate binders – vascular calcification, stiffening, and premature aging of arteries [198]. Recent guidelines from KDIGO [52, 199], the National

Institute for Health and Care Excellence (NICE) [200], and the European Society for Pediatric Nephrology [132, 133] have therefore argued for the use of vitamin D preparations and calcium-based phosphate binders as first-line treatment in children, reserving non-calcium-based binders only for those with hypercalcemia.

Given the association of high PTH levels with reduced bone mineralization and vascular calcification, children are likely to need calcitriol or other active vitamin D analog therapy. A recent Cochrane review has examined vitamin D therapy for bone disease in children with CKD stages 2–5 and on dialysis. Bone disease, as assessed by changes in PTH levels, was improved by all vitamin D preparations regardless of preparation or route or frequency of administration [201]. High PTH levels were independently associated with reduced tibial cortical BMD Z-scores [202] and are associated with coronary artery calcification in children on dialysis [52].

The use of calcimimetics presents a paradigm shift in our management of mineral dysregulation in CKD [203–205]. They allow for higher vitamin D usage and are overall thought to be safe in children [205]; however, there are few studies on long-term effects, particularly on the growing skeleton. Parathyroidectomy may be required as a "last ditch" attempt in controlling the hypercalcemia of tertiary hyperparathyroidism when dietary and pharmacological interventions have failed [206].

Prevention and Treatment of Lipid Abnormalities

General measures to prevent dyslipidemia in CKD patients include prevention or treatment of malnutrition, correction of metabolic acidosis, hyperparathyroidism, and anemia, all of which may contribute to dyslipidemia [37, 207, 208]. In addition, referring to evidence from the general population, therapeutic life-style modification (diet, exercise, weight reduction) is recommended for adults and children with CKD-related dyslipidemia [209]. However, the lipid-lowering effect of lifestyle modifications in CKD patients is not very impressive. Nonetheless, diet and physical exercise may exert beneficial effects on cardiovascular health independent of those on dyslipidemia. In a study more than 25 years ago, dietary supplementation of fish oil effectively improved lipid profiles in a small cohort of children receiving renal replacement therapy [210].

Statins effectively lower cholesterol and triglyceride levels in CKD patients by up to 30% [209]. The 2013 K/DIGO guidelines recommend using statins in pre-dialysis CKD and after kidney transplantation in adults. However, results from large randomized prospective trials in hemodialyzed adults (4D [211], AURORA [212], and SHARP [213]) [155] and subsequent metaanalyses [214, 215] showed no effect of statin therapy on overall patient mortality despite significant reduction of lipid levels. Thus, K/DIGO guidelines do not recommend statin use in adults on dialysis.

In children, statins are used reluctantly as the impact of HMG-CoA reductase inhibitors on nutrition, growth, and pubertal maturation has not been fully elucidated. Thus, due to the very limited available data for children, including those with pre-dialysis CKD, dialysis, and after transplantation, K/DIGO guidelines do not recommend the use of statins in children with CKD aged <10 years [209]. However, the KDOQI Working Group emphasized that patients (boys aged >10 years and postmenarchal girls) with severely elevated LDL-C or with multiple additional CV risk factors such as family history of premature coronary disease, diabetes, hypertension, smoking, and ESRD might be candidates for earlier statin use (lowest dose possible) [209]. Although bile acid resins are safe to use in CKD children of all ages without dose adjustment, adherence to therapy is often poor due to a high incidence of adverse gastrointestinal side effects.

Supportive Treatment

Several supportive measures for the optimal care of dialysis patients will also contribute to an improved cardiovascular outcome [216]. This includes optimal nutrition (with tube feeding as necessary), prevention or correction of hypoalbu-

minemia, anemia, and metabolic acidosis. A healthy lifestyle with adequate physical activity and avoidance of smoking should be encouraged. The use of statins, folic acid, and antioxidants remains controversial as discussed above.

Conclusion

As the management of children with CKD continues to improve, children and young adults with CKD no longer die from renal failure, but do so from CVD. Prevention of important modifiable risk factors, in particular, hypertension and mineral dysregulation are key issues in the reduction of CVD in our patients.

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112–9.
2. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation. 2002;106(1):100–5.
3. Gruppen MP, Groothoff JW, Prins M, van der Wouw P, Offringa M, Bos WJ, et al. Cardiac disease in young adult patients with end-stage renal disease since childhood: a Dutch cohort study. Kidney Int. 2003;63(3):1058–65.
4. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. J Pediatr. 2002;141(2):191–7.
5. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
6. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62(2):648–53.
7. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. JAMA. 2013;309(18):1921–9.
8. US Renal Data System: USRDS 2018 Annual Data Report: Mortality and causes of death.
9. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol. 2012;23(4):578–85.
10. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998;32(5):853–906.
11. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
12. McGill HC Jr, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, et al. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. Circulation. 2000;102(4):374–9.
13. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338(23):1650–6.
14. Group. JAMA. 1990;264:3018–24. PRGRoaiymtslccasAprftPDoAiYPR.
15. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP 3rd, Herderick EE, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. JAMA. 1999;281(8):727–35.
16. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2006;114(24):2710–38.
17. Schaefer F, Doyon A, Azukaitis K, Bayazit A, Canpolat N, Duzova A, et al. Cardiovascular phenotypes in children with CKD: the 4C study. Clin J Am Soc Nephrol. 2017;12(1):19–28.
18. Wong CJ, Moxey-Mims M, Jerry-Fluker J, Warady BA, Furth SL. CKiD (CKD in children) prospective cohort study: a review of current findings. Am J Kidney Dis. 2012;60(6):1002–11.
19. Lingens N, Dobos E, Witte K, Busch C, Lemmer B, Klaus G, et al. Twenty-four-hour ambulatory blood pressure profiles in pediatric patients after renal transplantation. Pediatr Nephrol. 1997;11(1):23–6.
20. Seeman T, Simkova E, Kreisinger J, Vondrak K, Dusek J, Gilik J, et al. Control of hypertension in children after renal transplantation. Pediatr Transplant. 2006;10(3):316–22.
21. Mitsnefes M, Stablein D. Hypertension in pediatric patients on long-term dialysis: a report of the North American Pediatric Renal Transplant

Cooperative Study (NAPRTCS). Am J Kidney Dis. 2005;45(2):309–15.
22. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, Boguszewska-Baczkowska H, Drozdz D, Kollataj B, et al. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland--a nationwide survey. Nephrol Dial Transplant. 2006;21(3):736–42.
23. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. Circulation. 2003;107(6):864–8.
24. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF. Severe left ventricular hypertrophy in pediatric dialysis: prevalence and predictors. Pediatr Nephrol. 2000;14(10–11):898–902.
25. Litwin M, Wuhl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol. 2005;16(5):1494–500.
26. Wroblewski K, Hincz K, Miklaszewska M, Zachwieja K, Wiercinski R, Stankiewicz R, et al. Antihypertensive treatment prescription in pediatric dialysis patients in Poland: a comparison between two nationwide studies 2003/2004-2013. Adv Clin Exp Med. 2017;26(8):1263–8.
27. van Stralen KJ, Borzych-Duzalka D, Hataya H, Kennedy SE, Jager KJ, Verrina E, et al. Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. Kidney Int. 2014;86(1):168–74.
28. Chaudhuri A, Sutherland SM, Begin B, Salsbery K, McCabe L, Potter D, et al. Role of twenty-four-hour ambulatory blood pressure monitoring in children on dialysis. Clin J Am Soc Nephrol. 2011;6(4):870–6.
29. VanDeVoorde RG, Barletta GM, Chand DH, Dresner IG, Lane J, Leiser J, et al. Blood pressure control in pediatric hemodialysis: the Midwest Pediatric Nephrology Consortium Study. Pediatr Nephrol. 2007;22(4):547–53.
30. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25(3):867–73.
31. Mitsnefes MM, Barletta GM, Dresner IG, Chand DH, Geary D, Lin JJ, et al. Severe cardiac hypertrophy and long-term dialysis: the Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol. 2006;21(8):1167–70.
32. Ulinski T, Genty J, Viau C, Tillous-Borde I, Deschenes G. Reduction of left ventricular hypertrophy in children undergoing hemodialysis. Pediatr Nephrol. 2006;21(8):1171–8.
33. Lee JH, Park YS. The B-type natriuretic peptide is a useful biomarker for the estimation of volume overload in children with hypertension in children on peritoneal dialysis. Nephrology (Carlton). 2018;24:341.
34. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int. 2000;58(1):293–301.
35. Saland JM, Pierce CB, Mitsnefes MM, Flynn JT, Goebel J, Kupferman JC, et al. Dyslipidemia in children with chronic kidney disease. Kidney Int. 2010;78(11):1154–63.
36. Cheng SC, Chu TS, Huang KY, Chen YM, Chang WK, Tsai TJ, et al. Association of hypertriglyceridemia and insulin resistance in uremic patients undergoing CAPD. Perit Dial Int: journal of the International Society for Peritoneal Dialysis. 2001;21(3):282–9.
37. Mak RH. 1,25-Dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia. Kidney Int. 1998;53(5):1353–7.
38. Mak RH. Effect of metabolic acidosis on hyperlipidemia in uremia. Pediatr Nephrol. 1999;13(9):891–3.
39. Chan PC, Persaud J, Varghese Z, Kingstone D, Baillod RA, Moorhead JF. Apolipoprotein B turnover in dialysis patients: its relationship to pathogenesis of hyperlipidemia. Clin Nephrol. 1989;31(2):88–95.
40. Horkko S, Huttunen K, Kesaniemi YA. Decreased clearance of low-density lipoprotein in uremic patients under dialysis treatment. Kidney Int. 1995;47(6):1732–40.
41. Saland JM, Ginsberg H, Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology, and management. Curr Opin Pediatr. 2002;14(2):197–204.
42. Wang X, Axelsson J, Nordfors L, Qureshi AR, Avesani C, Barany P, et al. Changes in fat mass after initiation of maintenance dialysis is influenced by the uncoupling protein 2 exon 8 insertion/deletion polymorphism. Nephrol Dial Transplant. 2007;22(1):196–202.
43. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis. 2001;38(6):1343–50.
44. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63(3):793–808.
45. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607–17.
46. Prie D, Urena Torres P, Friedlander G. Latest findings in phosphate homeostasis. Kidney Int. 2009;75(9):882–9.
47. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–8.
48. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.

49. Giachelli CM. Vascular calcification: in vitro evidence for the role of inorganic phosphate. J Am Soc Nephrol. 2003;14(9 Suppl 4):S300–4.
50. Shroff RC, Shanahan CM. The vascular biology of calcification. Semin Dial. 2007;20(2):103–9.
51. Block GA, Kilpatrick RD, Lowe KA, Wang W, Danese MD. CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis. Clin J Am Soc Nephrol. 2013;8(12):2132–40.
52. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder: synopsis of the kidney disease: improving global outcomes 2017 clinical practice guideline update. Ann Intern Med. 2018;168(6):422–30.
53. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009:S1–130.
54. Sigrist MK, McIntyre CW. Vascular calcification is associated with impaired microcirculatory function in chronic haemodialysis patients. Nephron Clin Pract. 2008;108(2):c121–6.
55. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004;15(7):1943–51.
56. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62(1):245–52.
57. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62(5):1524–38.
58. Wanner C, Zimmermann J, Schwedler S, Metzger T. Inflammation and cardiovascular risk in dialysis patients. Kidney Int Suppl. 2002;80:99–102.
59. Herzig KA, Purdie DM, Chang W, Brown AM, Hawley CM, Campbell SB, et al. Is C-reactive protein a useful predictor of outcome in peritoneal dialysis patients? J Am Soc Nephrol. 2001;12(4):814–21.
60. Bakkaloglu SA, Saygili A, Sever L, Noyan A, Akman S, Ekim M, et al. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish Pediatric Peritoneal Dialysis Study Group (TUPEPD) report. Nephrol Dial Transplant. 2009;24(11):3525–32.
61. Aguilera A, Sanchez-Tomero JA, Bajo MA, Ruiz-Caravaca ML, Alvarez V, del Peso G, et al. Malnutrition-inflammation syndrome is associated with endothelial dysfunction in peritoneal dialysis patients. Adv Perit Dial. 2003;19:240–5.
62. Pecoits-Filho R, Sylvestre LC, Stenvinkel P. Chronic kidney disease and inflammation in pediatric patients: from bench to playground. Pediatr Nephrol. 2005;20(6):714–20.
63. Ketteler M, Wanner C, Metzger T, Bongartz P, Westenfeld R, Gladziwa U, et al. Deficiencies of calcium-regulatory proteins in dialysis patients: a novel concept of cardiovascular calcification in uremia. Kidney Int Suppl. 2003;84:S84–7.
64. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, et al. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. 2005;20(8):1676–85.
65. Levin A, Li YC. Vitamin D and its analogues: do they protect against cardiovascular disease in patients with kidney disease? Kidney Int. 2005;68(5):1973–81.
66. Shroff R, Egerton M, Bridel M, Shah V, Donald AE, Cole TJ, et al. A bimodal association of vitamin D levels and vascular disease in children on dialysis. J Am Soc Nephrol. 2008;19(6):1239–46.
67. Sasaki T, Watanabe M, Nagai Y, Hoshi T, Takasawa M, Nukata M, et al. Association of plasma homocysteine concentration with atherosclerotic carotid plaques and lacunar infarction. Stroke. 2002;33(6):1493–6.
68. Taruangsri P, Ong-Ajyooth L, Ong-Ajyooth S, Chaiyasoot W, Leowattana W, Sritippayawan S, et al. Relationship between hyperhomocysteinemia and atherosclerosis in chronic hemodialysis patients. J Med Assoc Thail. 2005;88(10):1373–81.
69. Civilibal M, Caliskan S, Oflaz H, Sever L, Candan C, Canpolat N, et al. Traditional and "new" cardiovascular risk markers and factors in pediatric dialysis patients. Pediatr Nephrol. 2007;22(7):1021–9.
70. Bennett-Richards K, Kattenhorn M, Donald A, Oakley G, Varghese Z, Rees L, et al. Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure? Circulation. 2002;105(15):1810–5.
71. Ebbing M, Bonaa KH, Nygard O, Arnesen E, Ueland PM, Nordrehaug JE, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA. 2009;302(19):2119–26.
72. Fadrowski JJ, Pierce CB, Cole SR, Moxey-Mims M, Warady BA, Furth SL. Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. Clin J Am Soc Nephrol. 2008;3(2):457–62.
73. Staples AO, Wong CS, Smith JM, Gipson DS, Filler G, Warady BA, et al. Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(1):48–56.
74. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol. 2003;18(10):1055–62.
75. Feber J, Wong H, Geier P, Chaudry B, Filler G. Complications of chronic kidney disease in children post-renal transplantation - a single center experience. Pediatr Transplant. 2008;12(1):80–4.

76. Borzych-Duzalka D, Bilginer Y, Ha IS, Bak M, Rees L, Cano F, et al. Management of anemia in children receiving chronic peritoneal dialysis. J Am Soc Nephrol. 2013;24(4):665–76.
77. White CT, Schisler T, Er L, Djurdjev O, Matsuda-Abedini M. CKD following kidney transplantation in children and adolescents. Am J Kidney Dis. 2008;51(6):996–1004.
78. Shroff RC, Donald AE, Hiorns MP, Watson A, Feather S, Milford D, et al. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol. 2007;18(11):2996–3003.
79. Querfeld U, Schaefer F. Cardiovascular risk factors in children on dialysis: an update. Pediatr Nephrol. 2018;35:41.
80. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349(5):446–56.
81. Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, et al. Mortality risk among hemodialysis patients receiving different vitamin D analogs. Kidney Int. 2006;70(10):1858–65.
82. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72(8):1004–13.
83. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92.
84. Shroff RC, Shah V, Hiorns MP, Schoppet M, Hofbauer LC, Hawa G, et al. The circulating calcification inhibitors, fetuin-A and osteoprotegerin, but not matrix Gla protein, are associated with vascular stiffness and calcification in children on dialysis. Nephrol Dial Transplant. 2008;23(10):3263–71.
85. Kanderian AS, Francis GS. Cardiac troponins and chronic kidney disease. Kidney Int. 2006;69(7):1112–4.
86. Johnstone LM, Jones CL, Grigg LE, Wilkinson JL, Walker RG, Powell HR. Left ventricular abnormalities in children, adolescents and young adults with renal disease. Kidney Int. 1996;50(3):998–1006.
87. Matteucci MC, Wuhl E, Picca S, Mastrostefano A, Rinelli G, Romano C, et al. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol. 2006;17(1):218–26.
88. Bakkaloglu SA, Kandur Y, Serdaroglu E, Noyan A, Bayazit AK, Sever L, et al. Effect of the timing of dialysis initiation on left ventricular hypertrophy and inflammation in pediatric patients. Pediatr Nephrol. 2017;32(9):1595–602.
89. Bakkaloglu SA, Borzych D, Soo Ha I, Serdaroglu E, Buscher R, Salas P, et al. Cardiac geometry in children receiving chronic peritoneal dialysis: findings from the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Clin J Am Soc Nephrol. 2011;6(8):1926–33.
90. Goren A, Glaser J, Drukker A. Diastolic function in children and adolescents on dialysis and after kidney transplantation: an echocardiographic assessment. Pediatr Nephrol. 1993;7(6):725–8.
91. Morris KP, Skinner JR, Wren C, Hunter S, Coulthard MG. Cardiac abnormalities in end stage renal failure and anaemia. Arch Dis Child. 1993;68(5):637–43.
92. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, et al. Impaired left ventricular diastolic function in children with chronic renal failure. Kidney Int. 2004;65(4):1461–6.
93. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, et al. Abnormal cardiac function in children after renal transplantation. Am J Kidney Dis. 2004;43(4):721–6.
94. Saygili A, Yildirim SV, Cengiz N, Uslu Y, Tokel K, Saatci U. Assessment of left ventricular diastolic function by Doppler tissue imaging in children with end-stage renal disease. Acta Paediatr. 2005;94(8):1055–9.
95. Weaver DJ Jr, Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, et al. Decreased maximal aerobic capacity in pediatric chronic kidney disease. J Am Soc Nephrol. 2008;19(3):624–30.
96. Chinali M, de Simone G, Matteucci MC, Picca S, Mastrostefano A, Anarat A, et al. Reduced systolic myocardial function in children with chronic renal insufficiency. J Am Soc Nephrol. 2007;18(2):593–8.
97. Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, et al. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. J Am Soc Echocardiogr. 2010;23(10):1019–24.
98. Kramann R, Erpenbeck J, Schneider RK, Rohl AB, Hein M, Brandenburg VM, et al. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. J Am Soc Nephrol. 2014;25(10):2351–65.
99. Chinali M, Matteucci MC, Franceschini A, Doyon A, Pongiglione G, Rinelli G, et al. Advanced parameters of cardiac mechanics in children with CKD: the 4C study. Clin J Am Soc Nephrol. 2015;10(8):1357–63.
100. Rumman RK, Slorach C, Hui W, Matsuda-Abedini M, Langlois V, Radhakrishnan S, et al. Cardiovascular structure and function in children with middle aortic syndrome and renal artery stenosis. Hypertension. 2017;70(6):1193–200.
101. Rumman RK, Ramroop R, Chanchlani R, Ghany M, Hebert D, Harvey EA, et al. Longitudinal assessment of myocardial function in childhood chronic kidney disease, during dialysis, and following kidney transplantation. Pediatr Nephrol. 2017;32(8):1401–10.
102. Malatesta-Muncher R, Wansapura J, Taylor M, Lindquist D, Hor K, Mitsnefes M. Early cardiac dysfunction in pediatric patients on maintenance dialysis and post kidney transplant. Pediatr Nephrol. 2012;27(7):1157–64.
103. Hothi DK, Rees L, Marek J, Burton J, McIntyre CW. Pediatric myocardial stunning underscores the

cardiac toxicity of conventional hemodialysis treatments. Clin J Am Soc Nephrol. 2009;4(4):790–7.
104. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
105. Eifinger F, Wahn F, Querfeld U, Pollok M, Gevargez A, Kriener P, et al. Coronary artery calcifications in children and young adults treated with renal replacement therapy. Nephrol Dial Transplant. 2000;15(11):1892–4.
106. Groothoff JW, Gruppen MP, Offringa M, de Groot E, Stok W, Bos WJ, et al. Increased arterial stiffness in young adults with end-stage renal disease since childhood. J Am Soc Nephrol. 2002;13(12):2953–61.
107. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascock BJ, Khoury PR, et al. Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: role of calcium-phosphorus metabolism. J Am Soc Nephrol. 2005;16(9):2796–803.
108. Covic A, Mardare N, Gusbeth-Tatomir P, Brumaru O, Gavrilovici C, Munteanu M, et al. Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant. 2006;21(3):729–35.
109. Briese S, Wiesner S, Will JC, Lembcke A, Opgen-Rhein B, Nissel R, et al. Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease-impact of calcium and vitamin D therapy. Nephrol Dial Transplant. 2006;21(7):1906–14.
110. Civilibal M, Caliskan S, Adaletli I, Oflaz H, Sever L, Candan C, et al. Coronary artery calcifications in children with end-stage renal disease. Pediatr Nephrol. 2006;21(10):1426–33.
111. Poyrazoglu HM, Dusunsel R, Yikilmaz A, Narin N, Anarat R, Gunduz Z, et al. Carotid artery thickness in children and young adults with end stage renal disease. Pediatr Nephrol. 2007;22(1):109–16.
112. Srivaths PR, Goldstein SL, Krishnamurthy R, Silverstein DM. High serum phosphorus and FGF 23 levels are associated with progression of coronary calcifications. Pediatr Nephrol. 2014;29(1):103–9.
113. Litwin M, Wuhl E, Jourdan C, Niemirska A, Schenk JP, Jobs K, et al. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant. 2008;23(8):2552–7.
114. Brady TM, Schneider MF, Flynn JT, Cox C, Samuels J, Saland J, et al. Carotid intima-media thickness in children with CKD: results from the CKiD study. Clin J Am Soc Nephrol. 2012;7(12):1930–7.
115. Srivaths PR, Goldstein SL, Silverstein DM, Krishnamurthy R, Brewer ED. Elevated FGF 23 and phosphorus are associated with coronary calcification in hemodialysis patients. Pediatr Nephrol. 2011;26(6):945–51.
116. Srivaths PR, Silverstein DM, Leung J, Krishnamurthy R, Goldstein SL. Malnutrition-inflammation-coronary calcification in pediatric patients receiving chronic hemodialysis. Hemodial Int Int Symp Home Hemodial. 2010;14(3):263–9.
117. Chen J, Budoff MJ, Reilly MP, Yang W, Rosas SE, Rahman M, et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. JAMA Cardiol. 2017;2(6):635–43.
118. Xie Q, Ge X, Shang D, Li Y, Yan H, Tian J, et al. Coronary artery calcification score as a predictor of all-cause mortality and cardiovascular outcome in peritoneal dialysis patients. Perit Dial Int: journal of the International Society for Peritoneal Dialysis. 2016;36(2):163–70.
119. Krmar RT, Balzano R, Jogestrand T, Cedazo-Minguez A, Englund MS, Berg UB. Prospective analysis of carotid arterial wall structure in pediatric renal transplants with ambulatory normotension and in treated hypertensive recipients. Pediatr Transplant. 2008;12(4):412–9.
120. Mitsnefes MM. Understanding carotid artery intima-media thickness in childhood: lessons from studies in children with renal transplants. Pediatr Transplant. 2008;12(4):377–80.
121. Shroff RC, McNair R, Figg N, Skepper JN, Schurgers L, Gupta A, et al. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation. 2008;118(17):1748–57.
122. Reynolds JL, Skepper JN, McNair R, Kasama T, Gupta K, Weissberg PL, et al. Multifunctional roles for serum protein fetuin-a in inhibition of human vascular smooth muscle cell calcification. J Am Soc Nephrol. 2005;16(10):2920–30.
123. van Summeren MJ, Hameleers JM, Schurgers LJ, Hoeks AP, Uiterwaal CS, Kruger T, et al. Circulating calcification inhibitors and vascular properties in children after renal transplantation. Pediatr Nephrol. 2008;23(6):985–93.
124. Schurgers LJ, Teunissen KJ, Knapen MH, Kwaijtaal M, van Diest R, Appels A, et al. Novel conformation-specific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. Arterioscler Thromb Vasc Biol. 2005;25(8):1629–33.
125. Smith ER, Ford ML, Tomlinson LA, Bodenham E, McMahon LP, Farese S, et al. Serum calcification propensity predicts all-cause mortality in predialysis CKD. J Am Soc Nephrol. 2014;25(2):339–48.
126. Pasch A, Block GA, Bachtler M, Smith ER, Jahnen-Dechent W, Arampatzis S, et al. Blood calcification propensity, cardiovascular events, and survival in patients receiving hemodialysis in the EVOLVE trial. Clin J Am Soc Nephrol. 2017;12(2):315–22.
127. Scialla JJ, Kao WH, Crainiceanu C, Sozio SM, Oberai PC, Shafi T, et al. Biomarkers of vascular calcification and mortality in patients with ESRD. Clin J Am Soc Nephrol. 2014;9(4):745–55.
128. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–81.

129. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31–8.
130. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int. 1999;56(2):383–92.
131. Doyon A, Schmiedchen B, Sander A, Bayazit A, Duzova A, Canpolat N, et al. Genetic, environmental, and disease-associated correlates of vitamin D status in children with CKD. Clin J Am Soc Nephrol. 2016;11(7):1145–53.
132. Shroff R, Wan M, Nagler EV, Bakkaloglu S, Cozzolino M, Bacchetta J, et al. Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease stages 2-5 and on dialysis. Nephrol Dial Transplant. 2017;32(7):1114–27.
133. Shroff R, Wan M, Nagler EV, Bakkaloglu S, Fischer DC, Bishop N, et al. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease stages 2-5 and on dialysis. Nephrol Dial Transplant. 2017;32(7):1098–113.
134. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110(2):229–38.
135. Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS, et al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci U S A. 2007;104(43):16810–5.
136. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr. 2005;94(4):483–92.
137. Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM. Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? Kidney Int. 2008;73(4):384–90.
138. Shroff RC, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, et al. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. J Am Soc Nephrol. 2010;21(1):103–12.
139. Liu Y, Drozdov I, Shroff R, Beltran LE, Shanahan CM. Prelamin A accelerates vascular calcification via activation of the DNA damage response and senescence-associated secretory phenotype in vascular smooth muscle cells. Circ Res. 2013;112(10):e99–109.
140. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, et al. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging. Arterioscler Thromb Vasc Biol. 2010;30(11):2301–9.
141. Gerhard-Herman M, Smoot LB, Wake N, Kieran MW, Kleinman ME, Miller DT, et al. Mechanisms of premature vascular aging in children with Hutchinson-Gilford progeria syndrome. Hypertension. 2012;59(1):92–7.
142. Sanchis P HC, Liu Y, Beltran LE, Ahmad S, Jacob AP, Furmanik M, Laycock J, Long DA, Shroff R, Shanahan CM. Arterial 'inflammaging' drives vascular calcification in children on dialysis. Kidney International Accepted for publication 2019.
143. Malluche HH, Blomquist G, Monier-Faugere MC, Cantor TL, Davenport DL. High parathyroid hormone level and osteoporosis predict progression of coronary artery calcification in patients on dialysis. J Am Soc Nephrol. 2015;26(10):2534–44.
144. Cejka D, Weber M, Diarra D, Reiter T, Kainberger F, Haas M. Inverse association between bone microarchitecture assessed by HR-pQCT and coronary artery calcification in patients with end-stage renal disease. Bone. 2014;64:33–8.
145. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945–53.
146. Bell L, Espinosa P. Intensive in-center hemodialysis for children: a case for longer dialysis duration. Hemodial Int Int Symp Home Hemodial. 2003;7(4):290–5.
147. Goldstein SL, Silverstein DM, Leung JC, Feig DI, Soletsky B, Knight C, et al. Frequent hemodialysis with NxStage system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008;23(1):129–35.
148. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14(3):297–303.
149. Maduell F, Navarro V, Torregrosa E, Rius A, Dicenta F, Cruz MC, et al. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. Kidney Int. 2003;64(1):305–13.
150. Punal J, Lema LV, Sanhez-Guisande D, Ruano-Ravina A. Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: a systematic review. Nephrol Dial Transplant. 2008;23(8):2634–46.
151. Coyte PC, Young LG, Tipper BL, Mitchell VM, Stoffman PR, Willumsen J, et al. An economic evaluation of hospital-based hemodialysis and home-based peritoneal dialysis for pediatric patients. Am J Kidney Dis. 1996;27(4):557–65.
152. McFarlane PA, Bayoumi AM, Pierratos A, Redelmeier DA. The impact of home nocturnal hemodialysis on end-stage renal disease therapies: a decision analysis. Kidney Int. 2006;69(5):798–805.
153. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147(3):383–7.
154. Blankestijn PJ, Ledebo I, Canaud B. Hemodiafiltration: clinical evidence and remaining questions. Kidney Int. 2010;77(7):581–7.

155. Ledebo I, Blankestijn PJ. Haemodiafiltration-optimal efficiency and safety. NDT Plus. 2010;3(1):8–16.
156. Mostovaya IM, Grooteman MP, Basile C, Davenport A, de Roij van Zuijdewijn CL, Wanner C, et al. High convection volume in online post-dilution haemodiafiltration: relevance, safety and costs. Clin Kidney J. 2015;8(4):368–73.
157. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24(3):487–97.
158. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28(1):192–202.
159. Peters SA, Bots ML, Canaud B, Davenport A, Grooteman MP, Kircelli F, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. Nephrol Dial Transplant. 2016;31(6):978–84.
160. Fadel FI, Makar SH, Zekri H, Ahmed DH, Aon AH. The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis. Saudi J Kidney Dis Transpl. 2015;26(1):39–46.
161. Morad AA, Bazaraa HM, Abdel Aziz RE, Abdel Halim DA, Shoman MG, Saleh ME. Role of online hemodiafiltration in improvement of inflammatory status in pediatric patients with end-stage renal disease. Iran J Kidney Dis. 2014;8(6):481–5.
162. Shroff R, Bayazit A, Stefanidis CJ, Askiti V, Azukaitis K, Canpolat N, et al. Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children - the HDF, heart and height (3H) study. BMC Nephrol. 2018;19(1):199.
163. Agbas A, Canpolat N, Caliskan S, Yilmaz A, Ekmekci H, Mayes M, et al. Hemodiafiltration is associated with reduced inflammation, oxidative stress and improved endothelial risk profile compared to high-flux hemodialysis in children. PLoS One. 2018;13(6):e0198320.
164. Hothi DK, Stronach L, Sinnott K. Home hemodialysis in children. Hemodial Int Int Symp Home Hemodial. 2016;20(3):349–57.
165. Hothi DK, Harvey E, Piva E, Keating L, Secker D, Geary DF. Calcium and phosphate balance in adolescents on home nocturnal haemodialysis. Pediatr Nephrol. 2006;21(6):835–41.
166. de Camargo MF, Henriques CL, Vieira S, Komi S, Leao ER, Nogueira PC. Growth of children with end-stage renal disease undergoing daily hemodialysis. Pediatr Nephrol. 2014;29(3):439–44.
167. Hoppe A, von Puttkamer C, Linke U, Kahler C, Booss M, Braunauer-Kolberg R, et al. A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr. 2011;158(1):95–9, 9 e1.
168. Thumfart J, Muller D, Wagner S, Jayanti A, Borzych-Duzalka D, Schaefer F, et al. Barriers for implementation of intensified hemodialysis: survey results from the International Pediatric Dialysis Network. Pediatr Nephrol. 2018;33(4):705–12.
169. Wuhl E, Fusch C, Scharer K, Mehls O, Schaefer F. Assessment of total body water in paediatric patients on dialysis. Nephrol Dial Transplant. 1996;11(1):75–80.
170. Krause I, Birk E, Davidovits M, Cleper R, Blieden L, Pinhas L, et al. Inferior vena cava diameter: a useful method for estimation of fluid status in children on haemodialysis. Nephrol Dial Transplant. 2001;16(6):1203–6.
171. Katzarski KS, Charra B, Luik AJ, Nisell J, Divino Filho JC, Leypoldt JK, et al. Fluid state and blood pressure control in patients treated with long and short haemodialysis. Nephrol Dial Transplant. 1999;14(2):369–75.
172. Muller D, Zimmering M, Chan CT, McFarlane PA, Pierratos A, Querfeld U. Intensified hemodialysis regimens: neglected treatment options for children and adolescents. Pediatr Nephrol. 2008;23(10):1729–36.
173. Thumfart J, Puttkamer CV, Wagner S, Querfeld U, Muller D. Hemodiafiltration in a pediatric nocturnal dialysis program. Pediatr Nephrol. 2014;29(8):1411–6.
174. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(4 Suppl 3):S1–153.
175. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr. 2009;22(6):709–14.
176. Foster BJ, Mackie AS, Mitsnefes M, Ali H, Mamber S, Colan SD. A novel method of expressing left ventricular mass relative to body size in children. Circulation. 2008;117(21):2769–75.
177. Borzych D, Bakkaloglu SA, Zaritsky J, Suarez A, Wong W, Ranchin B, et al. Defining left ventricular hypertrophy in children on peritoneal dialysis. Clin J Am Soc Nephrol. 2011;6(8):1934–43.
178. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.
179. Chinali M, Emma F, Esposito C, Rinelli G, Franceschini A, Doyon A, et al. Left ventricular mass indexing in infants, children, and adolescents: a simplified approach for the identification of left ventricular hypertrophy in clinical practice. J Pediatr. 2016;170:193–8.
180. K/DOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2004;42(4, Suppl 3):S1–S201.

181. Klaus G, Watson A, Edefonti A, Fischbach M, Ronnholm K, Schaefer F, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol. 2006;21(2):151–9.
182. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, et al. Phosphorus binders and survival on hemodialysis. J Am Soc Nephrol. 2009;20(2):388–96.
183. Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2010;25(3):385–94.
184. Salusky IB. A new era in phosphate binder therapy: what are the options? Kidney Int Suppl. 2006;105:S10–5.
185. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013;382(9900):1268–77.
186. Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB. Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. Pediatr Nephrol. 2003;18(12):1260–4.
187. Pieper AK, Haffner D, Hoppe B, Dittrich K, Offner G, Bonzel KE, et al. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. Am J Kidney Dis. 2006;47(4):625–35.
188. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, et al. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. J Am Soc Nephrol. 2005;16(8):2501–8.
189. Wesseling-Perry K, Harkins GC, Wang HJ, Sahney S, Gales B, Elashoff RM, et al. Response of different PTH assays to therapy with sevelamer or CaCO3 and active vitamin D sterols. Pediatr Nephrol. 2009;24(7):1355–61.
190. Hutchison AJ. Oral phosphate binders. Kidney Int. 2009;75(9):906–14.
191. Fathallah-Shaykh S, Drozdz D, Flynn J, Jenkins R, Wesseling-Perry K, Swartz SJ, et al. Efficacy and safety of sevelamer carbonate in hyperphosphatemic pediatric patients with chronic kidney disease. Pediatr Nephrol. 2018;33(2):325–33.
192. Denburg MR, Kumar J, Jemielita T, Brooks ER, Skversky A, Portale AA, et al. Fracture burden and risk factors in childhood CKD: results from the CKiD cohort study. J Am Soc Nephrol. 2016;27(2):543–50.
193. Wang C, Liu X, Zhou Y, Li S, Chen Y, Wang Y, et al. New conclusions regarding comparison of Sevelamer and calcium-based phosphate binders in coronary-artery calcification for dialysis patients: a meta-analysis of randomized controlled trials. PLoS One. 2015;10(7):e0133938.
194. Palmer SC, Gardner S, Tonelli M, Mavridis D, Johnson DW, Craig JC, et al. Phosphate-binding agents in adults with CKD: a network meta-analysis of randomized trials. Am J Kidney Dis. 2016;68(5):691–702.
195. Civilibal M, Caliskan S, Kurugoglu S, Candan C, Canpolat N, Sever L, et al. Progression of coronary calcification in pediatric chronic kidney disease stage 5. Pediatr Nephrol. 2009;24(3):555–63.
196. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int. 2007;72(9):1130–7.
197. Savica V, Calo LA, Monardo P, Davis PA, Granata A, Santoro D, et al. Salivary phosphate-binding chewing gum reduces hyperphosphatemia in dialysis patients. J Am Soc Nephrol. 2009;20(3):639–44.
198. Rees L, Shroff R. The demise of calcium-based phosphate binders-is this appropriate for children? Pediatr Nephrol. 2015;30(12):2061–71.
199. Ketteler M, Elder GJ, Evenepoel P, Ix JH, Jamal SA, Lafage-Proust MH, et al. Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a kidney disease: improving global outcomes controversies conference. Kidney Int. 2015;87(3):502–28.
200. Dasgupta I, Shroff R, Bennett-Jones D, McVeigh G, Group NHGD. Management of hyperphosphataemia in chronic kidney disease: summary of National Institute for Health and Clinical Excellence (NICE) guideline. Nephron Clin Pract. 2013;124(1–2):1–9.
201. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2015;(11):CD008327.
202. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, et al. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. J Clin Endocrinol Metab. 2013;98(5):1930–8.
203. Drueke TB. Treatment of secondary hyperparathyroidism of dialysis patients with calcimimetics as a valuable addition to established therapeutic means. Pediatr Nephrol. 2005;20(3):399–403.
204. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2010;(1):CD008327.
205. McKay CP, Portale A. Emerging topics in pediatric bone and mineral disorders 2008. Semin Nephrol. 2009;29(4):370–8.
206. Schaefer B, Schlosser K, Wuhl E, Schall P, Klaus G, Schaefer F, et al. Long-term control of parathyroid hormone and calcium-phosphate metabolism after parathyroidectomy in children with chronic kidney disease. Nephrol Dial Transplant. 2010;25(8):2590–5.
207. Mak RH. Metabolic effects of erythropoietin in patients on peritoneal dialysis. Pediatr Nephrol. 1998;12(8):660–5.
208. Mak RH. Effect of metabolic acidosis on insulin action and secretion in uremia. Kidney Int. 1998;54(2):603–7.

209. KDIGO. Clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3(3):259–305.
210. Goren A, Stankiewicz H, Goldstein R, Drukker A. Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. Pediatrics. 1991;88(2):265–8.
211. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48.
212. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407.
213. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.
214. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157(4):251–62.
215. Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013;34(24):1807–17.
216. Warady BA, Neu AM, Schaefer F. Optimal care of the infant, child, and adolescent on dialysis: 2014 update. Am J Kidney Dis. 2014;64(1):128–42.

Management of Hypertension in Pediatric Dialysis Patients

31

Elke Wühl and Joseph T. Flynn

Abbreviations

ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin converting enzyme inhibitor
BP	blood pressure
CAKUT	congenital anomalies of kidney and urinary tract
ESRD	end-stage renal disease
HD	hemodialysis
LVH	left ventricular hypertrophy
NO	nitric oxide
PD	peritoneal dialysis
PTH	parathyroid hormone
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone-system

Introduction

Patients on maintenance dialysis therapy have an excessively increased all-cause and cardiovascular morbidity and mortality compared with the general population. Adolescents and young adults may already have symptomatic cardiovascular disease, including ischemic heart disease and stroke, and at least every second child on dialysis presents with early signs of cardiovascular end-organ damage such as left ventricular hypertrophy (LVH) or alterations of vascular morphology and function. One of the main risk factors for the high cardiovascular morbidity and mortality is arterial hypertension. The percentage of hypertensive patients on maintenance dialysis is up to 80%, and while hypertension in mild-to-moderate chronic kidney disease (CKD) is mainly caused by underlying renal parenchymal disease, in dialysis patients the most important factor influencing blood pressure (BP) is fluid and salt overload.

The aim of this chapter is to review the prevalence and etiology of hypertension and associated cardiovascular morbidity and mortality in children on dialysis, as well as treatment strategies and targets.

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Prevalence of Hypertension in Pediatric Dialysis Patients

Hypertension is highly prevalent in the pediatric dialysis population. Almost 4 out of 5 children and adolescents requiring dialysis are hypertensive or have been prescribed antihypertensive medication.

In a survey of the European ERA/EDTA registry, comprising more than 1300 pediatric dialysis patients from 15 European countries, the prevalence of hypertension was 69.7% in hemodialysis (HD) and 68.2% in peritoneal dialysis (PD) patients. Forty-five percent of HD and 35% of PD patients had uncontrolled hypertension [72]. Similar findings have been seen in data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. In an analysis including almost 3500 children, 67.9% of patients were found to be hypertensive 6 months after initiation of dialysis [49]. In another study in long-term HD patients, hypertension was present in 79% of patients. Sixty-two percent of patients were on antihypertensive medication; however, hypertension was uncontrolled in 74% of treated patients. [22].

It should be noted that these epidemiologic data were derived from casual/office BP measurements with single BP recordings per patient reported to the registries. Hypertension was commonly defined as either systolic or diastolic BP above the 95th percentile for sex, age and height. For the interpretation of these data, consideration of the time of BP measurement is important. Predialysis measurements are usually higher compared with post-dialysis measurements, resulting in a higher probability to be classified as hypertensive when only pre-dialysis measurements are available. In HD patients, the median (or mean) interdialytic BP measured by ambulatory BP monitoring (ABPM) is usually lower compared with casual pre-dialysis measurements, resulting in a lower number of patients being classified as hypertensive by ABPM [51]. When the ABPM measurement duration has been extended from the conventional 24 h to 44 h, covering a complete midweek interdialytic period, a higher percentage of patients were diagnosed with hypertension and all BP indexes and loads were significantly higher on interdialytic day 2 compared to day 1 [51]. Volume fluctuations and fluid overload are probably the most important factors responsible for the poor diagnostic value of pre- and post-dialytic BP measurements to predict hypertension in the interdialytic period [3, 125].

It should also be noted that ABPM may identify patients with nocturnal or masked hypertension [21] and patients with reversed nocturnal dipping or altered circadian and ultradian BP rhythms. Unfortunately, data on hypertension prevalence according to interdialytic ABPM are scarce [21, 77].

Etiology of Hypertension in Pediatric Dialysis Patients

The dominant factor contributing to hypertension in dialysis patients is volume overload; other contributing factors include activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, endothelial dysfunction, increased arterial stiffness, hyperparathyroidism, and exposure to BP elevating drugs.

Additionally, registry studies have identified young age, being on HD, having glomerulopathies as the primary renal disease, and shorter duration of renal replacement therapy as risk factors for dialysis-associated pediatric hypertension [22, 49, 72].

Volume overload plays a pivotal role in the development of hypertension in dialysis patients. Several studies in humans have demonstrated a direct effect of extracellular volume on BP in HD patients [4, 61, 133], and interdialytic weight gain has been shown to correlate with higher systolic BP load in 44-h ABPM profiles on the second day of the BP recording [51]. As might be expected, attainment of dry weight and normalization of sodium balance were able to normalize BP without the need for antihypertensive medication [16].

In dialysis patients, extracellular volume, cardiac output, and BP are increased by impaired or absent ability of the kidneys to excrete sodium and water. These alterations are worsened by

insufficient intradialytic removal of fluid and salt. Therefore, in addition to an adequate dialysis prescription, interdialytic fluid restriction and limited salt intake are therapeutic cornerstones for the attainment of dry weight as part of the management of hypertension in dialysis patients. However, efforts to compensate for decreasing residual renal function and diuresis by increasing intradialytic sodium and water removal are often insufficient, as seen in one recent study, in which 25% of dialysis-associated hypertension was felt to be related to factors other than volume overload [32].

Loss of residual renal function is another risk factor for the development of hypertension. BP is inversely correlated to residual renal function and hypertensive children on dialysis have less residual urine output compared to normotensive children [130].

Fluid balance is inextricably linked to serum *sodium* concentration. However, the hypertensive effects of sodium are exerted by mechanisms both related and unrelated to extracellular volume expansion; elevated sodium concentration may also induce vasoconstriction by altering endothelial cell responses and further contribute to the development of hypertension [99].

It has been demonstrated that intradialytic salt exposure (i.e., the sodium content of the dialysate) has a direct impact on BP. HD patients set to time-averaged dialysate sodium concentrations of 147 mEq/L were found to have higher 24-h systolic BP levels compared to patients set to a sodium concentration of 138 mEq/L [124]. Additionally, a higher dialysate-to-plasma-sodium gradient may increase thirst and interdialytic weight gain, impeding attainment and maintenance of dry weight [115].

Contrary to the physiologically expected suppression of the *renin-angiotensin-aldosterone system* (RAAS) in a state of salt or fluid overload, plasma renin activity was found to be significantly higher in a study comparing hypertensive to normotensive dialysis patients. The study results strongly suggested that the RAAS is an important factor involved in the pathogenesis of hypertension in end-stage renal disease (ESRD), when sodium balance is adequately controlled [71]. In addition, the significant decline in BP that occurs following bilateral nephrectomy [138] points to volume-independent mechanisms of hypertension in dialysis patients.

Children with end-stage renal disease showed a 25-fold increase in angiotensin (1–7) compared to control values. These marked changes in plasma angiotensin (1–7) were associated with the presence of hypertension and progression of kidney dysfunction [121], while angiotensin II levels were similar and plasma renin activity was lower compared to hypertensive patients with non-ESRD CKD. In dialysis patients, angiotensin II was only poorly suppressed by angiotensin converting enzyme inhibitor (ACEi) treatment. The significance of the elevated angiotensin (1–7) levels is still not clear, but might be a consequence of the altered RAAS pathway in pediatric ESRD patients.

Dialysis patients also have higher *sympathetic nervous system* (SNS) activity and vascular resistance than healthy controls or ESRD patients after bilateral nephrectomies [26]. An early manifestation of abnormal activation of the SNS activity is the absence of the physiological nocturnal BP dipping in 24 h ambulatory BP monitoring [79].

Endothelial dysfunction, which participates in accelerated atherosclerosis, is a hallmark of CKD. Patients with ESRD display impaired endothelium-dependent vasodilatation, elevated soluble biomarkers of endothelial dysfunction, and increased oxidative stress. Several uremic toxins, mostly protein-bound, have been shown to have specific endothelial toxicity: e.g., asymmetric dimethylarginine (ADMA), homocysteine, and advanced glycosylation end-products (AGEs). These toxins are insufficiently or not removed by dialysis, promote pro-oxidative and pro-inflammatory response, and inhibit endothelial repair, thereby inducing endothelial damage [64].

The most important vasodilatory substance is nitric oxide (NO). The disturbed balance between decreased NO (mediator of vasodilatation) and increased endothelin-1 (ET-1; mediator of vasoconstriction) in dialysis patients results in *endo-*

thelial cell dysfunction with increased vasoconstriction. NO release is reduced by CKD-induced elevation of ADMA, an endogenous inhibitor of endothelial NO synthase. Increased levels of ADMA have been found to be directly associated with increased cardiovascular and all-cause mortality in the ESRD population [12]. Oxidative stress with increased reactive oxygen species (ROS) can also interfere with NO synthesis and availability.

As a result, *arterial stiffness*, usually a problem of vascular aging and arteriosclerosis, is accentuated in the presence of end-stage renal disease and hypertension. The stiffened, non-compliant arteries transmit each ejected pulse wave so quickly that the reflected pressure wave, coming backwards from the peripheral circulation, coincides with the still ongoing systole. The consequence is increased systolic BP and pulse pressure resulting in LVH [80]. Higher pulse wave velocity (PWV) due to increased vascular stiffness is also present in pediatric ESRD. PWV is elevated compared to age-, height-, and weight-matched controls [68]. However, the elevated PWV in pediatric ESRD patients was not clearly correlated with the BP level and was found to be persistently elevated despite the use of pharmacological vasodilatation.

Another study in pediatric ESRD patients showed that aortic distensibility, another measure of arterial stiffness, was lower (i.e., higher arterial stiffness) in both HD and PD patients compared to healthy controls. Children on HD had more severe impairment than PD patients [110].

Plasma levels of *renalase,* a protein released by the kidneys and responsible for the degradation of catecholamines, are markedly decreased in ESRD. Renalase deficiency and the resulting increase of circulating catecholamine levels may also contribute to hypertension and cardiovascular disease in ESRD [30, 137].

Secondary *hyperparathyroidism*, a complication of CKD, may be yet another contributor to the high prevalence of hypertension. A retrospective study in adults with pre-dialysis CKD demonstrated that systolic and diastolic BP were significantly increased in patients with elevated parathyroid hormone (PTH) levels [108]. A possible mechanism might be increased platelet cytosolic calcium in patients with elevated PTH. Mean BP correlated highly with cytosolic calcium and PTH. In contrast, treatment with vitamin D lowered cytosolic calcium, PTH, and mean BP significantly.

Therapy with *erythropoiesis stimulating agents*, i.e., erythropoietin, is also associated with an increase of the BP level and development of hypertension. The prevalence of BP increase in adults on erythropoietin therapy is given as high as 10–75%. In a study in 23 pediatric dialysis patients, hypertension developed or worsened in 67% of CAPD patients and 36% of HD patients after initiation of erythropoietin, while no differences were observed in plasma level of aldosterone or plasma renin activity [69].

Mechanisms involved in the development of hypertension and cardiovascular end-organ damage in pediatric dialysis patients are summarized in Fig. 31.1.

While most pediatric dialysis patients lack the cardiovascular and metabolic comorbidities that lead to hypertension in adults with ESRD, *underlying renal disease* is another important factor influencing the BP level in children with ESRD.

In glomerulopathies, activation of the RAAS, present from the earliest stages of glomerular disease through ESRD, may complicate BP control. Patients with glomerular disease are also less likely to be normotensive compared to patients with congenital anomalies of the kidney and the urinary tract (CAKUT; 12% vs. 31%) [49] and to have an approximately two-fold higher risk of uncontrolled hypertension [49, 72].

Patients with autosomal-recessive polycystic kidney disease may have very severe or therapy refractory hypertension, necessitating bilateral nephrectomy in some cases. In contrast, patients suffering from CAKUT are less prone to renal hypertension, and attainment of dry weight often succeeds in achieving BP control without the need of additional antihypertensive medication.

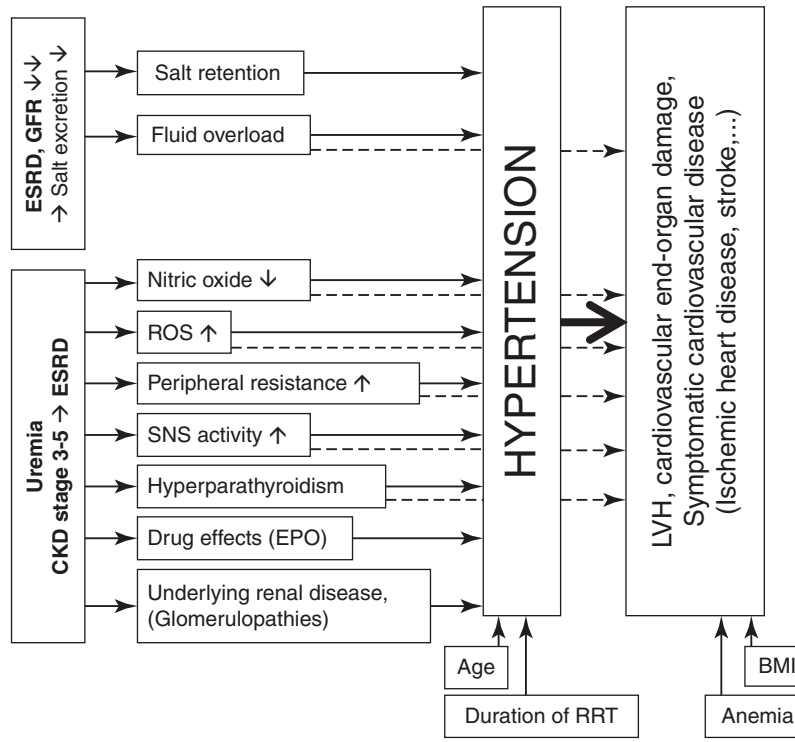

Fig. 31.1 Mechanisms involved in the development of hypertension in pediatric dialysis patients. BMI body mass index, CKD chronic kidney disease, EPO erythropoietin, ESRD end-stage renal disease, GFR glomerular filtration rate, ROS reactive oxygen species, RRT renal replacement therapy, SNS sympathetic nervous system

Short- and Long-Term Consequences of Hypertension

Hospitalization

Fluid overload and hypertension are a frequent cause for morbidity, accounting for 41% of hospitalizations in children on HD at the Texas Children's Hospital [44]. The risk of hospitalization correlated with the duration of the interdialytic interval. Children receiving chronic HD were more likely to be hospitalized for hypertension, fluid overload, or electrolyte abnormalities following a longer interdialytic interval. Accordingly, the odds ratio of hospital admission was 2.6 on Monday versus other days of the week, while the odds ratio of admission among PD patients was not significantly different on Mondays [126]. Thus, changes to the frequency and intensity of the dialysis treatment may effect admissions in this high-risk population.

Alterations of Vascular Morphology and Function

Increased arterial stiffness is a risk factor for mortality in adults with ESRD. A long-term outcome study including all living adult Dutch patients with childhood onset of ESRD between 1972 and 1992 at age 0–14 years showed a similar intima media thickness, but a reduced mean arterial wall distensibility and increased arterial stiffness compared to healthy controls. Systolic hypertension was the main determinant of these arterial wall changes [46].

The ESCAPE Trial group was able to provide clear evidence that CKD is associated with morphologic alterations of both muscular- and elastic-type arteries as early as in the second decade of life. The degree of pathology depended on the degree of renal dysfunction, correlated with systolic BP, and was most marked in patients on dialysis [78]. In another study including 39

children and adolescents on dialysis (15 HD, 24 PD), indexed diastolic BP was a significant predictor if cIMT [24].

Left Ventricular Hypertrophy

LVH is a common complication in dialysis patients. Forty-eight percent of PD patients were noted to have LVH and 75% had abnormal left ventricular geometry according to a registry analysis of the International Pediatric Peritoneal Dialysis Network (IPPN) [15]. In this analysis, hypertension, high body mass index, fluid overload, renal disease other than hypo/dysplasia, and hyperparathyroidism were predictors of LVH. The lower prevalence of LVH in patients with renal hypo/dysplasia is likely the result of lower BP and polyuria in these patients [15].

In HD patients, the prevalence of LVH was even higher at eighty-five percent, and abnormal left ventricular geometry was found in 80% of patients [91]. The impact of different BP parameters on LVH was analyzed in 25 PD patients, of whom 52% had LVH. Left ventricular mass index (LVMI) was significantly correlated with casual BP measurements and the majority of ABPM parameters [102]. In contrast, in 17 HD patients studied by casual BP measurements and 44-h ABPM, casual BP measurements did not correlate well with measures of cardiovascular end-organ damage, while nighttime BP during 44-h interdialytic ABPM most strongly predicted increased LVMI and LVH [66].

Forty-four-hour ABPM BP load was also correlated with a higher left ventricular mass index. Children with LVH had higher daytime and nighttime systolic BP loads, significantly higher daytime and nighttime diastolic BP loads, and a lesser degree of nocturnal dipping of systolic BP compared to children without LVH [51].

Cardiovascular Mortality

Twenty years ago, it was shown that overall mortality in children on dialysis was increased 1000-fold compared to the normal pediatric population [104] and 40–50% of deaths were from cardiovascular and cerebrovascular causes [47, 87, 101].

Encouragingly, over the past several decades the risk of death has decreased significantly in this population. For example, in the USRDS registry, cardiovascular mortality in pediatric dialysis patients has decreased significantly over the last 20 years, from 33.5/1000 patient-years in patients <5 years of age and 16.2/1000 patient-years in patients >5 years to 22.6 and 9.3/1000 patient-years, respectively [92].

In a European review, overall mortality was 28/1000 patient-years in children and adolescents who started dialysis between 2000 and 2013. Overall mortality risk was highest (36.0/1000) during the first year of dialysis and in the 0- to 5-year age group (49.4/1000), and cardiovascular events accounted for 18.3% of death. Children selected to start on HD had an increased mortality risk compared with those on PD, especially during the first year of dialysis [23].

Improved implementation of clinical practice guidelines, associated with better control of anemia, hyperparathyroidism, and BP, might have contributed to this reduction in mortality as recently shown by a NAPRTCS registry analysis [135]. Similarly, in a systematic review and meta-analysis of 8 trials including 1679 adult patients on dialysis and 495 cardiovascular events, BP lowering was associated with a lower risk of cardiovascular events, all cause-mortality and cardiovascular mortality [55].

Diagnosis of HTN in Dialysis Patients

Current European and American guidelines for evaluation and management of hypertension in children and adolescents [38, 82] do not specify different thresholds for diagnosing hypertension when it is known that the patient has a specific underlying diagnosis, such as renal disease; one would still make the diagnosis of hypertension once the BP had exceeded the specific age, sex, and height threshold. Given the close association

between CKD and hypertension in children and adolescents [119], it is likely that a pediatric dialysis patient would be hypertensive at the initiation of dialysis. Thus, the problem under consideration herein is more likely to be an issue of recognition of hypertension, as opposed to making an initial diagnosis of hypertension. Specifically, the problem is how to best diagnose hypertension in a dialysis patient when their measured BP in the clinic or dialysis unit does NOT exceed the thresholds found in the guidelines, but does at other times, a condition known as masked hypertension. Masked hypertension is particularly common in children and adolescents with pre-dialysis CKD [114].

Role of Ambulatory Blood Pressure Monitoring (ABPM)

24-h ABPM is a procedure whereby repeated BP measurements can be obtained outside of a clinical setting, including during sleep. A detailed discussion of ABPM is beyond the scope of this chapter; interested readers should consult other references [37, 83]. There are several distinct hypertension phenotypes that can be identified using the combination of clinic and ambulatory BP values (Table 31.1). All four phenotypes have been identified in adult HD patients [6]. While masked hypertension (and its opposite, white coat hypertension) can be diagnosed using resting BPs obtained in a non-clinical setting, ABPM is generally agreed to be the gold standard approach for identifying patients with these BP patterns [37]. As will be discussed in more detail below, widespread application of ABPM in patients undergoing dialysis is absolutely essential for optimal BP management in this high-risk population.

Table 31.1 Blood pressure phenotypes based on casual/office and ambulatory blood pressure values

Phenotype	Office BP	Ambulatory BP
Normotensive	Normal	Normal
Hypertensive	High	High
White coat hypertensive	High	Normal
Masked hypertensive	Normal	High

ABPM in Hemodialysis Patients

The assessment of BP in HD patients is challenging for many reasons, not the least of which is the timing of when BP is measured [74]. It is clear that pre- and post-dialysis BPs provide an inaccurate estimate of the interdialytic BP burden compared to assessment by ABPM [1]. Additionally, BPs obtained surrounding dialysis do not correlate with end organ damage such as elevated left ventricular mass index [2, 93, 94]. Forty-four-hour ABPM has demonstrated increased accuracy in detecting hypertension as compared to a 24-h assessment, likely due to the higher BPs seen in the day following dialysis (the second portion of 44-h ABPM). BP loads >25% on 44-h ABPM have been associated with higher left ventricular mass index in children on chronic HD as compared to assessment with 24-h ABPM [51]. Given these advantages, 44-h ABPM is felt to be the gold standard for BP assessment in HD patients [7].

ABPM in Peritoneal Dialysis Patients

Abnormal circadian BP patterns are common in adult PD patients, and blunted nocturnal dipping and higher BP loads on ABPM correlate with higher left ventricular mass index [13]. Similarly, among 47 children on PD, systolic BP loads on 24 h ABPM were associated with an increased risk of elevated left ventricular mass index [19]. In another study, ABPM was more sensitive in diagnosing hypertension as compared to clinic BPs among 25 pediatric PD patients (56 vs. 32%, $p < 0.05$) [102]. As with HD patients, these data support the routine use of ABPM in assessing BP in patients receiving PD.

Treatment of Hypertension

Adjustment of Dry Weight/Optimization of Dialysis

Dry Weight

Dry weight is defined as the lowest body weight at the end of dialysis at which the patient can remain normotensive without antihypertensive medication, despite fluid accumulation, until the

next dialysis treatment. Stated differently, dry weight is the lowest weight a patient can tolerate without having symptoms of hypotension [62]. When a patient is at their dry weight, it is thought that they are less likely to have hypertension from volume overload.

However, determination of dry weight is difficult. Typically, dry weight is often achieved by trial and error; dry weight is thought to have been achieved when the patient develops signs of hypotension, such as drop in BP, cramping, yawning, headache, abdominal pain, etc. Common clinical methods to assess dry weight include monitoring weight pre- and post-dialysis, examination for the presence of edema, jugular venous distension or crackles on lung auscultation, or detection of hypotension in those with intravascular volume depletion. Clinical assessment can be inaccurate in states of subtler volume excess/depletion. Markers such as change in weight are further confounded in a growing child. Due to the limitations of relying on clinical assessment to determine dry weight, different techniques have been studied to aid in the assessment and achievement of dry weight.

Biochemical markers of volume status include atrial natriuretic peptide, cyclic guanidine monophosphate, brain natriuretic peptide, and troponin T [31, 139]. Most of the biomarkers can be affected by various factors other than volume status, thus limiting their clinical utility. Ultrasound measurement of the inferior vena cava diameter and its collapsibility is a simple and noninvasive way to assess intravascular volume status. Challenges that prevent the broad use of this parameter include interoperator error and patient variability in diameter measurements [31, 62]. Bioelectrical impedance analysis, or bioimpedance, is a method that determines the electrical opposition (impedance) to the flow of an electric current through the body. Bioimpedance can be applied to both HD and PD patients [28]. In adults, bioimpedance analysis has shown that extracellular volume change correlated with the ultrafiltration volume [81]. Other studies in adults using bioimpedance have demonstrated the underestimation of ultrafiltration volumes by 30% based on ECF volumes pre and post HD [62].

Pediatric studies of bioimpedance have demonstrated the utility of this technique, showing good correlation of measured blood volume change to percentage body weight change [100], and serial clinical use to assess dry weight at a single center led to improvement in left ventricular mass index and reduction in LVH [103]. In one recent study, the assessment of dry weight by bioimpedance was compared to clinical assessment in 30 children with stage 5 CKD, 20 of whom were on dialysis (10 HD, 10 PD). Assessment by bioimpedance was felt to more accurately determine hydration status, and correlated with biomarkers of volume overload such as plasma N-terminal pro-B natriuretic peptide and cardiovascular markers such as LVH [32]. The technology does have limitations. Temperature and ion changes that occur during dialysis may effect electrical impedance, as may patient factors such as electrolyte imbalance, hematocrit values, and protein levels [62].

Relative plasma volume monitoring during HD provides insight into the relative rate of ultrafiltration compared to the rate of refilling of plasma volume from the extravascular space. Photo-optical technology measures hematocrit or protein values. An increase in hematocrit or protein concentration is inversely proportional to the change in plasma volume. The use of this technology in adults has led to mixed results, with some reporting improvement in determining and achieving dry weight [111, 127] and some reporting improvement in casual BPs [27] and lower systolic BP as measured by 44 h ABPM [122]. Several pediatric studies have studied the use of plasma volume monitoring [20, 63, 90, 105]. In a multicenter prospective study of 20 pediatric patients, plasma volume monitoring was used to target the 100% ultrafiltration goal, with 50% to be removed in the first hour (max plasma volume change of 8–12% per hour) and the remaining 50% over the subsequent time (max plasma volume change of 5% per hour). They demonstrated a decrease in dialysis-associated morbidity, reduction in antihypertensive medication usage, and improved ABPM profiles. There was no

change in weight or left ventricular mass index at the end of the 6-month study, which the authors attributed to somatic growth in their young patients [105]. In 9 pediatric HD patients, systematic use of plasma volume monitoring to challenge dry weight and reduce antihypertensive use resulted in mean dry weight reduction, decreased BP measured both casually and by ABPM, and a reduction in antihypertensive burden [20].

Lung ultrasound has also been used to assess volume status. In the setting of extracellular fluid excess, hydrostatic forces will create a transudative effusion that leads to a decrease in the acoustic mismatch between lung and surrounding tissues. This creates a partial reflection and discrete hyper-echogenic reverberation of the ultrasound beam arising from the pleural line known as "B-lines" [11]. In adults, lung ultrasound findings including B-lines correlated with other markers of fluid overload including: clinical parameters [98, 131], B type natriuretic peptide, inferior vena cava diameter, and bioimpedance [18, 134]. In a single-center study of 96 patients on HD where lung ultrasound, bioimpedance, and echocardiography were prospectively studied for their ability to predict mortality, predialysis B-line score and left ventricular mass index were significantly associated with survival [123]. A recent pediatric study that included patients with ESRD treated with both modalities of dialysis and patients with acute kidney injury demonstrated a significant correlation between B-lines and volume excess as determined by target weight [11]. Among 13 children on dialysis in which objective parameters of volume excess were studied including lung ultrasound, bioimpedance, clinical parameters, and inferior vena cava parameter, only lung ultrasound correlated significantly with volume overload [10, 11].

Clearly, each of these approaches to determining dry weight has advantages and disadvantages, many of which will depend on local expertise as well as the availability of each technique. While the utilization of a combination of techniques may be ideal [112], each dialysis center should follow a standardized approach that allows for longitudinal evaluation of each patient.

Optimization of Dialysis

For both HD and PD, optimization of dialysis with respect to control of BP means utilizing different approaches to reduce volume overload during the dialysis treatment. Just as important is avoidance of intradialytic hypotension, which may be associated with myocardial stunning [57, 58, 88], and prevention of excessive interdialytic weight gain.

Adjusting the duration of therapy and/or the concentration of dialysate sodium is the main strategy used in HD to improve fluid removal. Currently, there is increasing evidence that reduction in dialysate sodium at or slightly below the patient's pre-dialysis serum concentration leads to reduction in thirst, interdialytic weight gain, and hypertension [17, 97, 129]. A small pediatric study consisting of 5 patients demonstrated a reduction in interdialytic weight gain and predialysis BP when dialysate sodium was reduced from 140 to 138 mEq/L [85]. A systematic review of 23 studies comparing high vs. low dialysate sodium concentration in chronic adult HD patients demonstrated that while BP was unaffected by the concentration of dialysate sodium, there was an increase in interdialytic weight gain in the higher dialysate sodium group and increased intradialytic hypotension in the low dialysate sodium group [17]. It is, in turn, important not to reduce the dialysate sodium too far. Mortality was assessed in 3 observational studies and demonstrated reduced mortality overall with higher dialysate sodium concentrations, but was confounded by patients' serum sodium concentrations, which demonstrated an inverse relationship between serum sodium concentration and death [17, 53, 54]. Specifically, Hecking et al. demonstrated lower serum sodium (<137 mEq/L) was associated with the highest risk of death, while dialyzing against a bath >140 mEq/L was protective [54].

Increasing dialysis treatment time is another factor associated with improved outcomes. Adult and pediatric studies have demonstrated improved control of BP, faster achievement of dry weight, and reduction in medication burden including antihypertensive medications with increased

dialysis time in both adults [40, 42, 128] and children [45, 56]. Increasing time also allows for a reduction in the ultrafiltration rate, which reduces the risk of myocardial stunning [88]. The current recommendation in adult HD patients is to reduce the ultrafiltration rate to <13 ml/kg/h, although even rates <10 ml/kg/h have been associated with increased morbidity and mortality [95, 116].

It should be emphasized that the phenomenon of myocardial stunning is not limited to adult dialysis patients. Work by Hothi and colleagues has shown that excessive intradialytic BP reduction was associated with myocardial stunning in pediatric HD patients [57, 58]. However, no "ideal" rate of ultrafiltration has been determined for pediatric HD patients. In the absence of data, many pediatric dialysis centers, at least in the United States, have been following the recommendation for adults mentioned above. Further discussion on avoidance of intradialytic hypotension can be found in a recent review by Raina et al., in which the lack of evidence-based approaches to this issue in pediatric HD patients is emphasized [107].

Optimization of sodium and water removal in PD can be achieved by managing osmotic potential (dialysate dextrose concentration, dwell time) and surface area recruitment and hydrostatic pressure (fill volume). The 3 pore model theory of peritoneal transport [109] describes 3 various sized pores of the peritoneal endothelium through which transport of water and solutes occurs. The smallest pores are the aquaporin channels, via which only water can be transported; these are activated by intraperitoneal hyperosmolarity created by dextrose-based solutions. There are also small pores that allow transport of both small solutes and water, and large pores that transport macromolecules. Water removal is optimized by short dwell times to maintain the higher osmotic potential of the dialysate, and lower fill volumes to reduce hydrostatic pressure that would counteract the osmotic potential. In contrast, solute removal (including sodium) is optimized by increased fill volumes that increase the recruitment of peritoneal surface area, and longer dwell time [36].

The drawback of using higher dialysate dextrose concentrations is the production of glucose degradation products that are toxic to the peritoneum [33]. This can be avoided in part by the use of icodextrin, a maltodextrin polymer produced by the metabolism of cornstarch. Icodextrin is absorbed from the peritoneal space much more slowly via the lymphatics and thus maintains the osmotic potential longer. It further exerts its effect via colloid osmosis, and therefore exerts its effects via the small pores and not the aquaporin channels, thus leading to less sodium sieving [39]. However, icodextrin is only meant to be used for the long dwell, as metabolism over time increases its colloid potential. Studies in adults have demonstrated equivalent ultrafiltration of icodextrin over 10 h and superior ultrafiltration beyond that time as compared to 4.25% dextrose solutions [25, 96]. A recent retrospective study of 50 pediatric patients who used icodextrin for a long daytime dwell demonstrated improved ultrafiltration overall and improved ultrafiltration with increasing patient age [113].

Finally, adapted automated PD, where the PD cycler alternates between short dwells with low fill volumes to enhance ultrafiltration and long dwells with large fill volumes to enhance solute clearance [9, 34, 35], can be used to improve BP control. In a prospective, crossover study in adults, adapted PD resulted in increased sodium and water removal and improved BPs as compared to conventional PD [35]. To date, no studies of this approach to PD in children have been reported.

Dietary Intervention: Fluid and Salt Intake

The observation that dietary sodium restriction and ultrafiltration led to improved BP management was noted by Belding Scribner when treating the first patient to receive chronic dialysis, who suffered from malignant hypertension [118]. Controlling dietary sodium intake facilitates achievement of dry weight [70], and is associated with decreased thirst, lower interdialytic weight

gain, improved BP control, lower LVMI, and decreased mortality in adults [67, 84, 86]. It is important to recognize that fluid restriction will not be possible if sodium intake is not reduced, as increased sodium intake will inexorably increase thirst, which leads to greater interdialytic weight gain [76]. While most studies of sodium intake and dialysis have focused on HD patients, a limited number of studies in in adults undergoing PD have shown that a reduction in sodium intake reduces fluid overload and reduces BP in this population as well [60].

Restriction of sodium intake, although ideal, is difficult to achieve given the high sodium intake of many children, including those with CKD. Despite guidelines recommending limiting daily sodium intake in children with kidney disease and hypertension to between 1500 mg and 2300 mg [65], data from a registry of children with CKD stage 2–4 demonstrated that sodium intake was greater than 3000 mg daily, with 25% of adolescents consuming more than 5000 mg of sodium per day [59]. A study examining sodium intake among school-aged children found that the top ten food categories that contributed to 48% of the salt intake are from processed foods, with the exception of cow's milk, which naturally has sodium [106]. Similar studies in American adults demonstrated that 70.9% of the salt consumed was sodium added to food outside the home [50]. Renal dieticians are key members of the treatment team because of their role educating the patient and their family on low sodium food with high nutritional content. The social worker can also play a role by providing better access to these often more expensive foods.

Pharmacological Treatment

All classes of antihypertensive medications are useful for BP control in the dialysis population, although the choice of agent needs to be individualized [43]. Dosing of many agents may need to be adjusted in dialysis patients, as summarized in Table 31.2. However, it should be noted that antihypertensive medications are ineffective when volume excess is the etiology of hypertension, and studies have demonstrated that reliance on antihypertensive medications instead of correction of volume overload leads to persistent hypertension [5].

Antihypertensive medication use in dialysis patients has been shown to not only reduce BP, but to also improve intermediate markers of cardiovascular disease. In a recent randomized, controlled trial in hypertensive chronic adult HD patients with LVH, lisinopril or atenolol given three times a week after dialysis lowered BP on 44 h ABPM and led to regression of LVH. However, when monthly home BPs were assessed, the lisinopril group had higher BPs despite a greater number of antihypertensive agents and reduction in dry weight; this and other events in the study suggested that atenolol was overall superior to lisinopril [8].

In our experience in children, beta-adrenergic blockers and agents affecting the RAAS are the most effective classes of antihypertensive agents once volume overload has been corrected. Long-acting vasodilating medications (i.e., amlodipine, minoxidil) are best avoided as they may impair the ability to correct volume overload with fluid removal during dialysis. Clonidine may also have a role given the activation of the sympathetic nervous system in ESRD [117].

There has been an increased interest in the use of diuretics in dialysis patients who still have residual renal function [73, 132]. In patients with preserved residual renal function, loop diuretics may enhance urine output and limit interdialytic weight gain [75]. A recent study comparing patients who continued loop diuretics after HD initiation to those who did not showed that those who continued diuretics had lower rates of hospitalization and intradialytic hypotension, as well as lower interdialytic weight gain over the first year of dialysis, but there was no difference in mortality [120]. In PD, one small study showed that the use of oral loop diuretics led to better volume control in the first year after dialysis initiation [89]. There have also been studies showing that the use of potassium-sparing diuretics in PD patients is useful for correction of hypokalemia [41]. There is one study of pediatric PD patients in which diuretic

Table 31.2 Antihypertensive medication dosing in children on dialysis[a]

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
Angiotensin receptor blockers	Candesartan	*1–6 years:* 0.2 mg/kg/day up to 0.4 mg/kg/day *6–17 years: <50 kg*: 4–16 mg QD *>50 kg:* 8–32 mg QD	K (L)	No known recommended adjustment but clearance reduced if GFR <30 mL/min; not removed by dialysis; give 50% of usual dose; consider dosing after HD session
	Losartan	0.75 mg/kg/day to 1.4 mg/kg/day; maximum 100 mg daily	K (L)	Not recommended if GFR <30 mL/min; not removed by dialysis
	Olmesartan	*20–35 kg:* 10–20 mg QD ≥*35 kg:* 20–40 mg QD	K (L)	Clearance reduced if GFR <20 mL/min; do not exceed 20 mg daily in such patients; not removed by dialysis
	Valsartan	*<6 years:* 5–10 mg/day up to 80 mg daily *6–17 years:* 1.3 mg/kg/day up to 2.7 mg/kg/day; maximum 160 mg daily	K (L)	Clearance reduced if GFR <30 mL/min; not removed by dialysis
Angiotensin converting enzyme inhibitors	Benazepril	0.2 mg/kg/day up to 0.6 mg/kg/day; maximum 40 mg daily	K (L)	No pediatric data. 20–50% removed by dialysis; Give 25–50% of usual dose; consider dosing after HD session
	Captopril	0.3–0.5 mg/kg/dose TID up to 0.6 mg/kg/day; maximum 450 mg daily	K	No pediatric data. 50% removed by dialysis. Give 25% of usual dose in HD patients; consider dosing after HD session. Give 50% QD of usual daily dose in PD.
	Enalapril[†]	0.08 mg/kg/day up to 0.6 mg/kg/day; maximum 40 mg daily	K (L)	Not studied in children with GFR <30 mL/min. 50% removed by dialysis. Give 50% of usual dose; consider dosing after HD session
	Fosinopril	0.1 mg/kg/day (up to 10 mg/day) up to 0.6 mg/kg/day; maximum 40 mg/day	K (L)	No known adjustments; not removed by dialysis
	Lisinopril[†]	0.07 mg/kg/day (up to 5 mg/day) up to 0.6 mg/kg/day; maximum 40 mg daily	K	Not studied in children with GFR <30 mL/min. 50% removed by dialysis. Give 25% of usual dose; consider dosing after HD session
	Quinapril	5–10 mg/day up to 80 mg daily	K (L)	No pediatric data. For adults with GFR 10–30 mL/min, do not exceed 2.5 mg/day; no data for GFR <10 mL/min
	Ramipril	1.6 mg/M^2/day QD up to 6 mg/M^2/day; maximum 20 mg daily	K (L)	No pediatric data. In adults with GFR <40 mL/min, give 25% of usual dose; 20% removal by dialysis. Consider dosing after HD session
α- and β-adrenergic antagonists	Carvedilol	0.1 mg/kg/dose BID (up to 6.25 mg) up to 0.5 mg/kg/dose; maximum 25 mg BID	L (K)	No adjustment needed; not removed by dialysis

Table 31.2 (continued)

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
	Labetalol	2–3 mg/kg/day BID up to 10–12 mg/kg/day; maximum 1200 mg daily	K (L)	No adjustment needed; not removed by dialysis
β-adrenergic antagonists	Atenolol	0.5–1 mg/kg/day up to 100 mg daily	K (L)	If GFR 15–35 mL/min, do not exceed 50 mg daily (reduction to 50% of usual dose); if GFR <15 mL/min, do not exceed 25 mg daily (reduction to 25% of usual dose). 50% removed by dialysis; consider dosing after HD session.
	Metoprolol	Immediate release: 1–2 mg/kg/day BID up to 6 mg/kg/day; maximum 200 mg daily Extended release: 1 mg/kg/day up to 2 mg/kg/day; maximum 200 mg daily	K (L)	No adjustment needed; not removed by dialysis
	Propranolol[†]	1 mg/kg/day TID-QID up to 8 mg/kg/day; maximum 640 mg daily	K	No adjustment recommended but can accumulate in renal impairment; not removed by dialysis
Calcium channel blockers	Amlodipine	0.06 mg/kg/day up to 0.6 mg/kg/day; maximum 10 mg daily	L	No adjustment needed; not removed by dialysis
	Diltiazem	1.5–2 mg/kg/day up to 6 mg/kg/day; maximum 360 mg daily	L (K)	No adjustment needed; not removed by dialysis
	Felodipine	2.5–10 mg/day; maximum 10 mg daily	L	No adjustment needed; not removed by dialysis
	Isradipine	0.05–0.15 mg/kg/dose TID/QID up to 0.8 mg/kg/day; maximum 20 mg daily	L	No adjustment needed; not removed by dialysis
	Extended-release nifedipine	0.25–0.5 mg/kg/day up to 3 mg/kg/day; maximum 120 mg daily	L	No adjustment needed; not removed by dialysis
Central α-agonist	Clonidine	5–20 mcg/kg/day BID up to 15 mcg/kg/day; maximum 0.9 mg daily	K (L)	No known adjustments; 5% removed on HD
Peripheral α-blockers	Prazosin	0.05–0.1 mg/kg/day TID up to 0.5 mg/kg/day; maximum 20 mg daily	L	No known adjustments; not removed by dialysis

(continued)

Table 31.2 (continued)

Class	Drug	Usual pediatric dosing range	Excretion	Modifications in dialysis
	Doxazosin	1 mg QD up to 4 mg daily; maximum adult dose is 16 mg daily	L	No known adjustments; not removed by dialysis
	Terazosin	1 mg QD up to 20 mg daily	L	No known adjustments; 10% removed on HD
Vasodilators	Hydralazine	0.25 mg/kg/dose TID up to 7.5 mg/kg/day; maximum 200 mg daily	L	No known adjustments; 25–40% removed by dialysis. Consider dosing after HD session.
	Minoxidil	0.1–0.2 mg/kg/day QD-BID up to 1 mg/kg/day; maximum 50 mg daily	L	No known adjustments
Diuretics	Chlorthalidone	0.3 mg/kg/day up to 2 mg/kg/day; maximum 50 mg daily	K (L)	Avoid in oligoanuria or with GFR <10 mL/min
	Furosemide	0.5–2 mg/kg/dose QD-QID up to 6 mg/kg/day; maximum 600 mg daily	K (L)	Avoid in oligoanuria; not removed by dialysis

[a]Recommendations represent the authors' opinions although every effort has been made to confirm by consulting appropriate references. Manufacturers' prescribing information is frequently updated and should be consulted whenever possible

[†]Commercially prepared suspension formulation available

Abbreviations used in table: *BID* twice daily, *GFR* glomerular filtration rate, *HD* hemodialysis, *K* Kidney, *kg* kilogram, *L* Liver, *mcg* microgram, *mg* milligram, *PD* peritoneal dialysis, *QD* once daily, *QID* four times daily, *TID* three times daily

use was retrospectively studied [48]. Children who received diuretics from the initiation of PD were 80% less likely to develop oligoanuria compared to those who did not receive diuretics; other outcomes were not examined.

Native Nephrectomy

Native kidney nephrectomy is typically considered the last resort in the treatment of hypertension in dialysis patients, reserved for those who remain hypertensive despite the measures discussed above (Fig. 31.2). The procedure has been shown to be effective in treating hypertension in children with ESRD [14], and newer surgical techniques may allow quick resumption of dialysis in children on PD who require this procedure [29].

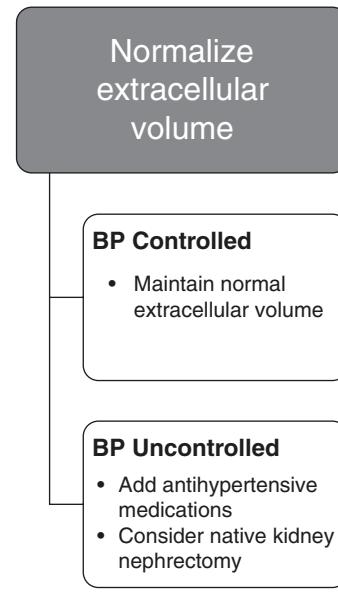

Fig. 31.2 Approach to management of hypertension in pediatric dialysis patients

There are two possible explanations for how nephrectomy can improve hypertension in patients on dialysis. As discussed earlier, the RAAS is a well-established cause of hypertension in CKD and in ESRD, and this may be related to the presence of native, diseased kidneys. Among 51 HD patients, plasma renin activity was higher among patients who had uncontrolled hypertension as compared to those whose BP was controlled by ultrafiltration and sodium restriction. Among the 18 who had uncontrolled hypertension, 17 had significant improvement in BPs after native nephrectomies [136]. In another study, treating patients with CKD with angiotensin converting enzyme inhibitors (ACEi) resulted in increased angiotensin 1–7 and decreased angiotensin II, whereas ESRD patients with ACEi therapy did not have a decrease in angiotensin II levels [121]. This may help explain why refractory hypertensive ESRD patients may benefit from native nephrectomies.

ESRD patients are also known to have increased sympathetic nervous system activity [26, 117]. The origin of the increased sympathetic nervous system activity may also be from the diseased native kidney. This was determined in an elegant study in transplant recipients who had continued activation of the sympathetic nervous system until they underwent native nephrectomies [52].

Summary

Hypertension is common among both PD and HD patients. It is an important modifiable condition, and one of the most important contributors to excess morbidity and mortality in this population. Accurate diagnosis with appropriate BP measurement, especially the use of ambulatory BP monitoring, is crucial in order to achieve optimal BP control. Management begins with the achievement of dry weight and avoidance of excessive interdialytic weight gain. When hypertension persists despite the achievement of euvolemia, antihypertensive medications may be required, and in some patients, native nephrectomies.

References

1. Agarwal R, Brim NJ, Mahenthiran J, Andersen MJ, Saha C. Out-of-hemodialysis-unit blood pressure is a superior determinant of left ventricular hypertrophy. Hypertension. 2006a;47(1):62–8.
2. Agarwal R, Peixoto AJ, Santos SF, Zoccali C. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol. 2006b;1(3):389–98.
3. Agarwal R, Saha C. Dialysis dose and the diagnosis of hypertension in hemodialysis patients. Blood Press Monit. 2007;12(5):281–7.
4. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. Hypertension. 2009;53(3):500–7.
5. Agarwal R, Weir MR. Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(7):1255–60.
6. Agarwal R, Sinha AD, Light RP. Toward a definition of masked hypertension and white-coat hypertension among hemodialysis patients. Clin J Am Soc Nephrol. 2011;6(8):2003–8.
7. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. J Am Soc Nephrol. 2014a;25(8):1630–46.
8. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant. 2014b;29(3):672–81.
9. Akonur A, Guest S, Sloand JA, Leypoldt JK. Automated peritoneal dialysis prescriptions for enhancing sodium and fluid removal: a predictive analysis of optimized, patient-specific dwell times for the day period. Perit Dial Int. 2013;33(6):646–54.
10. Allinovi M, Saleem MA, Burgess O, Armstrong C, Hayes W. Finding covert fluid: methods for detecting volume overload in children on dialysis. Pediatr Nephrol. 2016;31(12):2327–35.
11. Allinovi M, Saleem M, Romagnani P, Nazerian P, Hayes W. Lung ultrasound: a novel technique for detecting fluid overload in children on dialysis. Nephrol Dial Transplant. 2017;32(3):541–7.
12. Anderstam B, Katzarski K, Bergstrîm J. Serum levels of NO, NG-dimethyl-L-Arginine, a potential endogenous nitic oxide inhibitor in dialysis patients. J Am Soc Nephrol. 1997;8:1437–42.
13. Atas N, Erten Y, Okyay GU, Inal S, Topal S, Onec K, et al. Left ventricular hypertrophy and blood pressure control in automated and continuous ambulatory peritoneal dialysis patients. Ther Apher Dial. 2014;18(3):297–304.
14. Baez-Trinidad LG, Lendvay TS, Broecker BH, Smith EA, Warshaw BL, Hymes L, et al. Efficacy of nephrectomy for the treatment of nephrogenic

hypertension in a pediatric population. J Urol. 2003;170(4 Pt 2):1655–7. discussion 8
15. Bakkaloglu SA, Borzych D, Soo Ha I, Serdaroglu E, Buscher R, Salas P, et al. Cardiac geometry in children receiving chronic peritoneal dialysis: findings from the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Clin J Am Soc Nephrol. 2011;6(8):1926–33.
16. Bakris GL, Burkart JM, Weinhandl ED, McCullough PA, Kraus MA. Intensive hemodialysis, blood pressure, and antihypertensive medication use. Am J Kidney Dis. 2016;68(5S1):S15–23.
17. Basile C, Pisano A, Lisi P, Rossi L, Lomonte C, Bolignano D. High versus low dialysate sodium concentration in chronic haemodialysis patients: a systematic review of 23 studies. Nephrol Dial Transplant. 2016;31(4):548–63.
18. Basso F, Milan Manani S, Cruz DN, Teixeira C, Brendolan A, Nalesso F, et al. Comparison and reproducibility of techniques for fluid status assessment in chronic hemodialysis patients. Cardiorenal Med. 2013;3(2):104–12.
19. Bircan Z, Duzova A, Cakar N, Bayazit AK, Elhan A, Tutar E, et al. Predictors of left ventricular hypertrophy in children on chronic peritoneal dialysis. Pediatr Nephrol. 2010;25(7):1311–8.
20. Candan C, Sever L, Civilibal M, Caliskan S, Arisoy N. Blood volume monitoring to adjust dry weight in hypertensive pediatric hemodialysis patients. Pediatr Nephrol. 2009;24(3):581–7.
21. Chaudhuri A, Sutherland SM, Begin B, Salsbery K, McCabe L, Potter D, et al. Role of twenty-four-hour ambulatory blood pressure monitoring in children on dialysis. Clin J Am Soc Nephrol. 2011;6(4):870–6.
22. Chavers BM, Solid CA, Daniels FX, Chen SC, Collins AJ, Frankenfield DL, et al. Hypertension in pediatric long-term hemodialysis patients in the United States. Clin J Am Soc Nephrol. 2009;4(8):1363–9.
23. Chesnaye NC, Schaefer F, Groothoff JW, Bonthuis M, Reusz G, Heaf JG, et al. Mortality risk in European children with end-stage renal disease on dialysis. Kidney Int. 2016;89(6):1355–62.
24. Civilibal M, Caliskan S, Oflaz H, Sever L, Candan C, Canpolat N, et al. Traditional and 'new' cardiovascular risk markers and factors in pediatric dialysis patients. Pediatr Nephrol. 2007;22:1021–9.
25. Collins A, Mujais S. Advancing fluid management in peritoneal dialysis. Kidney Int Suppl. 2002;81:S1–2.
26. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327(27):1912–8.
27. Dasselaar JJ, Huisman RM, de Jong PE, Burgerhof JG, Franssen CF. Effects of relative blood volume-controlled hemodialysis on blood pressure and volume status in hypertensive patients. ASAIO J. 2007;53(3):357–64.
28. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int. 2014;86(3):489–96.
29. De Carli C, Guerra LA. Simultaneous bilateral laparoscopic nephrectomy in a child with peritoneal catheter dialysis using a 4-port trans-abdominal technique. Can Urol Assoc J. 2015;9(1–2):59–61.
30. Desir GV. Renalase deficiency in chronic kidney disease, and its contribution to hypertension and cardiovascular disease. Curr Opin Nephrol Hypertens. 2008;17(2):181–5.
31. Dou Y, Zhu F, Kotanko P. Assessment of extracellular fluid volume and fluid status in hemodialysis patients: current status and technical advances. Semin Dial. 2012;25(4):377–87.
32. Eng CSY, Bhowruth D, Mayes M, Stronach L, Blaauw M, Barber A, et al. Assessing the hydration status of children with chronic kidney disease and on dialysis: a comparison of techniques. Nephrol Dial Transplant. 2018;33(5):847–55.
33. Erixon M, Wieslander A, Linden T, Carlsson O, Forsback G, Svensson E, et al. How to avoid glucose degradation products in peritoneal dialysis fluids. Perit Dial Int. 2006;26(4):490–7.
34. Fischbach M, Issad B, Dubois V, Taamma R. The beneficial influence on the effectiveness of automated peritoneal dialysis of varying the dwell time (short/long) and fill volume (small/large): a randomized controlled trial. Perit Dial Int. 2011;31(4):450–8.
35. Fischbach M, Zaloszyc A, Schaefer B, Schmitt C. Adapted automated peritoneal dialysis. Adv Perit Dial. 2014;30:94–7.
36. Fischbach M, Schmitt CP, Shroff R, Zaloszyc A, Warady BA. Increasing sodium removal on peritoneal dialysis: applying dialysis mechanics to the peritoneal dialysis prescription. Kidney Int. 2016;89(4):761–6.
37. Flynn JT, Urbina EM. Pediatric ambulatory blood pressure monitoring: indications and interpretations. J Clin Hypertens (Greenwich). 2012;14(6):372–82.
38. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.
39. Frampton JE, Plosker GL. Icodextrin: a review of its use in peritoneal dialysis. Drugs. 2003;63(19):2079–105.
40. Frequent Hemodialysis Network (FHN) Trial Group, Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363(24):2287–300.
41. Fulop T, Zsom L, Rodriguez B, Afshan S, Davidson JV, Szarvas T, et al. Clinical utility of potassium-sparing diuretics to maintain normal serum potassium in peritoneal dialysis patients. Perit Dial Int. 2017;37(1):63–9.
42. Georgianos PI, Sarafidis PA, Sinha AD, Agarwal R. Adverse effects of conventional thrice-weekly

hemodialysis: is it time to avoid 3-day interdialytic intervals? Am J Nephrol. 2015;41(4–5):400–8.
43. Georgianos PI, Agarwal R. Pharmacotherapy of hypertension in chronic dialysis patients. Clin J Am Soc Nephrol. 2016;11(11):2062–75.
44. Goldstein SL, Smith CM, Currier H. Noninvasive interventions to decrease hospitalization and associated costs for pediatric patients receiving hemodialysis. J Am Soc Nephrol. 2003;14(8):2127–31.
45. Goldstein SL, Silverstein DM, Leung JC, Feig DI, Soletsky B, Knight C, et al. Frequent hemodialysis with NxStage system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008;23(1):129–35.
46. Groothoff JW, Gruppen MP, Offringa M, De Groot E, Stok W, Bos WJ, et al. Increased arterial stiffness in young adults with end-stage renal disease since childhood. J Am Soc Nephrol. 2002a;13:2953–61.
47. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, et al. Mortality and cause of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002b;61:621–9.
48. Ha IS, Yap HK, Munarriz RL, Zambrano PH, Flynn JT, Bilge I, et al. Risk factors for loss of residual renal function in children treated with chronic peritoneal dialysis. Kidney Int. 2015;88(3):605–13.
49. Halbach SM, Martz K, Mattoo T, Flynn J. Predictors of blood pressure and its control in pediatric patients receiving dialysis. J Pediatr. 2012;160(4):621–5. e1
50. Harnack LJ, Cogswell ME, Shikany JM, Gardner CD, Gillespie C, Loria CM, et al. Sources of sodium in US adults from 3 geographic regions. Circulation. 2017;135(19):1775–83.
51. Haskin O, Wong CJ, McCabe L, Begin B, Sutherland SM, Chaudhuri A. 44-h ambulatory blood pressure monitoring: revealing the true burden of hypertension in pediatric hemodialysis patients. Pediatr Nephrol. 2015;30(4):653–60.
52. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, et al. Sympathetic nerve activity in end-stage renal disease. Circulation. 2002;106(15):1974–9.
53. Hecking M, Karaboyas A, Saran R, Sen A, Horl WH, Pisoni RL, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2012a;59(2):238–48.
54. Hecking M, Karaboyas A, Saran R, Sen A, Inaba M, Rayner H, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. Clin J Am Soc Nephrol. 2012b;7(1):92–100.
55. Heerspink HJ, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2009;373(9668):1009–15.
56. Hoppe A, von Puttkamer C, Linke U, Kahler C, Booss M, Braunauer-Kolberg R, et al. A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr. 2011;158(1):95–9, e1.
57. Hothi DK, Rees L, Marek J, Burton J, McIntyre CW. Pediatric myocardial stunning underscores the cardiac toxicity of conventional hemodialysis treatments. Clin J Am Soc Nephrol. 2009;4(4):790–7.
58. Hothi DK, Rees L, McIntyre CW, Marek J. Hemodialysis-induced acute myocardial dyssynchronous impairment in children. Nephron Clin Pract. 2013;123(1–2):83–92.
59. Hui WF, Betoko A, Savant JD, Abraham AG, Greenbaum LA, Warady B, et al. Assessment of dietary intake of children with chronic kidney disease. Pediatr Nephrol. 2017;32(3):485–94.
60. Inal S, Erten Y, Tek N, Ulusal Okyay G, Onec K, Akbulut G, et al. The effect of dietary salt restriction on hypertension in peritoneal dialysis patients. Turk J Med Sci. 2014;44(5):814–9.
61. Inrig JK, Patel UD, Gillespie BS, Hasselblad V, Himmelfarb J, Reddan D, et al. Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. Am J Kidney Dis. 2007;50(1):108–18, e1–4.
62. Jaeger JQ, Mehta RL. Assessment of dry weight in hemodialysis: an overview. J Am Soc Nephrol. 1999;10(2):392–403.
63. Jain SR, Smith L, Brewer ED, Goldstein SL. Noninvasive intravascular monitoring in the pediatric hemodialysis population. Pediatr Nephrol. 2001;16(1):15–8.
64. Jourde-Chiche N, Dou L, Cerini C, Dignat-George F, Brunet P. Vascular incompetence in dialysis patients--protein-bound uremic toxins and endothelial dysfunction. Semin Dial. 2011;24(3):327–37.
65. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43:S1–S290.
66. Katsoufis CP, Seeherunvong W, Sasaki N, Abitbol CL, Chandar J, Freundlich M, et al. Forty-four-hour interdialytic ambulatory blood pressure monitoring and cardiovascular risk in pediatric hemodialysis patients. Clin Kidney J. 2014;7(1):33–9.
67. Kayikcioglu M, Tumuklu M, Ozkahya M, Ozdogan O, Asci G, Duman S, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. Nephrol Dial Transplant. 2009;24(3):956–62.
68. Kis E, Cseprekal O, Horvath Z, Katona G, Fekete BC, Hrapka E, et al. Pulse wave velocity in end-stage renal disease: influence of age and body dimensions. Pediatr Res. 2008;63(1):95–8.
69. Komatsu Y, Ito K. Erythropoietin associated hypertension among pediatric dialysis patients. Adv Perit Dial. 1992;8:448–52.
70. Kooman JP, van der Sande F, Leunissen K, Locatelli F. Sodium balance in hemodialysis therapy. Semin Dial. 2003;16(5):351–5.
71. Kornerup HJ. Hypertension in end-stage renal disease. The relationship between blood pressure,

plasma renin, plasma renin substrate and exchangeable sodium in chronic hemodialysis patients. Acta Med Scand. 1976;200(4):257–61.
72. Kramer AM, van Stralen KJ, Jager KJ, Schaefer F, Verrina E, Seeman T, et al. Demographics of blood pressure and hypertension in children on renal replacement therapy in Europe. Kidney Int. 2011;80:1092–8.
73. Kumra R, Bargman JM. A review of diuretic use in dialysis patients. Adv Perit Dial. 2014;30:115–9.
74. Lazar AE, Smith MC, Rahman M. Blood pressure measurement in hemodialysis patients. Semin Dial. 2004;17(4):250–4.
75. Lemes HP, Araujo S, Nascimento D, Cunha D, Garcia C, Queiroz V, et al. Use of small doses of furosemide in chronic kidney disease patients with residual renal function undergoing hemodialysis. Clin Exp Nephrol. 2011;15(4):554–9.
76. Lindley EJ. Reducing sodium intake in hemodialysis patients. Semin Dial. 2009;22(3):260–3.
77. Lingens N, Soergel M, Loirat C, Busch C, Lemmer B, SchÑrer K. Ambulatory blood pressure monitoring in paediatric patients treated by regular hemodialysis and peritoneal dialysis. Pediatr Nephrol. 1995;9:167–72.
78. Litwin M, Wühl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol. 2005;16:1494–500.
79. Liu M, Takahashi H, Morita Y, Maruyama S, Mizuno M, Yuzawa Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. Nephrol Dial Transplant. 2003;18:563–9.
80. London GM, Marchais SJ, Guerin AP. Arterial stiffness and function in end-stage renal disease. Adv Chronic Kidney Dis. 2004;11(2):202–9.
81. Lukaski HC, Bolonchuk WW. Estimation of body fluid volumes using tetrapolar bioelectrical impedance measurements. Aviat Space Environ Med. 1988;59(12):1163–9.
82. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34(10):1887–920.
83. Macumber I, Flynn JT. Ambulatory blood pressure monitoring in children and adolescents. In: White WB, editor. Blood pressure monitoring in cardiovascular medicine and therapeutics. 3rd ed. New York: Humana Press; 2016. p. 227–52.
84. Maduell F, Navarro V. Dietary salt intake and blood pressure control in haemodialysis patients. Nephrol Dial Transplant. 2000;15(12):2063.
85. Marsenic O, Anderson M, Couloures KG, Hong WS, Kevin Hall E, Dahl N. Effect of the decrease in dialysate sodium in pediatric patients on chronic hemodialysis. Hemodial Int. 2016;20(2):277–85.
86. Mc Causland FR, Waikar SS, Brunelli SM. Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. Kidney Int. 2012;82(2):204–11.
87. McDonald SP, Craig JC. Australian, New Zealand paediatric nephrology a. long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
88. McIntyre CW. Effects of hemodialysis on cardiac function. Kidney Int. 2009;76(4):371–5.
89. Medcalf JF, Harris KP, Walls J. Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. Kidney Int. 2001;59(3):1128–33.
90. Michael M, Brewer ED, Goldstein SL. Blood volume monitoring to achieve target weight in pediatric hemodialysis patients. Pediatr Nephrol. 2004;19(4):432–7.
91. Mitsnefes MM, Daniels SR, Schwartz SM, Khoury P, Strife CF. Changes in left ventricular mass in children and adolescents during chronic dialysis. Pediatr Nephrol. 2001;16(4):318–23.
92. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990–2010. JAMA. 2013;309(18):1921–9.
93. Moriya H, Ohtake T, Kobayashi S. Aortic stiffness, left ventricular hypertrophy and weekly averaged blood pressure (WAB) in patients on haemodialysis. Nephrol Dial Transplant. 2007;22(4):1198–204.
94. Moriya H, Oka M, Maesato K, Mano T, Ikee R, Ohtake T, et al. Weekly averaged blood pressure is more important than a single-point blood pressure measurement in the risk stratification of dialysis patients. Clin J Am Soc Nephrol. 2008;3(2):416–22.
95. Movilli E, Gaggia P, Zubani R, Camerini C, Vizzardi V, Parrinello G, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant. 2007;22(12):3547–52.
96. Mujais S, Vonesh E. Profiling of peritoneal ultrafiltration. Kidney Int Suppl. 2002;81:S17–22.
97. Munoz Mendoza J, Arramreddy R, Schiller B. Dialysate sodium: choosing the optimal hemodialysis bath. Am J Kidney Dis. 2015;66(4):710–20.
98. Noble VE, Murray AF, Capp R, Sylvia-Reardon MH, Steele DJR, Liteplo A. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. Chest. 2009;135(6):1433–9.
99. Oberleithner H, Riethmuller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. Proc Natl Acad Sci U S A. 2007;104(41):16281–6.
100. Oh G, Wong C, Begin B, Salsbery K, Sutherland S, Chaudhuri A. Whole-body single-frequency bioimpedance analysis in pediatric hemodialysis patients. Pediatr Nephrol. 2014;29(8):1417–23.

101. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation. 2002;106:100–5.
102. Ozcakar ZB, Yalcinkaya F, Tutar E, Cakar N, Ucar T, Elhan A, et al. Hypertension and left ventricular hypertrophy in pediatric peritoneal dialysis patients: ambulatory blood pressure monitoring and echocardiographic evaluation. Nephron Clin Pract. 2006;104(2):c101–6.
103. Paglialonga F, Ardissino G, Galli MA, Scarfia RV, Testa S, Edefonti A. Bioimpedance analysis and cardiovascular status in pediatric patients on chronic hemodialysis. Hemodial Int. 2012;16(Suppl 1):S20–5.
104. Parekh RS, Caroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. J Pediatr. 2002;141:191–7.
105. Patel HP, Goldstein SL, Mahan JD, Smith B, Fried CB, Currier H, et al. A standard, noninvasive monitoring of hematocrit algorithm improves blood pressure control in pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(2):252–7.
106. Quader ZS, Gillespie C, Sliwa SA, Ahuja JK, Burdg JP, Moshfegh A, et al. Sodium intake among US school-aged children: national health and nutrition examination survey, 2011–2012. J Acad Nutr Diet. 2017;117(1):39–47, e5.
107. Raina R, Lam S, Raheja H, Krishnappa V, Hothi D, Davenport A, et al. Pediatric intradialytic hypotension: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup. Pediatr Nephrol. 2019;34(5):925–41.
108. Raine AE, Bedford L, Simpson AW, Ashley CC, Brown R, Woodhead JS, et al. Hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure. Kidney Int. 1993;43:700–5.
109. Rippe B. A three-pore model of peritoneal transport. Perit Dial Int. 1993;13(Suppl 2):S35–8.
110. Robinson RF, Nahata MC, Sparks E, Daniels C, Batisky DL, Hayes JR, et al. Abnormal left ventricular mass and aortic distensibility in pediatric dialysis patients. Pediatr Nephrol. 2005;20(1):64–8.
111. Rodriguez HJ, Domenici R, Diroll A, Goykhman I. Assessment of dry weight by monitoring changes in blood volume during hemodialysis using CritLine. Kidney Int. 2005;68(2):854–61.
112. Ronco C, Kaushik M, Valle R, Aspromonte N, Peacock WF. Diagnosis and management of fluid overload in heart failure and cardio-renal syndrome: the "5B" approach. Semin Nephrol. 2012;32(1):129–41.
113. Rousso S, Banh TM, Ackerman S, Piva E, Licht C, Harvey EA. Impact of fill volume on ultrafiltration with icodextrin in children on chronic peritoneal dialysis. Pediatr Nephrol. 2016;31(10):1673–9.
114. Samuels J, Ng D, Flynn JT, Mitsnefes M, Poffenbarger T, Warady BA, et al. Ambulatory blood pressure patterns in children with chronic kidney disease. Hypertension. 2012;60(1):43–50.
115. Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. Clin J Am Soc Nephrol. 2008;3(2):522–30.
116. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int. 2006;69(7):1222–8.
117. Sata Y, Head GA, Denton K, May CN, Schlaich MP. Role of the sympathetic nervous system and its modulation in renal hypertension. Front Med (Lausanne). 2018;5:82.
118. Scribner BH, Buri R, Caner JE, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. Trans Am Soc Artif Intern Organs. 1960;6:114–22.
119. Shatat IF, Flynn JT. Hypertension in children with chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(4):378–84.
120. Sibbel S, Walker AG, Colson C, Tentori F, Brunelli SM, Flythe J. Association of continuation of loop diuretics at hemodialysis initiation with clinical outcomes. Clin J Am Soc Nephrol. 2019;14(1):95–102.
121. Simoes e Silva AC, Diniz JS, Pereira RM, Pinheiro SV, Santos RA. Circulating renin Angiotensin system in childhood chronic renal failure: marked increase of Angiotensin-(1-7) in end-stage renal disease. Pediatr Res. 2006;60(6):734–9.
122. Sinha AD, Light RP, Agarwal R. Relative plasma volume monitoring during hemodialysis AIDS the assessment of dry weight. Hypertension. 2010;55(2):305–11.
123. Siriopol D, Hogas S, Voroneanu L, Onofriescu M, Apetrii M, Oleniuc M, et al. Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters. Nephrol Dial Transplant. 2013;28(11):2851–9.
124. Song JH, Lee SW, Suh CK, Kim MJ. Time-averaged concentration of dialysate sodium relates with sodium load and interdialytic weight gain during sodium-profiling hemodialysis. Am J Kidney Dis. 2002;40(2):291–301.
125. Sorof JM, Brewer ED, Portman RJ. Ambulatory blood pressure monitoring and interdialytic weight gain in children receiving chronic hemodialysis. Am J Kidney Dis. 1999;33(4):667–74.
126. Springel T, Laskin B, Shults J, Keren R, Furth S. Longer interdialytic interval and cause-specific hospitalization in children receiving chronic dialysis. Nephrol Dial Transplant. 2013;28(10):2628–36.
127. Steuer RR, Germain MJ, Leypoldt JK, Cheung AK. Enhanced fluid removal guided by blood volume monitoring during chronic hemodialysis. Artif Organs. 1998;22(8):627–32.

128. Tandon T, Sinha AD, Agarwal R. Shorter delivered dialysis times associate with a higher and more difficult to treat blood pressure. Nephrol Dial Transplant. 2013;28(6):1562–8.
129. Thein H, Haloob I, Marshall MR. Associations of a facility level decrease in dialysate sodium concentration with blood pressure and interdialytic weight gain. Nephrol Dial Transplant. 2007;22(9):2630–9.
130. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, Boguszewska-Baczkowska H, Drozdz D, Kollataj B, et al. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland–a nationwide survey. Nephrol Dial Transplant. 2006;21:736–42.
131. Trezzi M, Torzillo D, Ceriani E, Costantino G, Caruso S, Damavandi PT, et al. Lung ultrasonography for the assessment of rapid extravascular water variation: evidence from hemodialysis patients. Intern Emerg Med. 2013;8(5):409–15.
132. Trinh E, Bargman JM. Are diuretics underutilized in dialysis patients? Semin Dial. 2016;29(5):338–41.
133. Van Buren PN, Inrig JK. Hypertension and hemodialysis: pathophysiology and outcomes in adult and pediatric populations. Pediatr Nephrol. 2012;27(3):339–50.
134. Vitturi N, Dugo M, Soattin M, Simoni F, Maresca L, Zagatti R, et al. Lung ultrasound during hemodialysis: the role in the assessment of volume status. Int Urol Nephrol. 2014;46(1):169–74.
135. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
136. Weidmann P, Maxwell MH, Lupu AN, Lewin AJ, Massry SG. Plasma renin activity and blood pressure in terminal renal failure. N Engl J Med. 1971;285(14):757–62.
137. Xu J, Li G, Wang P, Velazquez H, Yao X, Li Y, et al. Renalase is a novel, soluble monoamine oxidase that regulates cardiac function and blood pressure. J Clin Invest. 2005;115(5):1275–80.
138. Zazgornik J, Biesenbach G, Janko O, Gross C, Mair R, Brucke P, et al. Bilateral nephrectomy: the best, but often overlooked, treatment for refractory hypertension in hemodialysis patients. Am J Hypertens. 1998;11(11 Pt 1):1364–70.
139. Zhu F, Rosales L, Kotanko P. Techniques for assessing fluids status in patients with kidney disease. Curr Opin Nephrol Hypertens. 2016;25(6):473–9.

32 Management of Anemia in Children Receiving Chronic Dialysis

Meredith A. Atkinson and Bradley A. Warady

Introduction

In 1839, the Scottish physician Robert Christison noted that anemia was a common feature of kidney disease, writing that "no other natural disease came as close to hemorrhage for impoverishing the red particles of the blood" [1, 2]. Anemia is a comorbidity affecting nearly all children treated with chronic dialysis, and its management remains challenging for clinicians. The emergence of recombinant human erythropoietin (rHuEPO) more than 30 years ago revolutionized anemia management in the dialysis population and eliminated dependence on red blood cell transfusions for most patients. Increased understanding of the molecular regulation of EPO production and iron metabolism has opened the door for the development of novel erythropoiesis-stimulating agents (ESA) and renal anemia therapies.

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Normal Erythropoiesis and Disordered Mechanisms in Kidney Disease

The erythropoietic systems maintain homeostasis in the red blood cell supply in order to ensure adequate tissue oxygen delivery; to achieve this, erythrocytes lost to senescence and bleeding must be continually replaced. Erythropoiesis consists of the generation of mature red cells from pluripotent stem cells and includes two distinct phases: an earlier erythropoietin (EPO)-dependent phase which includes the proliferation and maturation of erythroid precursors and a second phase of differentiation of proerythroblasts to red cells which is strongly iron-dependent [3] (Fig. 32.1).

The glycoprotein hormone EPO is the 30.4-kDa product of the *EPO* gene on chromosome 7 and is unique among hematopoietic growth factors in being produced outside the bone marrow [5–8]. It is also the key stimulus for erythrocyte production in mammals [1, 9]. Prenatally, the liver is the primary site of EPO production, but this shifts to the kidney after birth, with a small additional amount continually produced by the liver (and which may increase significantly in the absence of kidneys) [6]. In the kidney, EPO is produced by the interstitial fibroblast-like cells in the peritubular capillary beds of the renal cortex [6, 9]. After injury, the cells transdifferentiate into myofibroblasts which synthesize collagen, losing the ability to produce EPO [6]. Once syn-

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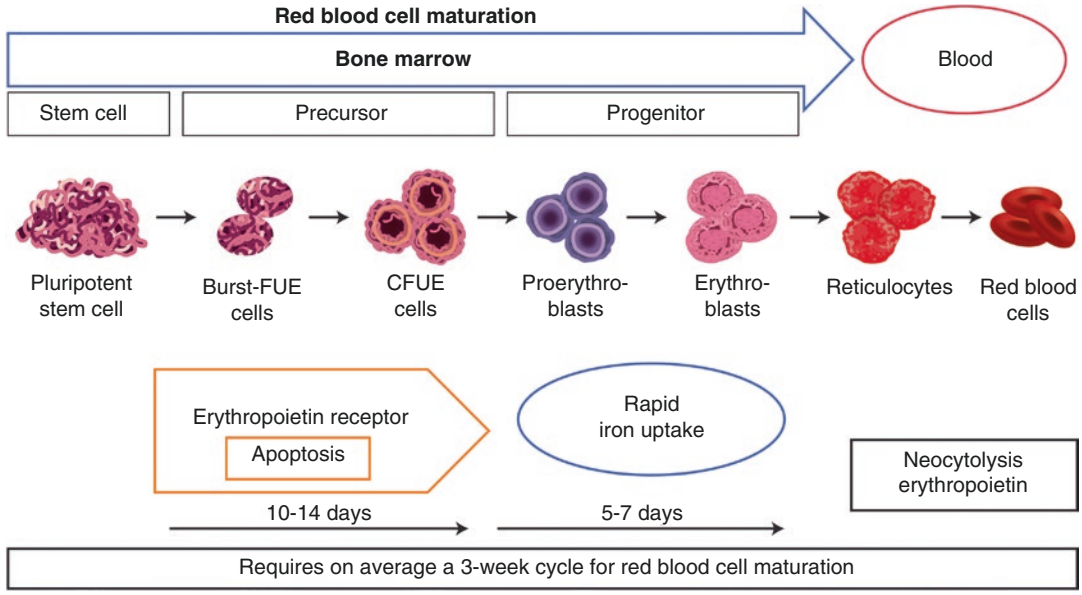

Fig. 32.1 Red blood cell maturation cycle. (Modified from Ref. 4)

thesized, EPO is not stored intracellularly but rather is secreted directly into the bloodstream, where its volume of distribution approximates that of the plasma volume space and circulates with a half-life of approximately 5–12 h [1].

Erythrocyte progenitor cells in the bone marrow are the principal targets of EPO, which maintains erythropoiesis by preventing programmed cell death. In normal, non-hypoxic conditions, the relatively low baseline level of EPO allows only a small fraction of progenitor cells to survive and proliferate, while the remaining cells undergo apoptosis [9]. However, when blood EPO concentration rises because of either endogenous production or after administration of rHuEPO, erythroid progenitors escape from apoptosis, proliferate, and mature into reticulocytes. Significant resulting reticulocytosis becomes apparent 3–4 days after an acute increase in plasma EPO [9].

Hypoxia Stimulates New Red Blood Cell Production

The cellular sensing of tissue hypoxia, the key signal leading to upregulation of EPO production, leads to EPO gene transcription through the actions of hypoxia-inducible factors (HIF). The HIFs are a family of transcription regulators which respond to the oxygen level and control the rate of gene transcription by binding to specific DNA sequences [10]. HIF-1 is a dimer consisting of HIF-α and HIF-β subunits [10]. HIF-α is continually produced, but in the presence of normoxia is "marked" (hydroxylated) for degradation by the HIF-prolyl hydroxylases, enzymes which require oxygen as a co-substrate [1] (Fig. 32.2). Once hydroxylated, HIF-α is recognized by the von Hippel-Lindau protein, polyubiquinated, and destroyed [1]. In contrast, HIF-β is also transcribed at a constant level, but is not sensitive to normoxic degradation [1]. When tissue hypoxia occurs, HIF-α accumulates and translocates to the cell nucleus where it forms a heterodimer with HIF-β and binds to the hypoxia response element of the EPO gene [1, 5, 11] (Fig. 32.3).

The HIF pathway also regulates iron homeostasis both directly and indirectly to meet the demands for increased iron associated with erythropoiesis. The production of HIF-2 in the small intestine activates iron absorption genes on the apical duodenal surface to foster reduction of dietary iron (Fe^{3+}) to ferrous iron (Fe^{2+}) which can be imported into enterocytes [12].

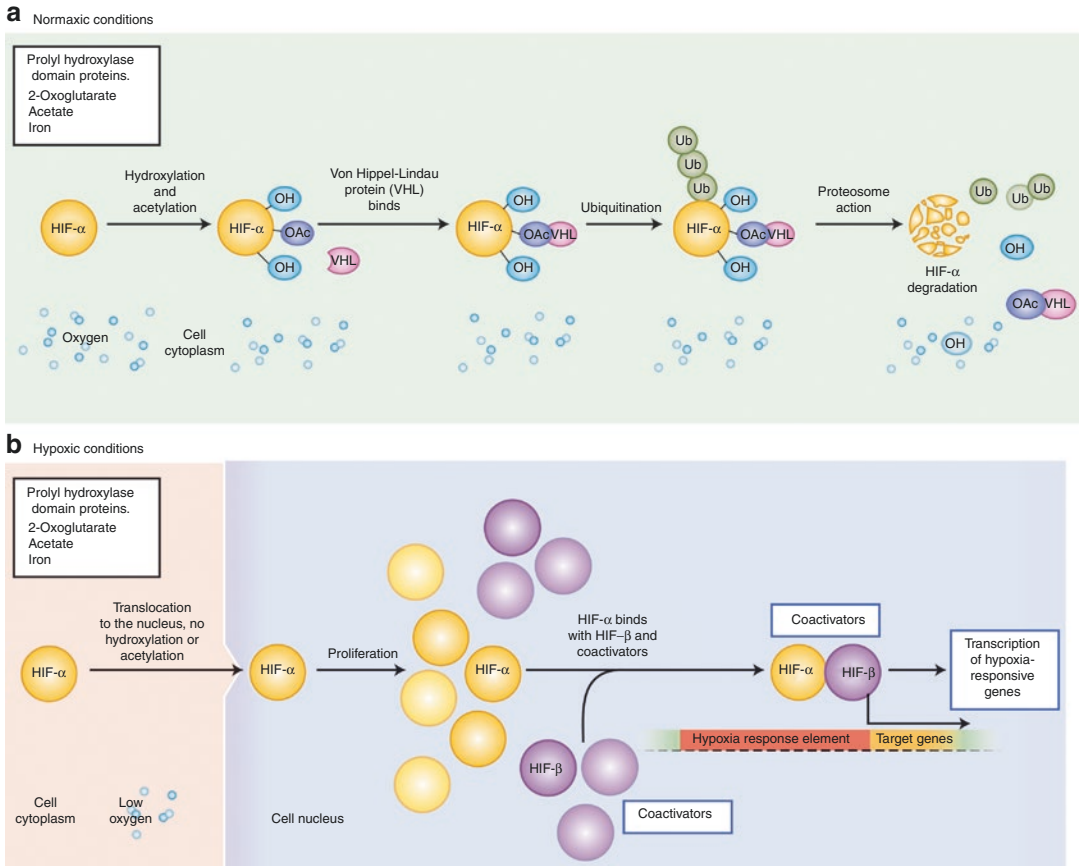

Fig. 32.2 Role of hypoxia-inducible factor α (HIF-α) under normoxic and hypoxic conditions. (Modified from Ref. 10)

Decreased EPO production by injured fibroblast-like epithelial cells is not the only mechanism by which endogenous EPO production is decreased in kidney disease. The kidney functions as a "critmeter" in that it senses oxygen tension and then regulates red cell mass by secreting EPO [7]. Diminished oxygen consumption by diseased renal tissue leads to dysregulation of EPO production by increasing tissue oxygen pressure, which in turn leads to decreased HIF stability [7]. The result is decreased EPO transcription occurring independently of damage to EPO-producing cells.

The action of EPO is mediated through its binding to the EPO receptor, which is found on the cell membrane of erythroid precursors in the bone marrow. Once the EPO receptor is activated, a critical cascade of signal transduction results in increased survival of the red blood cell precursors [1, 13]. Once bound to its receptor, EPO rapidly disappears from the circulation, indicating likely internalization [1, 13]. The degree of EPO receptor binding depends on the carbohydrate content of EPO, with decreased binding affinity with increasing glycosylation of the EPO molecule; this likely accounts for the prolonged in vivo half-life of hyper-glycosylated EPO analogues as will be discussed later in this chapter [9, 14, 15].

Iron Is Required for the Synthesis of Hemoglobin

Iron is required for many physiologic functions including oxygen transport and cell growth and

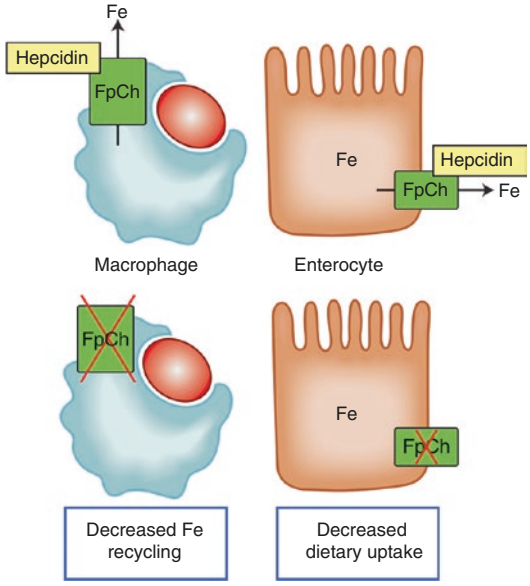

Fig. 32.3 Mechanism of action of hepcidin via direct binding to and downregulation of ferroportin (Contributed by Cindy N. Roy, PhD, Baltimore, MD; [Modified from Ref. 19]). Fe iron, FpCh ferroportin channel

survival. The typical adult human body contains about 3.5 g of iron, and most of that (2.1 g) is incorporated into hemoglobin [16]. Effective erythropoiesis depends not only on erythropoietin production, but also on the availability of iron, and incorporation of iron into erythroblasts is a rate-limiting step in the maturation of red blood cells in the bone marrow. Once iron is absorbed, there is no specific mechanism for its excretion from the body, and so most iron utilized in erythropoiesis is recycled from iron already present in hemoglobin.

Iron is essential for hemoglobin synthesis [3]. Hemoglobin consists of four heme groups, each of which requires the incorporation of one Fe^{2+} ion for oxygen binding [17]. Each mature red blood cell contains approximately 300 million hemoglobin molecules, and two-thirds of total body iron is located in the erythroid compartment [17]. To produce billions of erythrocytes daily, approximately 25 mg of iron must be made available to the bone marrow [3]. The majority of this iron is supplied by macrophages which recycle iron from senescent red blood cells, while only 1–2 mg of iron daily comes from intestinal absorption [3]. Transferrin is the glycoprotein iron transporter that binds tightly but reversibly to iron in plasma, preventing the oxidative stress that freely circulating iron would induce. Iron that has been transported into the circulation bound to transferrin is released to erythroblasts via the interaction of transferrin with the transferrin receptor and receptor-mediated endocytosis [3].

Hepcidin Regulates the Ferroportin-Based Movement of Iron

The iron-regulatory protein hepcidin, a 25-amino acid antimicrobial peptide encoded by the *HAMP* gene and produced by hepatocytes, has emerged as the key regulator of iron homeostasis [18]. Hepcidin regulates both intestinal iron absorption and body iron distribution through its posttranslational suppression of cell-membrane expression of ferroportin, which is the sole cellular iron exporter. Small intestinal ferroportin expression is upregulated in iron deficiency by HIF-2 [12]. Hepcidin binding to ferroportin causes internalization and lysosomal degradation of ferroportin, which results in downregulation of dietary iron absorption via intestinal enterocytes, and inhibits the release of stored iron from reticuloendothelial cells [19] (Fig. 32.3).

In this way, hepcidin prevents the utilization of absorbed or stored iron for erythropoiesis by the bone marrow, a process which in the short term may serve as a host-defense mechanism intended to sequester iron from invading pathogens or malignant cells [20]. A number of pathways have been shown to regulate *HAMP* gene expression via mechanisms involving iron status, erythropoiesis, and inflammation. Iron loading has been shown to increase the production of hepcidin, and hepcidin expression is modulated based on circulating levels of transferrin-bound iron via a BMP-SMAD signaling pathway [6, 17]. Erythropoietin-stimulated erythroblasts produce erythroferrone, a hormone which acts directly on hepatocytes to suppress *HAMP* mRNA and decrease hepcidin production, with a resultant increased iron acquisition from absorption and storage sites [3, 6, 17]. The reduc-

tion in erythroblast number resulting from EPO deficiency diminishes the production of erythroferrone and prevents it from checking hepcidin production [6].

Hepcidin expression is induced by inflammation in general and in particular by the inflammatory cytokine IL-6. It is cleared from the circulation by glomerular filtration, leading to increased levels in the setting of decreased renal function [21]. Hepcidin has been found to be elevated in both adults and children with CKD and on dialysis, and levels are positively correlated with serum ferritin levels [22, 23]. Hepcidin is also cleared from the circulation by hemodialysis [23]. A study in the CKiD cohort found that in children with mild-to-moderate CKD, higher hepcidin levels were associated with lower hemoglobin and an increased risk for incident anemia [21].

Epidemiology of Anemia in Children on Dialysis

Definition of Anemia

The application of adult normative hemoglobin thresholds has been shown to substantially underestimate the prevalence of anemia in children with kidney disease, as normal hemoglobin levels vary by age and sex [24–27]. In 2006, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) published clinical practice guidelines which utilized National Health and Nutrition Examination Survey III data from 1988 to 1994 to define anemia, which reports age- and sex-specific 5th percentile values [25]. Subsequently in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for anemia utilized World Health Organization age-specific hemoglobin values to define the level at which an evaluation for the cause of anemia in patients with CKD should be initiated [28]. KDIGO also recommends that hemoglobin should be measured at least every 3 months in those on dialysis and more frequently for clinical indications. In those patients already determined to be anemic, the hemoglobin should be assessed monthly in those patients treated with an ESA [28]. The most recent clinical practice guidelines regarding anemia in CKD were published in 2017 by the Renal Association (RA) in the United Kingdom. The diagnosis of anemia in pediatric patients was recommended at a hemoglobin level less than10.5 g/dL in children younger than 2 years old and less than 11 g/dL in children >2 years old [29] (Table 32.1).

Table 32.1 Definitions of anemia in children with kidney disease

KDOQI		
Age group (years)	5th percentile hemoglobin level (g/dL)	
	Boys	Girls
1–2	10.7	10.8
3–5	11.2	11.1
6–8	11.5	11.5
9–11	12.0	11.9
12–14	12.4	11.7
15–19	13.5	11.5
KDIGO		
Age group (years)	Hemoglobin level (g/dL)	
0.5–5	<11.0	
5–12	<11.0	
12–15	<12.0	
>15 and adult	<13.0 (males)	
	<12.0 (females)	
RA		
Age group (years)	Hemoglobin level (g/dL)	
<2	Hb 10.5 g/dL	
≥2	Hb 11 g/dL	

Incidence, Prevalence, and Risk Factors

Anemia is one of the most common and clinically significant complications in children on dialysis, with many patients requiring treatment with an ESA starting in later-stage CKD, before the initiation of dialysis. Within the Chronic Kidney Disease in Children (CKiD) cohort study, the median hemoglobin declined as the measured glomerular filtration rate (GFR) decreased below a level of 43 ml/min/1.73 m^2 [30]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) cohort has consistently shown that the risk for anemia increases as the CKD stage advances, with a prevalence of 73% at stage 3, 87%

at stage 4, and >93% at stage 5 [31, 32]. Furthermore, of children prescribed an erythropoiesis-stimulating agent (ESA), over 20% of those with stage 4 CKD and over 40% of children with stage 5 CKD demonstrate persistently low hemoglobin levels [31]. In the International Pediatric Peritoneal Dialysis Network (IPPN) registry, low serum albumin, increased parathyroid hormone (PTH) levels, high serum ferritin, and the use of bio-incompatible dialysate were associated with low hemoglobin levels [33]. Severe anemia in this registry was also associated with risk factors for manifestations of fluid overload including low urine output, high ultrafiltration requirements, hypertension, left ventricular hypertrophy, and high transporter state by peritoneal equilibration test [33]. This suggests that some dialysis patients with anemia, including apparent ESA-resistant anemia, may have low hemoglobin levels due to dilution of red cell mass secondary to volume overload rather than to an impaired erythropoietic response. Careful attention to volume status and "challenging" dry weight with increased ultrafiltration in patients with treatment-resistant anemia will help to clarify the contribution of volume overload to low hemoglobin concentration.

Race is also a recognized risk factor for anemia. Among children enrolled in the CKiD study, African-Americans have consistently demonstrated lower hemoglobin levels than Caucasian children, even after adjusting for the level of kidney function [24]. Normal hemoglobin levels also vary in healthy children by race, and whereas differences in the prevalence of hemoglobinopathy traits, iron deficiency, or socioeconomic status do not fully explain this disparity, genetic polymorphisms may contribute to these differences [34, 35]. Existing anemia management guidelines do not recommend varying hemoglobin targets or modification of the approach to treatment by race [34].

Adverse Associations

Risk of Death and Hospitalization

Studies in adults with ESKD have consistently demonstrated a reduced risk of death and hospitalization when hemoglobin levels are ≥11 g/dL. In children, however, there is less systematic evidence concerning the risks of anemia, and clinical practice recommendations for anemia management are often based primarily on adult studies. In observational studies, lower hemoglobin levels in children on dialysis have been strongly and independently associated with increased mortality risk. Warady and Ho demonstrated an association between a baseline hematocrit of <33% at 30 days post-initiation of dialysis and an increased risk of prolonged hospitalization and death in incident ESKD patients less than 18 years of age from the NAPRTCS registry [36]. Using data from the US Centers for Medicare and Medicaid Services' ESRD Clinical Performance Measures Project linked with the US Renal Data System hospitalization and mortality records, Amaral et al. assessed whether achieving hemoglobin levels of >11 g/dL in 677 adolescents on hemodialysis was associated with a decreased risk of death. In this retrospective cohort study, 11.7% of children with a hemoglobin of <11 g/dL at study entry died, compared to 5% of those with an initial hemoglobin of ≥11 g/dL ($P < 0.0001$) [37]. In a multivariate analysis, hemoglobin of ≥11 g/dL was still associated with a decreased risk of death. When hemoglobin was re-categorized into hemoglobin levels of <10, ≥10 to <11, ≥11 to ≤12, and >12 g/dL, the risk of mortality declined as the hemoglobin level increased. At hemoglobin levels of 11 to ≤12 g/dL versus <10 g/dL, the mortality risk decreased by 70% (HR, 0.30; 95% CI, 0.19–0.74). This observational study's findings were consistent with the experience reported in the adult literature, showing decreased mortality in ESKD patients who meet hemoglobin targets of >11 g/dL for adolescents on hemodialysis.

In 2013, Borzych-Duzalka et al. found that anemia in children on chronic peritoneal dialysis was associated with an increased risk for mortality and that the risk for death on dialysis was independently and inversely associated with hemoglobin [33]. Survival rates were higher in children with mean hemoglobin >11 g/dL compared to those with lower values [33]. Examining the US pediatric peritoneal dialysis population,

Dahlinghaus et al. found that hemoglobin ≥11 g/dL was associated with lower hospitalization risk, but not with a decrease in mortality risk. Hemoglobin levels ≥12 g/dL were not associated with a decreased risk of hospitalization compared to levels of 11–12 g/dL [38]. Published in 2017, a 40-year retrospective cohort study of children on dialysis by Adamczuk et al. found that the mean hemoglobin level was higher among survivors compared to non-survivors and was a significant prognostic indicator. The survivors were more frequently treated with ESAs, suggesting that treatment of anemia is important in decreasing mortality in patients on dialysis [39]. Rheault et al. found that the hazards for both all-cause mortality and all-cause hospitalizations were significantly lower in children on hemodialysis with hemoglobin ≥12 g/dL and that cardiovascular hospitalizations were significantly higher in those with hemoglobin <10 g/dL [40].

Quality of Life and Physical and Cognitive Function

Anemia of CKD has long been associated with a negative impact on quality of life. Several studies have revealed that the treatment of anemia in CKD improves quality of life in adults with CKD and ESKD [41–43]. A single blinded, placebo-controlled crossover study in 11 children with ESKD showed improvement in exercise tolerance, physical performance, and school attendance with correction of anemia [44]. Treatment of anemia using recombinant human erythropoietin in a multicenter pediatric study of 44 children with chronic kidney failure undergoing HD also showed marked improvement in their quality of life, particularly in activity levels [45]. Another cross-sectional study by Gerson et al. examined the link between caregiver-reported QoL and anemia in a cross-sectional assessment of 116 adolescents with renal insufficiency on dialysis and post-kidney transplantation. The authors found that anemia was associated with poorer quality of life [46]. By caregiver assessment, adolescents with kidney disease and anemia (defined as hematocrit of <36%) were less satisfied with their health, participated in fewer activities at school and with friends, and were less physically active. These findings mirrored findings of studies examining the correlation between anemia and quality of life in adults. Correction of anemia has also been associated with better physical function in children with ESKD. In a small series, children on chronic PD treated with rHuEPO with resulting increased hematocrit demonstrated significantly improved exercise capacity as measured by peak oxygen consumption and treadmill time [47].

Regarding cognitive function, one multicenter trial of subcutaneous erythropoietin showed increased Wechsler intelligence scores in 11 children with chronic kidney failure who were treated for anemia over a 12-month period [48]. In the adult literature, several studies have demonstrated significant improvement in electrophysiological markers of cognitive function with improvement of anemia in patients with chronic and end-stage kidney disease, but further study is sorely needed in the pediatric dialysis population [49–54].

Cardiac Function

There is observational evidence of an association between anemia and left ventricular hypertrophy in adults, but evidence supporting cardiac benefits of anemia treatment in children is much more limited [55, 56]. Adverse cardiovascular events and left ventricular remodeling have both been associated with anemia in children with CKD and ESKD [57–59]. A single blinded crossover trial of 11 children aged 2–12 years on dialysis demonstrated an improvement in cardiac index by 6 months and a significant reduction in left ventricular (LV) mass by 12 months in those treated with rHuEPO [60]. Two additional observational studies of patients with severe left ventricular hypertrophy (LVH) demonstrated that children with lower hemoglobin levels had more severe LVH and lower LV compliance [61, 62]. Anemia has been identified as an independent predictor of LVH, even after controlling for blood pressure, in children with pre-dialysis CKD [63].

Clinical Management of Anemia

Symptoms of Anemia

The clinical presentation of anemia depends on the rate of hemoglobin decline as erythropoietin production slows and the adaptability of the heart and lungs to a decreased hemoglobin concentration. In the case of blood loss during hemodialysis, the rate of ultrafiltration will determine severity of symptoms. Symptoms of anemia may include fatigue, pallor, somnolence, tachypnea, tachycardia, depression, impaired cognition or muscle function, and loss of appetite. If anemia is more acute from blood loss, patients may experience dyspnea, dizziness, or headache. Patients with concurrent iron deficiency may have fatigue and lethargy out of proportion to their degree of anemia [64].

Initial Diagnostic Evaluation of Anemia

Prior to initiating treatment with an ESA in anemic children with kidney disease, other potentially correctable causes of anemia should be ruled out (Table 32.2).

Table 32.2 Potential causes of anemia in children with chronic kidney disease

Erythropoietin deficiency and/or dysregulation
Iron-restricted erythropoiesis
Absolute iron deficiency
Functional iron deficiency
Impaired iron trafficking
Inflammation and hepcidin upregulation
Chronic blood loss
Frequent phlebotomy
Hemodialysis circuit losses
GI losses
Menstrual losses
Acute blood loss
Surgical losses
GI losses
Uremia and oxidative stress
Hyperparathyroidism and myelofibrosis
Hypervolemia
Nutritional deficiencies
B12, folate, carnitine, vitamin C, copper
Medications
Angiotensin-converting enzyme inhibitors
Non-adherence with anemia therapies
Drug toxicity
Pure red cell aplasia associated with erythropoiesis-stimulating agents
Infectious causes
Parvovirus B19-induced aplastic anemia
Infection-associated inflammation

Because anemia in children on dialysis may not be associated solely with erythropoietin deficiency, incident anemia should prompt an initial laboratory evaluation to include assessment of red cell indices and iron stores and other correctable nutritional deficiencies [28]. Deficiencies of B_{12}, folate, carnitine, vitamin C, and copper may also contribute to anemia in CKD. The B vitamins are water soluble and are removed during dialysis, and B12 deficiency causes megaloblastic anemia because B12 is needed for DNA synthesis [65]. Folate is also required for DNA synthesis during erythropoiesis and deficiency is associated with a macrocytic anemia. In a small study, when a deficiency in folate was corrected in 15 children on dialysis, 11 demonstrated increased hemoglobin with the mean level increased by 8%. ESA dose requirements decreased as well, with a mean decrease of 20 units/kg [66, 67]. Chronic hemodialysis is a leading cause of secondary carnitine deficiency due to its ready dialyzability [68]. Some studies have suggested that L-carnitine supplementation can prolong red blood cell life span and stimulate erythropoiesis by inhibiting apoptosis, but there have been no large-scale randomized clinical trials conducted to evaluate whether supplementation is effective as an adjunctive treatment for anemia in dialysis patients [68]. Vitamin C enhances absorption of dietary iron, contributes to the mobilization of intracellular stored iron, and increases carnitine synthesis, but there have been no clinical trials to assess the effects of vitamin C supplementation on anemia in dialysis patients [69]. Caution is also warranted as excessive vitamin C ingestion can be associated with renal oxalate deposition and acute kidney injury, both of which could have a negative impact on residual kidney function [70]. Copper deficiency is relatively rare, but can arise from excessive

zinc intake and may be associated with a microcytic anemia and leukopenia, and is correctable with supplementation [71]. Anemia with concurrent lymphopenia or thrombocytopenia should prompt an evaluation for malignancy, autoimmune disease, or drug toxicity.

Uremia itself contributes to anemia in children on dialysis. Accumulated uremic toxins and associated oxidative stress can induce changes in erythrocyte cell membranes and cytoskeletons which promote hemolysis and a shortened cell life span, with red cell survival time decreased by as much as 50% compared to healthy subjects [72]. Thus, inadequate dialysis may contribute to the risk for anemia. In adults on chronic hemodialysis, more hours of dialysis per week have been associated with higher hemoglobin levels and a lower required ESA dose [73, 74].

Erythropoietin Levels

EPO deficiency is a diagnosis of exclusion. In the setting of normal renal function, plasma EPO levels increase exponentially with decreasing hemoglobin, and values may rise from the normal range of approximately 15 units/liter to as high as 10,000 units/liter [9]. Thus, measuring plasma levels of EPO in children with kidney disease is not useful to clarify the contribution of relative EPO deficiency to anemia, because even if EPO levels are detectable above the normal range, they may still be inappropriately low for the degree of anemia present.

Laboratory Assessment of Iron Status

In clinical practice, the most commonly utilized biomarkers of stored iron remain serum ferritin and transferrin saturation (TSAT). KDIGO recommends iron supplementation in children on dialysis to maintain TSAT >20% and ferritin >100 ng/mL and recommends IV iron supplementation in children on hemodialysis [28]. Both ferritin and TSAT have limited sensitivity and specificity to predict bone marrow iron stores and erythropoietic response to iron supplementation. Distinguishing hepcidin-mediated impaired iron trafficking from absolute iron deficiency anemia presents a clinical challenge, as both disorders are characterized by a microcytic anemia with low reticulocyte counts, decreased serum iron concentration, and low transferrin saturation. However, serum ferritin levels can be helpful in distinguishing the disorders; absolute iron deficiency is associated with a low ferritin concentration, while impaired trafficking is characterized by normal or elevated serum ferritin, reflecting iron sequestration in the reticuloendothelial system. In contrast, in patients with functional iron deficiency on ESA therapy, the rate of enteral iron absorption or release from reticuloendothelial cells is inadequate to meet the demands for erythropoiesis; these patients often have low TSAT values with normal or high levels of ferritin, suggesting that patients may benefit from treatment with intravenous iron [75, 76]. The limitations of serum ferritin as a marker of accessible stored iron are, however, well established, including higher ferritin levels being associated with lower hemoglobin levels and ferritin serving as an acute phase reactant [33, 77]. Although ferritin is measured in serum, its function is as an intracellular iron-storage protein. Although we assume in clinical practice that the serum concentrations reflect some steady-state "leakage" of intracellular ferritin, the process by which ferritin enters the circulation is not well understood [76].

TSAT has recognized limitations as well, including diurnal fluctuations and reduction in the setting of malnutrition and chronic disease [78]. There is thus a need for diagnostic tests which more accurately predict the need for or response to iron therapy. A study in pediatric dialysis patients found that the reticulocyte hemoglobin content (Ret-He), which is not an acute phase reactant and reflects iron availability for incorporation into reticulocytes over the previous 2–4 days, performed better than either ferritin or TSAT to distinguish between iron deficiency and suboptimal ESA dosing [78]. Thus, Ret-He may be an attractive alternative indicator of iron status in clinical practice, although it remains limited currently as it is only measured by flow cytometry [78]. Percentage of hypochro-

mic red blood cells (% HRC) is another laboratory marker of iron status that can assess iron availability for incorporation into red cells. % HRC >6% suggests poor hemoglobin production due to iron deficiency and may be helpful in distinguishing patients with elevated ferritin levels who may benefit from additional, potentially intravenous iron supplementation [79]. %HRC also requires flow cytometry for measurement, which may limit its availability in clinical laboratories which measure hemoglobin by electrical impedance and do not have access to the equipment or software required for testing [80].

Goal Hemoglobin Levels in Children on Dialysis

There have been a series of clinical practice guidelines for the management of anemia in dialysis patients published over the last 10–15 years, which have included recommendations for target hemoglobin levels. In 2007, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), in response to data from adult trials in which the use of ESAs to target higher hemoglobin levels was associated with adverse outcomes, published a revised recommendation advising that in patients receiving an ESA, the hemoglobin target should generally be in the range of 11–12 g/dL and should not exceed 13 g/dL [81]. Subsequently, the KDIGO guidelines were created from systematic literature searches and supplemental evidence from October 2010 to March 2012. They did not recommend a hemoglobin threshold for initiation of ESAs in pediatric patients, but recommended that providers consider all potential benefits and harms prior to starting ESA therapy. For pediatric patients on ESAs, the target hemoglobin recommended was 11–12 g/dl [28]. The National Institute for Health and Care Excellence (NICE) in the United Kingdom last updated its guidelines in 2015. For patients who are on ESAs, the recommended hemoglobin target was 10 to 12 g/dL in children >2 years old and adults and 9.5–11.5 g/dL in children younger than 2 years old [82]. In terms of initiation of ESA treatment, a common threshold in clinical practice is a hemoglobin <10 g/dL.

Recombinant Human Erythropoietin Therapy

Available Forms of rHuEPO

The human *EPO* gene was isolated in 1985, with commercial production of rHuEPO beginning soon thereafter. Epoetin alfa was approved by the US Food and Drug Administration in 1989 [8]. The development and widespread use of rHuEPO in both adults and children eliminated dependence on red blood cell transfusions which could be complicated by transfusion-associated viral infections, iron overload, and allosensitization [83]. Both endogenous and recombinant EPO have microheterogeneity in carbohydrate structures with variation in sialic acid content, and the molecules with increased sialic acid content demonstrate increased in vivo half-life [84]. The observation that the biologic properties of specific rHuEPO products varied with their molecular structure led to the hypothesis that reengineering the EPO molecule with the addition of carbohydrate chains, and increasing sialic acid content, could enhance potency and increase half-life [85] (Fig. 32.4). Now there are several types of both short- and long-acting ESAs available worldwide, and new formulations continue to emerge requiring ongoing attention to the relative safety and efficacy in children compared to adults.

Epoetin

Epoetin alfa was the first rHuEPO commercialized in the United States, followed by epoetin beta in Europe. Epoetins alfa and beta, both produced in Chinese hamster ovary cells, have minor structural differences but the same physiological effects [84]. There is no definitive evidence of superiority in patient outcomes for any particular epoetin brand [28]. As the patents for the first epoetins expired, biosimilar agents showing only minor differences in clinically inactive components to those of the licensed products emerged and were approved in the United States and Europe; this process will likely continue,

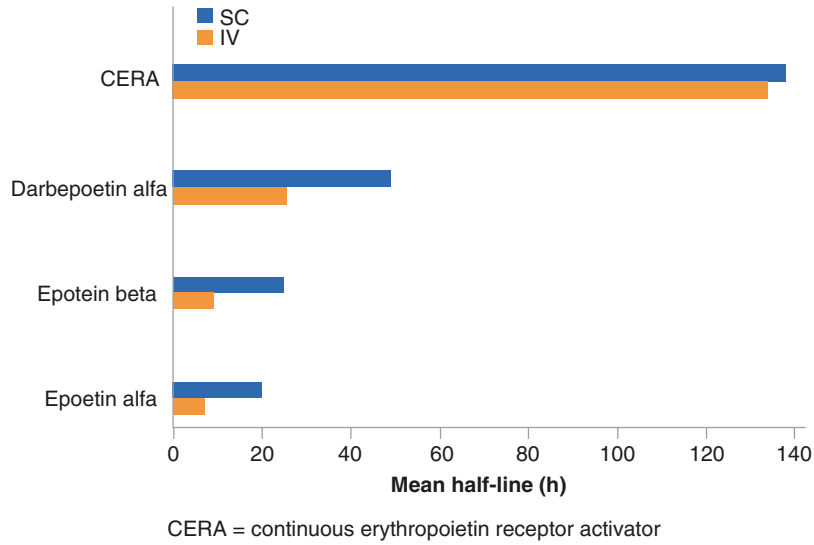

Fig. 32.4 Mean in vivo half-lives of available erythropoiesis-stimulating agents

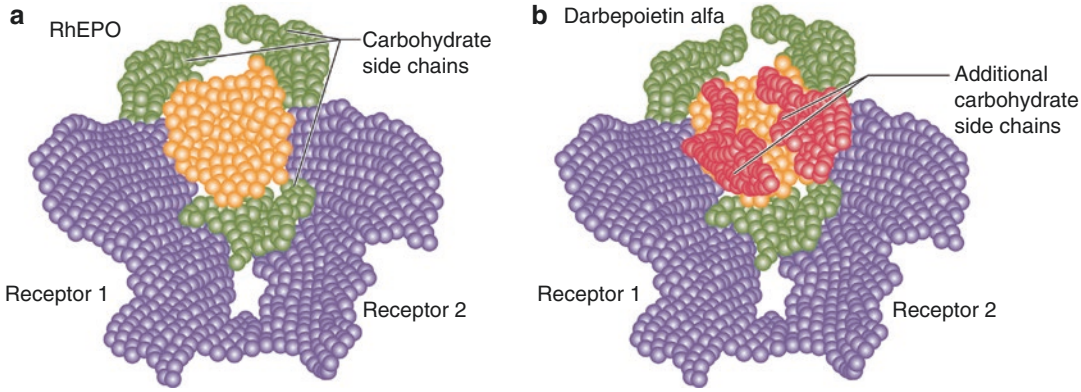

Fig. 32.5 Molecular structures of rhEPO (**a**) and darbepoetin alfa (**b**). (Modified from Refs. 84, 85)

leading to wider entry of these agents into the clinical markets [86]. Short-acting epoetin formulations achieve maximum efficacy when dosed one to three times weekly and demonstrate a longer half-life when given subcutaneously (19–24 h) than intravenously (6–8 h) [81].

Darbepoetin Alfa

Darbepoetin alfa is an erythropoietin analogue with two additional sialic acid-containing carbohydrates resulting in extended in vivo biological activity. Darbepoetin alfa has been shown to have equivalent efficacy as rHuEPO to maintain hemoglobin when dosed weekly or every other week in children with CKD [28, 66, 87, 88] (Fig. 32.5).

Darbepoetin alfa may be administered intravenously or subcutaneously, and while the drug clearance, half-life, and bioavailability are similar in adults and children regardless of the route of administration, absorption when given subcutaneously may be more rapid in children [81]. The longer dosing interval inherent to treatment with darbepoetin compared to rHuEPO has made subcutaneous darbepoetin alfa an attractive alternative for anemia management in younger children, with the potential for improving adherence due to the need for less frequent drug administration. A randomized clinical trial in children with

CKD stages 4 and 5 demonstrated that darbepoetin alfa is as safe and effective as rHuEPO for the correction of anemia [88]. A longitudinal European registry study similarly demonstrated that children treated with darbepoetin alfa did not experience increased rates of adverse events such as infection or severe hypertension [89]. A potential limitation of darbepoetin alfa in children, however, is the reported discomfort associated with injection. In a blinded, randomized, controlled trial, children who received subcutaneous darbepoetin alfa reported higher levels of post-injection pain by a visual analogue scale compared to those who got epoetin beta, consistent with an increased impression of pain as reported by their parents and nurses [90]. A potential explanation is the more physiological pH of the buffer in the epoetin beta preparation than the darbepoetin alfa preparation [83]. Other pediatric studies have, however, not found pain to be more frequent or severe in patients receiving darbepoetin [88].

CERA

Continuous erythropoietin receptor activator (CERA) is an EPO analogue that was created by the integration of a single 30-kDa polymer chain into the EPO molecule, increasing its molecular weight to twice that of epoetin and extending its elimination half-life to around 130 h [91] (Fig. 32.6).

Unlike endogenous EPO and epoetin, which are internalized and degraded following binding to the EPO receptor, CERA escapes degradation by dissociating from the receptor, allowing sustained in vivo efficacy of the compound [92]. A study in children on peritoneal dialysis demonstrated that CERA safely and effectively maintained hemoglobin levels when dosed once or twice monthly, although the doses required to meet goal hemoglobin levels were higher than those required in previously published adult studies [93]. A study in 64 children on hemodialysis aged 6–17 found that CERA given once every 4 weeks was efficacious in maintaining hemoglobin levels with a safety profile consistent with that of adults [94].

ESA Dosing for Children

rHuEPO quantities are traditionally expressed as units, with 1 unit equaling the erythropoietic effect of bone marrow stimulation with 5 μmol of cobalt chloride, an historic treatment for anemia prior to the rHuEPO era [1]. Darbepoetin alfa

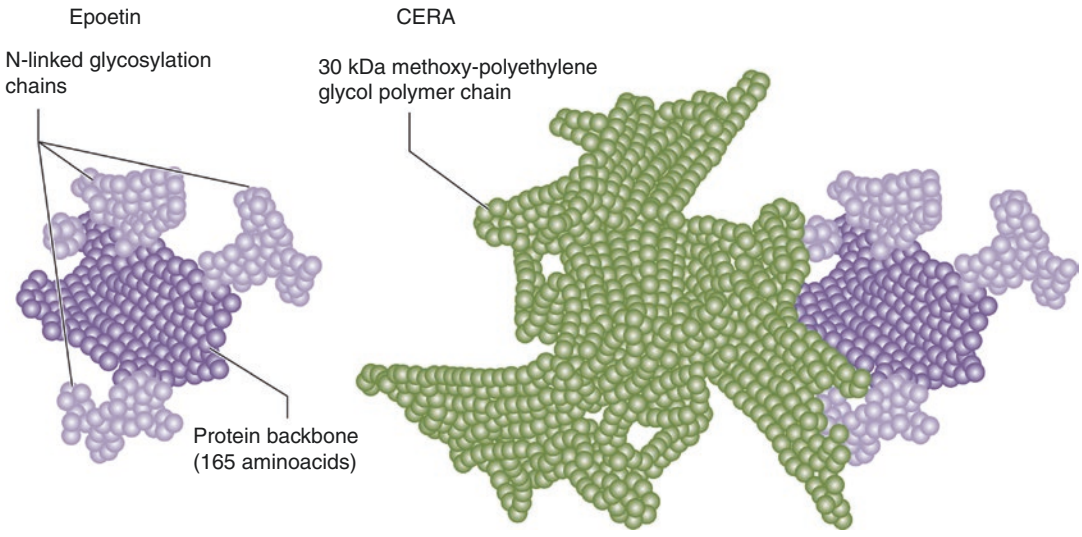

Fig. 32.6 Comparison of molecular structures of epoetin and CERA. (Modified from Ref. 91)

quantity is expressed in micrograms, with the biological activity of 1 μg corresponding to that of 200 units of rHuEPO [9]. The starting dose for epoetin alfa or beta is generally 20–50 IU/kg three times weekly (given subcutaneously or intravenously) [28]. The initial recommended darbepoetin alfa dose is 0.45 μg/kg subcutaneously or intravenously dosed once weekly or 0.75 μg/kg dosed every 2 weeks [28]. The CERA dose is measured in micrograms. In the study of children on chronic hemodialysis performed to determine the required starting dose of CERA based on the previous weekly epoetin alfa/beta or darbepoetin alfa doses, a conversion factor of 4 μg of CERA every 4 weeks for each weekly dose of 125 IU epoetin alfa or beta, or 0.55 μg darbepoetin, was found to be most efficacious [94]. Published CERA dosing recommendations in children are intended for transition from another ESA. The goal after ESA initiation is for a rate of increase in hemoglobin concentration of no more than 1–2 g/dL per month [28] (Table 32.3).

ESA dose adjustments after treatment initiation should generally not be made until after the first 4 weeks of therapy, and no more often than every 2 weeks in the outpatient setting, as the effects of therapy are not likely to be seen after shorter intervals [28]. Decisions on dosing adjustments should be made based on the hemoglobin rate of rise after initiation and the stability of hemoglobin during maintenance therapy [21].

Table 32.3 Erythropoiesis stimulating agent dosing guide for initiation in children

	Starting dose	Interval	Route
Epoetin alfa/beta	20–50 IU/kg	Three times per week	SC or IV
Darbepoetin alfa	0.45 μg/kg 0.75 μg/kg	Weekly Every 2 weeks	SC or IV
CERA	4 μg per each prior weekly dose of: 125 IU epoetin 0.55 μg darbepoetin	Every 4 weeks	SC or IV

SC subcutaneously, *IV* intravenously

When a decrease in hemoglobin is necessary, ESA dose should be decreased but not necessarily held, as a pattern of holding and reinitiating ESA therapy can lead to hemoglobin cycling around the desired target range [95]. Long-acting ESAs like darbepoetin alfa and CERA, with their increased half-life and lower binding affinity for the EPO receptor, stimulate erythropoiesis for longer periods of time and thus may cause higher-than-intended hemoglobin levels in clinical practice. This can be avoided by using lower starting doses and making less frequent dose adjustments than in children treated with short-acting ESAs [87].

Children May Require Higher Absolute ESA Doses than Adults

The dosing requirements of rHuEPO differ between children and adults. Young children have been reported to require higher weight-related rHuEPO doses than adults, ranging from 275–350 units/kg/week for infants to 200–250 units/kg/week for older children [96]. Despite their lower body weight, children and adolescents on chronic hemodialysis have also been found to require higher absolute doses of rHuEPO than adults to maintain hemoglobin in goal range [97, 98]. In contrast to typical drug dosing in children which is based on body size to account for a decreased volume of distribution, rHuEPO dose requirements appear to be independent of weight [97, 99]. The potential mechanisms for increased rHuEPO dose requirement in children are not clear, but may include increased presence of non-hematopoietic erythropoietin binding sites (e.g., endothelial, kidney, brain, and skeletal muscle cells) resulting in increased drug clearance or increased erythropoietin demand during periods of accelerated body growth [9, 96, 99]. Data from the International Pediatric Peritoneal Dialysis Network (IPPN) showed that the weekly ESA dose scaled to body weight was inversely correlated with age, but when normalized to body surface area the dose was independent of age, with a median (IQR) weekly ESA dose of 4208 (2582, 6863) units per m^2 [33]. It has also been shown

that an absolute rHuEPO dose of 1000 units given IV to both adults and children can increase hemoglobin by 0.4 g/dL, suggesting that dosing schemes based on hemoglobin deficit rather than weight may be useful [61, 99]. The doses of CERA required by children have also been reported as higher than those required in adults [93]. Finally, studies in adults with non-dialysis CKD have shown epoetin alfa administered subcutaneously at higher doses but extended intervals (ranging from 20,000 to 80,000 units every 2 or 4 weeks) to be non-inferior to weekly dosing regimens in maintaining hemoglobin [100, 101]. This could be an attractive option for allowing less-frequent ESA dosing in regions where darbepoetin alfa is not readily available, although extended interval epoetin alfa dosing has not yet been systematically assessed in children.

Safety of ESA Therapy

Although there are benefits associated with ESA use, clinical trials in adults have raised concern about the safety of using escalating ESA doses to normalize hemoglobin. The CHOIR trial performed in adults with non-dialysis CKD found that using epoetin alfa to target a higher hemoglobin level was associated with an increased risk for death, MI, stroke, or CHF [49]. In the 2009 TREAT trial, adults with CKD receiving darbepoetin to achieve hemoglobin >13 g/dL also demonstrated an increased risk for stroke [102]. Consequently, in 2011 the US FDA changed the ESA product labeling to recommend the lowest possible ESA dose to prevent red blood cell transfusions and that the dose should be reduced or interrupted for hemoglobin >11 g/dL [103]. However, this label change did not distinguish between pediatric and adult CKD patients. Although no such randomized controlled trials have been conducted in pediatric patients, observational data has demonstrated that higher ESA doses are associated with an increased risk for mortality in children on chronic dialysis [33, 38, 104]. No clinical trials in adults have identified whether the higher hemoglobin level or the higher ESA dose specifically contributes to the increased risk for adverse outcomes, but a prospective study in adults on dialysis found that those with naturally occurring higher hemoglobin levels >12 g/dL were not at increased risk for mortality [105, 106]. In a similar study conducted in ESA-treated children on dialysis, Rheault et al. demonstrated that hemoglobin level >12 g/dL was not associated with an increased risk for either mortality or hospitalization [40].

The specific mechanisms for the adverse cardiovascular outcomes observed with ESA use have yet to be defined, but may include trophic effects on vascular endothelial or smooth muscle cells [107]. Greater blood viscosity at higher hemoglobin concentrations may also contribute by increasing vascular endothelial wall stress [1]. While exposure to supraphysiologic EPO concentrations may have detrimental off-target effects, the disparate burden and duration of cardiovascular disease and other comorbidities including diabetes in adults compared to children may result in the risk for such ESA-associated outcomes being substantially lower in children on dialysis. However, given the lack of evidence, similar levels of caution are applied to ESA use in children. Other reported side effects of ESAs include hypertension, which seems to be independent of achieved hemoglobin level, and increased risk for vascular access thrombosis [108].

Novel Erythropoiesis-Stimulating Agents

Novel ESA-independent CKD-related anemia therapies are in varying stages of development. Small-molecule hypoxia-inducible factor (HIF) stabilizers/prolyl hydroxylase domain inhibitors modulate HIF-controlled gene products and are capable of inducing endogenous erythropoietin production even in the setting of decreased renal oxygen consumption, likely by increasing hepatic erythropoietin production [12]. They have been shown to increase hemoglobin and decrease hepcidin in adult trials, but trials have not yet been conducted in children [109–111]. Inhibitors of HIF can be administered orally in highly bioavailable preparations. Investigational strategies for direct hepcidin modulation include monoclonal antibodies aimed directly at hepcidin or at the

inflammatory stimuli that induce its production, including IL-6 [111]. Fully human anti-hepcidin antibodies have been successfully developed and applied in animal models [112].

ESA Hyporesponsiveness: Definition and Risk Factors

There will be patients who, despite iron supplementation combined with escalating ESA dosing, fail to increase hemoglobin levels above 10 g/dL. KDIGO defines *initial* ESA hyporesponsiveness as no increase in hemoglobin concentration from baseline after the first month of appropriate weight-based dosing and *acquired* ESA hyporesponsiveness as a requirement for two increases in ESA doses up to 50% beyond the dose which they had previously required to maintain a stable hemoglobin concentration [28]. An alternative definition is a persistent hemoglobin deficit after 3 months of high-dose ESA treatment (rHuEPO in excess of 400 units/kg weekly or darbepoetin alfa in excess of 1 μg/kg weekly) [67, 113].

In the IPPN registry, ESA resistance and escalated ESA dosing have been associated with inflammation, fluid retention, and hyperparathyroidism [33]. The observational association between higher ESA doses and mortality in pediatric patients may, in turn, reflect the impact of chronic inflammatory processes which negatively impact patient survival, rather than a direct ESA effect on the risk for death. While ESA hyporesponsiveness may be chronic, it can also be seen in the context of shorter-term clinical events such as infections or surgical procedures which may negatively impact the response to ESA therapy. Thus, the potential risks and benefits of escalation in ESA dose vs. administration of intravenous iron vs. red blood cell transfusion in this setting must be assessed for individual patients [28]. Attention should also be paid to determining whether affected patients may be suffering from vitamin or mineral deficiencies resulting from malnutrition. Other potential causes of ESA hyporesponsiveness include the following:

Bone Disease Secondary to Hyperparathyroidism

Severe hyperparathyroidism can contribute to anemia and ESA hyporesponsiveness due to decreased bone marrow production of red blood cells due to myelofibrosis [96, 114, 115].

Medications

There are a variety of medications that can contribute to anemia in dialysis patients including, but not limited to, ACE inhibitors and antimetabolites causing bone marrow suppression. A review of the medication list for potential medications contributing to anemia should be undertaken for any dialysis patient with ESA-resistant anemia.

Aluminum Toxicity

Although aluminum-based compounds are used far less frequently in the management of hyperphosphatemia than in the past, awareness of aluminum toxicity is important. Chronic use of aluminum-based antacids and phosphate binders remains the most common cause of aluminum toxicity in patients with ESKD. In animal studies, aluminum has been shown to induce partial resistance to EPO and to increase heme oxygenase activity, which subsequently increases destruction of the heme protein [116, 117].

Hypervolemia

Patients with less residual urine output and who are clinically judged to be fluid-overloaded demonstrate lower hemoglobin levels, suggesting that some portion of treatment-resistant anemia may in fact be due to the chronic dilution of the red cell mass in an expanded extracellular volume [33]. This should be addressed with more effective ultrafiltration.

Anti-rHuEPO Antibodies

ESA-induced pure red cell aplasia (PRCA) is an increasingly rare hematologic disorder that was first described in the late 1990s. PRCA is characterized by a severe and progressive normocytic anemia, reticulocytopenia, and the almost complete absence of erythroid precursors in the bone marrow, with affected patients becoming transfusion dependent [118]. ESA-induced PRCA is secondary to the development of neutralizing antibodies which block the interaction between an ESA (including epoetin alfa or beta, darbepoetin alfa, or endogenous EPO) and its receptor [118]. Most initial cases of ESA-induced PRCA were seen in countries where epoetin alfa formulated with a polysorbate 80 stabilizer was administered to CKD patients subcutaneously; regulatory advisories have subsequently discouraged this practice [119].

Red Blood Cell Transfusion

Despite best efforts in anemia management, and often in the setting of ESA hyporesponsiveness, patients sometimes do require packed red blood cell transfusion. The decision to transfuse should not be based on an arbitrary hemoglobin level, but rather guided by symptoms and after weighing the specific risks and benefits for the individual patient. Red blood cell transfusions are associated with an increased risk for the development of human leukocyte antigen (HLA) antibodies. In adults, leukoreduction of blood products is an ineffective means to decrease HLA sensitization, and red cell transfusions lead to clinically significant increases in HLA antibody strength and breadth [120, 121]. These antibodies serve as a barrier to future transplantation and may adversely affect graft outcomes [120, 121]. More studies are needed to define the risks associated with red cell transfusion in children with regard to HLA sensitization and graft outcomes.

Iron Therapy

KDIGO recommends iron supplementation in children on dialysis to maintain TSAT >20% and ferritin >100 ng/mL and recommends intravenous iron supplementation in children on hemodialysis [28].

Oral Iron Supplementation

Most children on dialysis will require iron supplementation as part of their anemia treatment plan in order to maintain hemoglobin levels and replete iron stores. Children on hemodialysis in particular may have chronic blood loss via the dialysis circuit which exacerbates iron deficiency. Enteral iron supplementation is relatively inexpensive, highly available, and generally safe and efficacious in children with chronic kidney disease, although GI side effects of nausea or constipation are sometimes reported. Although true intolerance is relatively rare, it may be a contributing factor to the poor adherence that may arise to prescribed oral supplementation. In addition, co-administration of iron with phosphate binders or antacids can limit absorption due to changes in gastric pH [64]. The usual dosing range for oral iron supplementation is 3–6 mg/kg/day of elemental iron, either daily or divided into two daily doses. The most commonly available oral iron preparations come in ferrous ($Fe2^{+}$) or ferric ($Fe3^{+}$) forms, including ferrous sulfate and ferric iron polymaltose complexes [16]. Ferrous sulfate has better bioavailability (10–15%) than ferric iron and is available in prolonged release forms [16]. Some ferric polymaltose complex formulations are available with added vitamins C, B12, and folic acid to enhance iron absorption and replete other vitamins associated with red blood cell production. However, there is no evidence that ferric iron formulations are superior to ferrous preparations for oral supplementation in children on dialysis.

Intravenous Iron Supplementation

Children on dialysis often benefit from iron preparations administered intravenously due to the poor enteral absorption or poor tolerance associated with oral administration. There are an increasing number of available iron preparations for clinicians opting for intravenous therapy (Table 32.4).

Early IV iron compounds were formulated as inorganic iron oxyhydroxide complexes, which could result in the release of labile iron directly into the plasma leading to the formation of highly reactive free radicals associated with severe toxicity, including hypotension. Newer preparations surround the iron oxyhydroxide core with carbohydrate shells of different sizes and polysaccharide branch characteristics [123]. The shell characteristics determine how long the iron remains circulating, with larger molecular weight formulations such as iron dextran resulting in longer plasma residence, while products with smaller shells are more labile and likely to release iron directly into the plasma before it can be metabolized in the reticuloendothelial system [124–126]. Intravenous iron therapy can be delivered as a loading phase, using consecutive doses to replete iron stores, or as smaller maintenance doses given weekly.

IV iron has been shown to be effective in repleting iron stores in children. In 2005, Gillespie and Wolf published a meta-analysis that combined clinical data on IV iron use in children on HD [127]. They evaluated nine studies including eight cohort studies and one prospective trial with historical controls, and they showed increased hemoglobin, ferritin, and transferrin saturation levels and reduced use of ESAs with IV iron use. In 2004, Warady et al. performed an RCT to examine the preferential route of iron administration for children. The authors prospectively randomized 35 iron-replete children <20 years old with ESKD on hemodialysis to receive either IV iron dextran with each dialysis session ($n = 18$) or oral iron daily ($n = 17$) for up to 16 weeks. In both groups the hemoglobin was stable, but the IV iron group experienced a significant increase in serum ferritin and the oral iron group did not. There was no statistically significant difference in ESA dosing detected between the two groups [128]. Sodium ferric gluconate complex has also been shown in pediatric studies to safely and effectively increase and maintain iron parameters in children undergoing

Table 32.4 Physiochemical characteristics and pharmacokinetics of iron formulations for intravenous administration (with permission [122])

Properties	Ferumoxytol	Ferric carboxy maltose	Iron dextran	Iron sucrose	Ferric gluconate
Molecular mass (D)	731,000	150,000	410,000	252,000	200,000
Carbohydrate shell	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Dextran polysaccharide	Sucrose	Gluconate, loosely associated sucrose
Median shell/ particle diameter (nm)	26.3	23.1	12.2	8.3	8.6
Relative catalytic iron release	+	+	++	+++	+++
Relative stability of elemental iron within the carbohydrate shell	High	High	High	Medium	Low
Relative osmolality	Isotonic	Isotonic	Isotonic	Hypertonic	Hypertonic
Administration (iv push) rates	30 mg/s	Bolus push	50 mg (1 ml)/ min	Approximately 20 mg/min	12.5 mg/min
$t_{1/2}$ (h)	Approximately 15	7–12	5–20	6	Approximately 1

hemodialysis, with pharmacokinetic data demonstrating that mean serum iron concentrations increase in a dose-dependent manner after intravenous administration [129–131].

Iron Safety

Given trial evidence in adults that higher ESA doses are associated with adverse cardiovascular outcomes, using IV iron to reduce ESA dose requirements is an attractive treatment option. However, the administration of IV iron, even with new formulations, is not without risk. Concerns about potential adverse effects of IV iron supplementation include iron overload, adverse reactions including anaphylaxis, and increased risk when administered in the context of active infections. There have not been any pediatric studies focused on the long-term effects of IV iron supplementation in patients on chronic dialysis. The DRIVE trial, conducted in adults on dialysis, demonstrated that IV ferric gluconate was effective at raising hemoglobin and decreasing ESA dose requirements in patients with ferritin levels 500–1200 ng/mL and TSATs ≤25%, dispelling the widely held belief that patients with ferritin levels in this range were unlikely to benefit from IV iron [132]. However, further study is needed to determine whether IV iron supplementation is effective and safe in children with higher ferritin levels. KDIGO recommends avoidance of IV iron in patients with active systemic infections [28]. There is biologic plausibility to this, as iron may impair neutrophil and T-cell function and serve as a growth factor for pathogens [133]. However, there have been few studies testing this hypothesis. Ishida et al. showed, using observational data, that adults on hemodialysis who received IV iron within 14 days of hospitalization for a bacterial infection had no increased risk for 30-day or 1-year mortality or readmission or death within 30 days, but no comparable studies have been conducted in children [133]. Goldstein et al. conducted a RCT in 145 children with CKD to compare the safety and efficacy of varying doses of iron sucrose. They showed that a 0.5 mg/kg dose was non-inferior to higher-dosing regimens (1 mg/kg and 2 mg/kg) in terms of reaching a composite endpoint of hemoglobin in the range of 10.5–14 g/dL, TSAT 20–50%, and a stable ESA dose, supporting the practice of utilizing the lowest effective dose of IV iron in children [134].

Dialysis contributes to oxidative stress, the result of pro-oxidant molecules overwhelming the antioxidant defense mechanisms [135]. Studies performed in adults on hemodialysis have demonstrated that IV iron infusions are associated with an increased accumulation of biomarkers of oxidative stress [135]. Bolus or rapid IV infusion may be more likely to trigger an oxidative response and slow IV intradialytic infusion may be preferable in minimizing inflammatory or oxidative response, but no studies have specifically examined this in children [136–138]. There is a shortage of research to evaluate the effect of differences in formulation and pharmacokinetics of such agents and to determine whether repeated induction of oxidative stress has longer-term sequelae in terms of inflammation and cellular and tissue iron deposition.

Novel Routes of Iron Supplementation

Ferric pyrophosphate citrate (FPC, Triferic®) was approved by the US FDA in April 2016 for the replacement of iron to maintain hemoglobin in adults on hemodialysis [139]. FPC is dissolved in dialysate and administered via dialysis. In contrast to the IV iron administration of other iron preparations which can lead to the presence of non-transferrin-bound iron in the circulation and potentially trigger the generation of pro-oxidant and atherogenic molecules, FPC is quickly transferrin bound and removed from the circulation [140]. Pratt et al. conducted a pediatric study in which FPC was administered via the dialysate (added to bicarbonate concentrate) or intravenously (via the venous blood return line) to 22 hemodialysis patients <18 years of age during dialysis treatment and found it was well tolerated [141]. The mean serum total iron concentrations peaked 3–4 h after administration, and iron expo-

sure based on maximum serum concentration was greater after dialysate administration compared to the intravenous route [141]. Serum iron concentrations were also higher in 12–<18-year-old subjects after dosing compared to <12-year-olds [141]. Ferric citrate is a novel oral phosphate binder which also supplies elemental iron and has the potential benefit of providing therapy for at least two CKD comorbidities in a single agent, a potentially adherence-enhancing strategy. The ferric ion in ferric citrate combines with dietary phosphorus in the GI tract, but the excess ferric ions are reduced by the bowel mucosa to ferrous iron and absorbed into the systemic circulation [142]. Although ferric pyrophosphate citrate and oral ferric citrate have been approved for use in adults, the safety and efficacy of these agents have yet to be systematically assessed in children with CKD.

Future Directions

Anemia remains one of the most common comorbidities affecting children on dialysis, with dysregulated erythropoietin production and iron-restricted erythropoiesis the mechanisms targeted by most currently available clinical therapies. An ongoing treatment challenge is identifying the optimal target hemoglobin levels for children in terms of promoting survival, growth, cognitive function, and overall health, as the recommendations for "target" hemoglobin levels in dialysis patients are largely based on data extrapolated from adult studies. It is critical that emerging anemia therapies continue to have their safety and efficacy assessed in pediatric dialysis populations so that our patients can benefit from advances in treatment strategies.

References

1. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. Am J Kidney Dis. 2018;71(3):423–35.
2. Christison R. On granular degeneration of the kidneys and its connexions with dropsy inflammations and other diseases. Edinburgh: Black; 1839.
3. Camaschella C, Pagani A, Nai A, Silvestri L. The mutual control of iron and erythropoiesis. Int J Lab Hematol. 2016;38:20–6.
4. Lankhorst CE, Wish JB. Anemia in renal disease: diagnosis and management. Blood Rev. 2010;24(1):39–47.
5. Foley RN. Erythropoietin: physiology and molecular mechanisms. Heart Fail Rev. 2008;13(4):405–14.
6. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015;11(7):394–410.
7. Donnelly S. Why is erythropoietin made in the kidney? The kidney functions as a critmeter. Am. J. Kidney Dis. 2001;543:73–87.
8. Atkinson M, Warady B. Anemia in chronic kidney disease. Pediatr. Nephrol. 2018;33(2):227–38.
9. Jelkmann W. Molecular biology of erythropoietin. Intern Med. 2004;43(8):649–59.
10. West JB. Physiological effects of chronic hypoxia. N Engl J Med. 2017;376:1965–71.
11. Locatelli F, Fishbane S, Block GA, MacDougall IC. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. Am J Nephrol. 2017;45(3):187–99.
12. Kular D, Macdougall IC. HIF stabilizers in the management of renal anemia: from bench to bedside to pediatrics. Pediatr Nephrol. 2019;34(3):365–78.
13. Richmond TD, Chohan M, Barber DL. Turning cells red: signal transduction mediated by erythropoietin. Trends Cell Biol. 2005;15(3):146–55.
14. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Br J Cancer. 2001;16(Suppl 3):3–13.
15. Jelkmann W. The enigma of the metabolic fate of circulating erythropoietin (Epo) in view of the pharmacokinetics of the recombinant drugs rhEpo and NESP. Eur J Haematol. 2002;69(5–6):265–74.
16. Santiago P. Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview. Sci World J. 2012;2012:846824.
17. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone Hepcidin. Adv Nutr. 2017;8(1):126–36.
18. Poli M, Asperti M, Ruzzenenti P, Regoni M, Arosio P. Hepcidin antagonists for potential treatments of disorders with hepcidin excess. Front Pharmacol. 2014;5:86.
19. Atkinson MA, White CT. Hepcidin in anemia of chronic kidney disease: review for the pediatric nephrologist. Pediatr Nephrol. 2012;27(1):33–40.
20. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood. 2003;102(3):783–8.
21. Atkinson MA, Kim JY, Roy CN, Warady BA, White CT, Furth SL. Hepcidin and risk of anemia in CKD: a cross-sectional and longitudinal analysis in the CKiD cohort. Pediatr Nephrol. 2015;30(4):635–43.
22. Zaritsky J, et al. Hepcidin–a potential novel biomarker for iron status in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1051–6.

23. Zaritsky J, et al. Reduction of serum hepcidin by hemodialysis in pediatric and adult patients. Clin J Am Soc Nephrol. 2010;5(6):1010–4.
24. Atkinson MA, et al. Hemoglobin differences by race in children with CKD. Am J Kidney Dis. Jun. 2010;55(6):1009–17.
25. Hollowell JG, et al. Hematological and iron-related analytes–reference data for persons aged 1 year and over: United States, 1988–94. Vital Health Stat. 2005;11(247):1–156.
26. Jackson RT. Separate hemoglobin standards for blacks and whites: a critical review of the case for separate and unequal hemoglobin standards. Med Hypotheses. 1990;32(3):181–9.
27. Filler G, Mylrea K, Feber J, Wong H. How to define anemia in children with chronic kidney disease? Pediatr Nephrol. 2007;2(5):702–7.
28. KDIGO Anemia Workgroup. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
29. Mikhail A, et al. Renal association clinical practice guideline on anaemia of chronic kidney disease. BMC Nephrol. 2017;18(1):345.
30. Fadrowski JJ, Pierce CB, Cole SR, Moxey-Mims M, Warady BA, Furth SL. Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. Clin J Am Soc Nephrol. 2008;3(2):457–62.
31. Atkinson MA, Martz K, Warady BA, Neu AM. Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS. Pediatr Nephrol. 2010;25(9):1699–706.
32. Staples AO, et al. Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(1):48–56.
33. Borzych-Duzalka D, et al. Management of anemia in children receiving chronic peritoneal dialysis. J Am Soc Nephrol. 2013;24(4):665–76.
34. Robins EB, Blum S. Hematologic reference values for African American children and adolescents. Am J Hematol. 2007;82(7):611–4.
35. Atkinson MA, et al. Genetic associations of hemoglobin in children with chronic kidney disease in the PediGFR Consortium. Pediatr Res. 2019;85(3):324–8.
36. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol. 2003;18(10):1055–62.
37. Amaral S, Hwang W, Fivush B, Neu A, Frankenfield D, Furth S. Association of mortality and hospitalization with achievement of adult hemoglobin targets in adolescents maintained on hemodialysis. J Am Soc Nephrol. 2006;17(10):2878–85.
38. Dahlinghaus EK, Neu AM, Atkinson MA, Fadrowski JJ. Hemoglobin level and risk of hospitalization and mortality in children on peritoneal dialysis. Pediatr Nephrol. 2014;29(12):2387–94.
39. Adamczuk D, Roszkowska-Blaim M. Long-term outcomes in children with chronic kidney disease stage 5 over the last 40 years. Arch Med Sci. 2017;3(3):635–44.
40. Rheault MN, Molony JT, Nevins T, Herzog CA, Chavers BM. Hemoglobin of 12 g/dl and above is not associated with increased cardiovascular morbidity in children on hemodialysis. Kidney Int. 2017;91(1):177–82.
41. Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. J Am Soc Nephrol. 1996;7(5):763–73.
42. Moreno F, Aracil FJ, Perez R, Valderrabano F. Controlled study on the improvement of quality of life in elderly hemodialysis patients after correcting end-stage renal disease-related anemia with erythropoietin. Am J Kidney Dis. 1996;27(4):548–56.
43. Bárány P, Freyschuss U, Pettersson E, Bergström J. Treatment of anaemia in haemodialysis patients with erythropoietin: long-term effects on exercise capacity. Clin Sci (Lond). 1993;84(4):441–7.
44. Morris KP, Sharp J, Watson S, Coulthard MG. Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia. Arch Dis Child. 1993;69(5):580–6.
45. Van Damme-Lombaerts R, Broyer M, Businger J, Baldauf C, Stocker H. A study of recombinant human erythropoietin in the treatment of anaemia of chronic renal failure in children on haemodialysis. Pediatr Nephrol. 1994;8(3):338–42.
46. Gerson A, et al. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis. 2004;44(6):1017–23.
47. Warady BA, Sabath RJ, Smith CA, Alon U, Hellerstein S. Recombinant human erythropoietin therapy in pediatric patients receiving long-term peritoneal dialysis. Pediatr Nephrol. 1991;5(6):718–23.
48. Burke JR. Low-dose subcutaneous recombinant erythropoietin in children with chronic renal failure. Australian and New Zealand Paediatric Nephrology Association. Pediatr Nephrol. 1995;9(5):558–61.
49. Singh AK, et al. Correction of Anemia with Epoetin Alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085–98.
50. Pickett JL, Theberge DC, Brown WS, Schweitzer SU, Nissenson AR. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis. 1999;33(6):1122–30.
51. Marsh JT, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int. 1991;39(1):155–63.
52. Grimm G, Stockenhuber F, Schneeweiss B, Madl C, Zeitlhofer J, Schneider B. Improvement of brain function in hemodialysis patients treated with erythropoietin. Kidney Int. 1990;38(3):480–6.
53. Sagalés T, Gimeno V, Planella MJ, Raguer N, Bartolome J. Effects of rHuEPO on Q-EEG and event-related potentials in chronic renal failure. Kidney Int. 1993;44(5):1109–15.
54. Metry G, et al. Effect of normalization of hematocrit on brain circulation and metabolism in hemodialysis patients. J Am Soc Nephrol. 1999;10(4):854–63.

55. Levin A, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999;34(1):125–34.
56. Levin A, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis. 2005;46(5):799–811.
57. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62(2):648–53.
58. Matteucci MC, et al. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol. 2005;17(1):218–26.
59. El-Husseini AA, Sheashaa HA, Hassan NA, El-Demerdash FM, Sobh MA, Ghoneim MA. Echocardiographic changes and risk factors for left ventricular hypertrophy in children and adolescents after renal transplantation. Pediatr Transplant. 2004;8(3):249–54.
60. Morris KP, Skinner JR, Hunter S, Coulthard MG. Short term correction of anaemia with recombinant human erythropoietin and reduction of cardiac output in end stage renal failure. Arch Dis Child. 1993;68(5):644–8.
61. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF. Severe left ventricular hypertrophy in pediatric dialysis: prevalence and predictors. Pediatr Nephrol. 2000;14(10–11):898–902.
62. Mitsnefes MM, et al. Impaired left ventricular diastolic function in children with chronic renal failure. Kidney Int. 2004;65(4):1461–6.
63. Kupferman JC, et al. BP control and left ventricular hypertrophy regression in children with CKD. J Am Soc Nephrol. 2014;25(1):167–74.
64. Yorgin P, Zaritsky JJ. Management of renal anemia in children with chronic kidney disease in pediatric dialysis. 2nd ed. New York: Springer; 2012.
65. Foulks CJ, Mills GM, Wright LF. Parathyroid hormone and anaemia – an erythrocyte osmotic fragility study in primary and secondary hyperparathyroidism. Postgrad Med J. 1989;65(761):136–9.
66. Atkinson MA, Furth SL. Anemia in children with chronic kidney disease. Nat Rev Nephrol. Nov. 2011;7(11):635–41.
67. Bamgbola OF, Kaskel F. Role of folate deficiency on erythropoietin resistance in pediatric and adolescent patients on chronic dialysis. Pediatr Nephrol. 2005;20(11):1622–9.
68. Calò LA, Vertolli U, Davis PA, Savica V. L carnitine in hemodialysis patients. Hemodial Int. 2012;16(3):428–34.
69. Raimann JG, Levin NW, Craig RG, Sirover W, Kotanko P, Handelman G. Is vitamin C intake too low in Dialysis patients? Semin Dial. 2013;26(1):1–5.
70. Nasr SH, Kashtanova Y, Levchuk V, Markowitz GS. Secondary oxalosis due to excess vitamin C intake. Kidney Int. 2006;70(10):1672.
71. Lazarchick J. Update on anemia and neutropenia in copper deficiency. Curr Opin Hematol. 2012;19(1):58–60.
72. Nangaku M, Eckardt KU. Pathogenesis of renal anemia. Semin Nephrol. 2006;26(4):261–8.
73. Geerlings W, et al. Factors influencing anaemia in dialysis patients. A special survey by the edta-era registry. Nephrol Dial Transplant. 1993;8(7):585.
74. Djuric P, Dimkovic N, Djuric Z, Popovic J, Tosic J, Jankovic A. Influence of hemodialysis duration per week on parameters of dialysis adequacy and cardiovascular morbidity. Med Pregl Rev. 2014;10(6):388–95.
75. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010;116(23):4754–61.
76. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631–4.
77. Atkinson MA, et al. Association between common iron store markers and hemoglobin in children with chronic kidney disease. Pediatr Nephrol. 2012;27(12):2275–83.
78. Davidkova S, Prestidge TD, Reed PW, Kara T, Wong W, Prestidge C. Comparison of reticulocyte hemoglobin equivalent with traditional markers of iron and erythropoiesis in pediatric dialysis. Pediatr Nephrol. 2016;31(5):819–26.
79. Ratcliffe LEK, et al. Diagnosis and management of iron deficiency in CKD: a summary of the NICE guideline recommendations and their rationale. Am J Kidney Dis. 2016;67(4):548–58.
80. Urrechaga E, Borque L, Escanero JF. Biomarkers of hypochromia: The contemporary assessment of iron status and erythropoiesis. BioMed Res Int. 2013;2013:603786.
81. KDOQI. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis. 2007;50(3):471–530.
82. "Chronic kidney disease: managing anaemia | Guidance and guidelines | NICE."
83. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987;316(2):73–8.
84. Elliott S, Pham E, Macdougall IC. Erythropoietins: a common mechanism of action. Exp Hematol. 2008;36(12):1573–84.
85. Elliott S, et al. Enhancement of therapeutic protein in vivo activities through glycoengineering. Nat Biotechnol. 2003;21(4):414.
86. Wish JB, et al. Introduction of biosimilar therapeutics into nephrology practice in the United States: report of a scientific workshop sponsored by the National Kidney Foundation. Am J Kidney Dis. 2016;68(6):843–52.

87. Hörl WH. Differentiating factors between erythropoiesis-stimulating agents: an update to selection for anaemia of chronic kidney disease. Drugs. 2013;73(2):117–30.
88. Warady BA, Arar MY, Lerner G, Nakanishi AM, Stehman-Breen C. Darbepoetin alfa for the treatment of anemia in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2006;21(8):1144–52.
89. Schaefer F, et al. Safety and usage of darbepoetin alfa in children with chronic kidney disease: prospective registry study. Pediatr Nephrol. Mar. 2016;31(3):443–53.
90. Schmitt CP, Nau B, Brummer C, Rosenkranz J, Schaefer F. Increased injection pain with darbepoetin-α compared to epoetin-β in paediatric dialysis patients. Nephrol Dial Transplant. 2006;21(12):3520–4.
91. Macdougall IC, Eckardt KU. Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia. Lancet. 2006;368(9539):947–53.
92. Jelkmann W. Recombinant EPO production – points the nephrologist should know. Nephrol Dial Transplant. 2007;22(10):2749–53.
93. Cano F, et al. Continuous EPO receptor activator therapy of anemia in children under peritoneal dialysis. Pediatr Nephrol. 2011;24(4):665–76.
94. Fischbach M, Wühl E, Reigner SCM, Morgan Z, Schaefer F. Efficacy and long-term safety of C.E.R.A. maintenance in Pediatric Hemodialysis patients with Anemia of CKD. Clin J Am Soc Nephrol. 2018;13(1):81–90.
95. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int. 2005;68(3):1337–43.
96. Koshy SM, Geary DF. Anemia in children with chronic kidney disease. Pediatr Nephrol. 2008;23(2):209–19.
97. Port RE, Kiepe D, Van Guilder M, Jelliffe RW, Mehls O. Recombinant human erythropoietin for the treatment of renal anaemia in children – no justification for bodyweight-adjusted dosage. Clin Pharmacokinet. 2004;46(5):461–6.
98. Bamgbola OF, Kaskel FJ, Coco M. Analyses of age, gender and other risk factors of erythropoietin resistance in pediatric and adult dialysis cohorts. Pediatr Nephrol. 2009;24(3):571–9.
99. Port RE, Mehls O. Erythropoietin dosing in children with chronic kidney disease: based on body size or on hemoglobin deficit? Pediatr Nephrol. 2009;24(3):435–7.
100. McGowan T, Vaccaro NM, Beaver JS, Massarella J, Wolfson M. Pharmacokinetic and pharmacodynamic profiles of extended dosing of epoetin alfa in anemic patients who have chronic kidney disease and are not on dialysis. Clin J Am Soc Nephrol. 2008;4(11):1731–40.
101. Pergola PE, Gartenberg G, Fu M, Sun S, Wolfson M, Bowers P. A randomized controlled study comparing once-weekly to every-2-week and every-4-week dosing of epoetin alfa in CKD patients with anemia. Clin J Am Soc Nephrol. 2010;5(4):598–606.
102. Pfeffer MA, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–32.
103. Kliger AS, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013;62(5):849–59.
104. Lestz RM, Fivush BA, Atkinson MA. Association of higher erythropoiesis stimulating agent dose and mortality in children on dialysis. Pediatr Nephrol. 2014;29(10):2021–8.
105. Badve SV, Hawley CM, Johnson DW. Is the problem with the vehicle or the destination? Does high-dose ESA or high haemoglobin contribute to poor outcomes in CKD? Nephrology. 2011;16(2):144–53.
106. Goodkin DA, et al. Naturally occurring higher hemoglobin concentration does not increase mortality among hemodialysis patients. J Am Soc Nephrol. 2011;22(2):358–65.
107. Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents–time for a reevaluation. N Engl J Med. 2010;362(3):189–92.
108. Besarab A, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 2002;339(9):584–90.
109. Brigandi RA, et al. A novel hypoxia-inducible factor−prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: a 28-day, phase 2A randomized trial. Am J Kidney Dis. 2016;67(6):861–71.
110. Besarab A, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015;30(10):1665–73.
111. Schmid H, Jelkmann W. Investigational therapies for renal disease-induced anemia. Expert Opin Investig Drugs. 2016;25(8):901–16.
112. Cooke KS, et al. A fully human anti-hepcidin antibody modulates iron metabolism in both mice and nonhuman primates. Blood. 2013;122(17):3054–61.
113. Gilbertson DT, Peng Y, Arneson TJ, Dunning S, Collins AJ. Comparison of methodologies to define hemodialysis patients hyporesponsive to epoetin and impact on counts and characteristics. BMC Nephrol. 2013;14:44.
114. Chutia H, Ruram A, Bhattacharyya H, Boruah P, Nath C. Association of secondary hyperparathyroidism with hemoglobin level in patients with chronic kidney disease. J Lab Physicians. 2013;5(1):51–4.
115. Rao DS, Shih M, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in Uremia. N Engl J Med. 2002;328(3):171–5.
116. Fulton B, Jeffery EH. Heme oxygenase induction. Biol Trace Elem Res. 2008;81(6):1661–5.
117. Losekann A, et al. Aluminium intoxication in the rat induces partial resistance to the effect of recombinant human erythropoietin. Nephrol Dial Transplant. 1990;5(4):258–63.

118. Pollack AH, Oron AP, Flynn JT, Munshi R. Using dynamic treatment regimes to understand erythropoietin-stimulating agent hyporesponsiveness. Pediatr Nephrol. 2018;33(8):1411–7.
119. Bennett CL, et al. Linking drugs to obscure illnesses: lessons from pure red cell aplasia, nephrogenic systemic fibrosis, and Reye's syndrome. a report from the Southern Network on Adverse Reactions (SONAR). J Gen Intern Med. 2012;27(12):1697–703.
120. Yabu JM, et al. Sensitization from transfusion in patients awaiting primary kidney transplant. Nephrol Dial Transplant. 2013;28(11):2908–18.
121. Obrador GT, Macdougall IC. Effect of red cell transfusions on future kidney transplantation. CJASN. 2013;8(5):852–60.
122. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? CJASN. 2006;1(Suppl 1):S9–18.
123. Charytan DM, et al. Considerations and challenges in defining optimal iron utilization in hemodialysis. J Am Soc Nephrol. 2015;26(6):1238–47.
124. Anirban G, Kohli HS, Jha V, Gupta KL, Sakhuja V. The comparative safety of various intravenous iron preparations in chronic kidney disease patients. Ren Fail. 2008;30(6):629–38.
125. Pai AB. Iron oxide nanoparticle formulations for supplementation. Met Ions Life Sci. 2019;19 https://doi.org/10.1515/9783110527872-012.
126. Pai AB, et al. In vitro and in vivo DFO-chelatable labile iron release profiles among commercially available intravenous iron nanoparticle formulations. Regul Toxicol. Pharmacol. 2018;97:17–23.
127. Gillespie RS, Wolf FM. Intravenous iron therapy in pediatric hemodialysis patients: a meta-analysis. Pediatr Nephrol. 2004;19(6):662–6.
128. Warady BA, et al. Iron therapy in the pediatric hemodialysis population. Pediatr Nephrol. 2004;19(6):655–61.
129. Warady BA, et al. Sodium ferric gluconate complex maintenance therapy in children on hemodialysis. Pediatr Nephrol. 2006;21(4):553–60.
130. Warady BA, et al. Sodium ferric gluconate complex therapy in anemic children on hemodialysis. Pediatr Nephrol. 2005;20(9):1320–7.
131. Warady BA, Seligman PA, Dahl NV. Single-dosage pharmacokinetics of sodium ferric gluconate complex in iron-deficient pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(6):1140–6.
132. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, Rizkala AR. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol. 2007;18(3):975–84.
133. Ishida JH, et al. Receipt of intravenous iron and clinical outcomes among hemodialysis patients hospitalized for infection. Clin J Am Soc Nephrol. 2015;10(10):1799–805.
134. Goldstein SL, Morris D, Warady BA. Comparison of the safety and efficacy of 3 iron sucrose iron maintenance regimens in children, adolescents, and young adults with CKD: a randomized controlled trial. Am J Kidney Dis. 2013;61(4):588–97.
135. Liakopoulos V, Roumeliotis S, Zarogiannis S, Eleftheriadis T, Mertens PR. Oxidative stress in hemodialysis: causative mechanisms, clinical implications, and possible therapeutic interventions. Semin Dial. 2019;32(1):58–71.
136. Kato A, Odamaki M, Takita T, Furuhashi M, Maruyama Y, Hishida A. C-reactive protein is a predictor of short-term mortality in hemodialysis patients. Am J Nephrol. 2001;21(2):176–8.
137. Goldstein SL, Currier H, Watters L, Hempe JM, Sheth RD, Silverstein D. Acute and chronic inflammation in Pediatric patients receiving hemodialysis. J Pediatr. 2003;143(5):653–7.
138. Weiss G, Meusburger E, Radacher G, Garimorth K, Neyer U, Mayer G. Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. Kidney Int. 2003;64(2):572–8.
139. C. for D. E. and Research, "Approval Package for Application Number 208551Orig1s000," 2016 [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208551Orig1s000Approv.pdf
140. Rooyakkers TM, et al. Ferric saccharate induces oxygen radical stress and endothelial dysfunction in vivo. Eur J Clin Invest. 2003;32(Suppl 1):9–16.
141. Pratt RD, Grimberg S, Zaritsky JJ, Warady BA. Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis. Pediatr Nephrol. 2018;33(11):2151–9.
142. Yagil Y, et al. Managing hyperphosphatemia in patients with chronic kidney disease on dialysis with ferric citrate: latest evidence and clinical usefulness. Ther Adv Chronic Dis. 2015;6(5):252–63.

33 Immune Function and Immunizations in Dialyzed Children

Annabelle N. Chua and Sevcan A. Bakkaloğlu

Introduction

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are associated with significant alterations in immune function. On the one hand, CKD is associated with a state of chronic inflammation, which in turn has been associated with increased muscle catabolism, vascular calcification, insulin resistance, and malnutrition [1]. However, patients with CKD and ESKD also have immunodeficiency, as manifested by an increased risk for infection and sepsis and impaired response to vaccinations [1]. Infection is a leading reported cause of death in children with ESKD [2, 3]. Peritoneal dialysis (PD) continues to be plagued with the infectious complication of peritonitis, and hemodialysis (HD) is complicated by the development of catheter-related bacteremia. Excluding transplantation, infection is reported to be the most common reason for dialysis modality termination in children [2]. The treatment and the prevention of infections are therefore important elements in the care of pediatric dialysis patients, both for reduction of mortality and morbidity, and in the setting of PD, for preservation of the peritoneal membrane function. This chapter will provide a brief review of currently available information regarding the immune dysfunction associated with CKD and ESKD. In addition, because delivery of routine childhood and supplemental vaccinations remains a cornerstone of infection prevention, data regarding response to immunizations in children with CKD and alterations to the routine immunization schedule for healthy children required for children with CKD will be presented.

Immune Dysfunction

Information regarding immune function in children with CKD or ESKD is sparse. The incidence of peritonitis and catheter-related infections in children is higher than that found in adults, and infants and children up to 6 years of age develop peritonitis more frequently than older children. Immaturity of the immune system also contributes to the immune system dysfunction in children with CKD and ESKD. Therefore, the results obtained from adults cannot be directly extrapolated to children. A complete review of innate and acquired immunity in CKD is beyond the scope of this chapter; however, the following provides a brief overview of this complex topic.

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White Blood Cell Differentiation and Function

Lymphopenia has been noted in adult dialysis patients; however, the percentages of B-cells, T-cells, and T-cell subsets are usually normal [4–11]. Several studies evaluating lymphocyte number and the percentages of B-cells, T-cells, T-cell subsets, and NK cells in the peripheral blood of children with CKD or ESKD have produced conflicting results [12–18]. Children with pre-dialytic CKD have been reported to have alterations in memory T-cell subsets, and reduced numbers of memory B-cells have been reported in children on dialysis [19, 20]. Possible explanations for the reduced numbers of memory B-cells are a general suppression, suboptimal T helper activity, or disturbances in the B-cell migration process caused by uremia or dialysis treatment. Irrespective of the mechanism of memory B-cell reduction, the consequence might be a lower capacity to mount a secondary immune response, resulting in a decreased response to vaccination and predisposition to increased infection rates [20, 21].

In addition to alterations in the number or percentage of T-cells, abnormalities of T-cell-mediated immune responses have been demonstrated in CKD [7, 22–25]. T-cells from dialysis-treated patients show a combination of reduced proliferation and signs of activation [26–28]. The abnormal T-cell proliferation of uremic patients might be due to a defect within the T-cell population itself, to circulating inhibiting factors in uremic serum, or to the function of accessory cells such as monocytes [25, 29–39]. In children, data on this subject are scarce and conflicting. Two studies could not establish a difference in lymphocyte proliferation between children with CKD, dialyzed or not, and healthy children [12, 13]. George et al. performed an analysis of T-cell populations in children with CKD and demonstrated significant skewing toward advanced differentiation phenotypes in both the CD8 and CD4 subsets, which may represent features of advanced immune exhaustion and senescence [40]. Various alterations in cytokine production, particularly IFN-γ (gamma), have been reported in children with CKD, with one study demonstrating normalization of these abnormalities with HD [17, 41, 42].

Phagocytic Cells and Receptors

Reduced chemotaxis, adhesion, migration, and phagocytosis characterize the dysfunction of neutrophils and monocytes demonstrated in patients on dialysis [27, 43–46]. Data on the characteristics and function of phagocytes in children with CKD are limited [47, 48]. Interestingly, one study demonstrated that treatment with recombinant human growth hormone enhanced the oxidative burst activity of neutrophils in uremic children [47]. Wasik and colleagues concluded that PD improves phagocytosis and intracellular killing of bacteria by peritoneal macrophages but not by peripheral blood neutrophils in ESKD patients [48]. In another study of pediatric patients with ESKD, marked dysregulation in inflammatory cell chemokine receptor expression and responsiveness was noted and was more pronounced in the subgroup of patients who had multiple serious bacterial infections in the preceding year [49].

Limited information is available on the impact of CKD on IgG receptor (Fcγ(gamma)R) and complement receptor (CR) expression or function [50–54]. These receptors are important components in the interaction between humoral and cellular immunity and facilitate the phagocytic process. Some authors described an increased CD16 (Fcγ(gamma)RIII)-positive monocyte population in adult PD and HD patients when compared to healthy controls, a phenotype that has been linked to tissue macrophages in the context of the state of maturation [50, 51]. In children with pre-dialytic CKD and ESKD, studies have demonstrated a lower expression of Fcγ(gamma)RII (CD32) on peripheral blood monocytes and neutrophils compared to healthy children [41, 55–58]. Furthermore, reduced CR type 1 (CR1) expression, which is important for inducing phagocytosis of complement-coated bacteria, on lymphocytes and increased expression of Fcγ(gamma)R and CR on peritoneal

macrophages and neutrophils have been shown in pediatric CKD patients [41, 55–58].

Immunoglobulins

Low levels of IgG and/or subclasses have been described in patients on PD, attributed to peritoneal loss in most of the studies [59–70]. However, two studies in children reported that the immunoglobulin deficiency was already present before dialysis started, which suggests inhibition of synthesis by the uremic state [63, 64]. In one study, a deficiency of one or more IgG subclasses was present in 40% of children with CKD, with IgG_2 being the major subclass affected [64]. Children receiving PD had the lowest serum Ig levels [64].

The role of serum IgG or subclass deficiency in the pathogenesis of PD-associated peritonitis is unclear. Studies in adults could not establish a relationship between the peritonitis incidence and IgG or subclass deficiency [65, 70]. In children, a study by Kuizon et al. found a significant relationship between IgG and the incidence of peritonitis [71]. In another study, although not all children with IgG deficiency had a high incidence of peritonitis, all of the children with a high number of peritonitis episodes were in the IgG-deficient group [64]. On the contrary, a study by Lalan et al. found that while hypogammaglobulinemia is a frequent complication of peritoneal dialysis during infancy, it was not associated with an increased risk of peritonitis, and some infants developed peritonitis even after therapeutic IVIG administration [72].

In summary, numerous abnormalities in immune function have been described in CKD; however, these deficiencies are not consistently seen in pediatric patients. In addition, although the uremic state is likely a major contributor to this immune dysfunction, it seems plausible that a variety of uremic toxins may impact the individual components of the immune reaction in disparate ways. For the dialysis patient, it follows that a dialysis prescription measured only in terms of small solute clearance cannot be expected to optimize all of the factors that influence immune function. In addition, the impact of the dialysis procedure itself on immune function and activation must be considered. Thus, specific CKD-related treatment strategies to improve immune function, beyond the obvious goals of optimizing nutrition and correcting mineral bone disorder, metabolic imbalance, and anemia, remain elusive. It bears mentioning that despite data demonstrating low IgG levels in children receiving PD, there are no data at this time to support the routine use of intravenous immunoglobulin infusions for peritonitis treatment or prevention. One treatment strategy that is available specifically to minimize risk for infection in pediatric dialysis patients is the timely delivery of routine and supplemental immunizations, and the remainder of the chapter focuses on this topic.

Immunizations

Children with CKD and dialysis may have reduced response to and/or reduced duration of antibody after immunization and therefore may be at increased risk for infection from vaccine-preventable diseases. In order to minimize this risk, they require all the recommended childhood immunizations according to the standard schedule and additional vaccines and booster doses [73–77].

The completion of the vaccination schedule before renal transplantation (RTx) is of particular importance. Due to the complexity of clinical care of these children, immunizations can be delayed, overlooked, or not properly recorded. In fact, in a recent retrospective case series, only 22 out of 254 dialysis patients (9%) presented complete vaccination coverage prior to RTx. In particular, vaccination coverage against hepatitis B and MMR was more reasonable compared to varicella and pneumococci (89%, 83%, 59%, and 42%, respectively) [78]. The United States Renal Data System (USRDS) 2013 report revealed that among prevalent pediatric dialysis patients, approximately 40% received seasonal influenza vaccine between 2008 and 2011, and only 16% received vaccination against *Streptococcus pneumoniae* [79].

Although immunization recommendations for dialysis patients slightly vary among countries

[80] and different health authorities [73–76], all inactivated vaccine and toxoids are safe and effective when used in dialysis patients with the same doses and schedules as recommended for immunocompetent persons. There is no contraindication for live vaccines (except a precaution for live-attenuated influenza vaccine) in dialysis patients unless they are on immunosuppressive medications [73–76].

Accordingly, diphtheria, tetanus, acellular pertussis (DTaP), *Haemophilus influenzae* type b, polio, measles-mumps-rubella (MMR), *Streptococcus pneumoniae*, varicella zoster, and hepatitis B vaccines continue to be recommended. Parallel to modifications in standard schedules, rotavirus vaccine, tetravalent conjugated meningococcal vaccine, hepatitis A vaccine, and finally human papillomavirus (HPV) vaccine have been included in the immunization schedule of dialysis patients. BCG vaccine is recommended before the age of 6 years in some countries [73–76, 80].

In the following sections, available data concerning vaccine response in pediatric dialysis patients is provided, and any modification of the standard schedule that may be required for children on dialysis will be discussed.

Diphtheria, Tetanus, and Pertussis Vaccine

Diphtheria/tetanus toxoids and acellular pertussis (DTaP) vaccine should be administered in infants as recommended for healthy children. After three primary dose series, booster doses at 12–23 months (DTaP-containing vaccines), 4–6 years, and 9–15 years of age (tetanus, reduced diphtheria, acellular pertussis – Tdap) are recommended. Thereafter, tetanus and diphtheria toxoids (Td) 10 years apart are given [73–76].

A multicenter study in infants vaccinated while on dialysis revealed protective antibody titers to both diphtheria and tetanus toxoids in 7/8 patients (88%) [81]. Studies in older children and young adults on dialysis showed seroconversion after diphtheria and/or tetanus toxoids at a rate of 69–89% compared to 93–100% in healthy children [82, 83]. On the other hand, in older children, the rates of patients with a positive pretransplant vaccination titer against DTP were 38.5%, 60.0%, and 21.3%, respectively [84]. Thus, in older children on dialysis, efforts should be made to ensure that booster immunizations against tetanus and diphtheria are provided.

Haemophilus influenzae Type b (Hib) Conjugate Vaccine

In a multicenter study performed by the Pediatric Peritoneal Dialysis Study Consortium, antibody levels were measured in ten infants vaccinated with Hib conjugate vaccine while on dialysis [85]. This study found that 9/10 (90%) patients had protective antibody levels after vaccination and that antibody levels remained protective for as long as 22 months postvaccination [85]. In another study, antibody levels measured 2 months after the third dose of Hib conjugate vaccine were protective in all 42 pediatric dialysis patients studied [86]. Thus, this vaccine appears to be highly immunogenic in pediatric dialysis patients, and these children should receive this vaccine according to the standard schedule.

Hepatitis B Vaccine

Suboptimal response to hepatitis B vaccine is well documented among adult dialysis patients, and as such the ACIP recommends that adult patients on dialysis receive an augmented dose of 40 μg of either Recombivax HB or Engerix-B [87]. In children, there are only a few studies. Two small case series of pediatric CKD/dialysis patients and RTx recipients demonstrated that three doses of 5 μg (age <10 years) or 10 μg (age >10 years) or 20 μg hepatitis B vaccines resulted in a protective antibody titer

of ≥10 mIU/mL in more than 90% of cases (91–97%), if checked 2 months after the final immunization [86, 88]. Another prospective study revealed a seroconversion rate of 72% ($n = 26/36$) following three dose series of 10 μg hepatitis B vaccine in children with CKD stages II–V [89]. Revaccination with full doses is recommended for persons who do not develop protective antibody levels. Despite vaccination, 15% of pediatric RTx candidates were seronegative [90].

Current recommendations specify that dialysis patients less than 20 years of age receive 10 μg hepatitis B immunization according to the standard schedule (0–1–6 months), with the caveat that "higher doses might be more immunogenic" in pediatric HD patients [74, 76]. A recent retrospective multicenter study on pediatric HD patients showed that seroconversion rates are highest when administered 10 μg multidose boosters (97%) or 20 μg single- or multidose boosters (86% and 83%) compared to the augmented (40 μg) booster dose(s). Therefore, no specific recommendations have been made for augmented doses for pediatric hemodialysis patients [91].

Regardless of the dose of vaccine given, the ACIP recommends that postvaccination testing be performed 1–2 months after the primary series is completed and that up to three additional doses be given to patients who do not develop protective antibody levels (>10 mIU/mL). Antibody levels should then be measured annually and booster doses provided to patients if antibody levels fall <10 mIU/mL [73–76]. Protective antibody levels waned more rapidly in children who were immunized after starting dialysis (median: 37 months) than in those who received primary hepatitis B immunizations during childhood (106.3 months). Additionally, a lower percentage of patients immunized post-transplant had protective antibody levels than those with pre-dialysis CKD and on dialysis (66.7% vs. 96.4%) [88]. Therefore, vaccination in early stages of CKD is recommended [92] or at least two immunizations be given prior to the point at which dialysis or transplant is necessary, whenever possible [88].

Inactivated Polio Virus Vaccine

Since 1999, the AAP and ACIP recommendations have specified that only inactivated vaccine (IPV), rather than the live-attenuated oral vaccine, be used for routine immunization in all children [93] including dialysis patients. Vaccine coverage rate among pediatric dialysis patients is around 81% in a European multicenter study [78]. Another study performed in older children on dialysis who had antibody levels measured after vaccination with IPV found that 42/49 (86%) patients either had protective antibody levels to all three serotypes prior to vaccination or had at least a fourfold increase in antibody levels following immunization [94]. Because this vaccine contains only inactivated virus, it may be safely given to dialysis patients who are also on immunosuppressive medications.

Measles, Mumps, Rubella Vaccine

Measles, mumps, and rubella (MMR) vaccine is one of the live-attenuated viral vaccines currently on the childhood immunization schedule. There is no contraindication for MMR in children on dialysis unless they are receiving immunosuppressive therapy including corticosteroids [95]. Once corticosteroids are discontinued, it is generally recommended that MMR vaccination be delayed for at least 1 month [95] and it should be given at least 1 month prior to RTx. Additionally, when MMR and varicella vaccines are given shortly before, simultaneously with, or after an antibody-containing blood product, response to the vaccine can be diminished. Therefore, these vaccines either should be administered ≥2 weeks before receipt of a blood product or should be

delayed 3–8 months after receipt of the blood product, depending on the type of product [96].

MMR vaccine can be used as early as 6 months of age. If transplant has not occurred by the age of 12 months, the schedule for the MMR vaccine should be restarted with two doses at a minimal interval of 4 weeks between doses [97, 98].

There have been several studies evaluating response to MMR in pediatric dialysis patients. In a study performed by Schulman et al., ten dialysis patients 15–33 months of age were vaccinated with MMR after which only 70% developed protective titers to measles, 50% to mumps, and 80% to rubella [99]. Furthermore, only 3/10 (30%) had protective titers to all three viruses [99]. A subsequent study performed by Flynn et al. vaccinated nine infants, six of whom were on dialysis, at a mean age of 11.6 months [100]. Eight of these patients were subsequently transplanted at a mean age of 16 months, and at the time of transplantation, 89% had protective titers to measles, 88% to mumps, 100% to rubella, and 88% to all three viruses [100]. Another study performed in Germany measured antibody levels in 62 pediatric dialysis patients 2 months after immunization with MMR and found that all patients had positive antibody titers [86]. However, a recent European survey showed that only 77.4% and 73.0% of RTx candidates (age at transplantation: 9.9 ± 5.8 years) were seropositive against measles and mumps, despite a complete childhood vaccination schedule [78]. Furthermore, another recent European multicenter study showed that one third of pediatric nephrology centers reported not checking MMR antibodies during dialysis period or pre-RTx preparations [80]. Although these data suggest that many pediatric patients on dialysis may respond well to MMR vaccine, because immunization posttransplant is contraindicated, antibody titers should be measured prior to proceeding to transplant, and repeat vaccination given to patients with negative titers [95] . It should be kept in mind that children who were seronegative or not vaccinated against measles during pretransplantation period may experience severe measles infection and fatal measles complications after RTx [101].

Varicella Zoster Vaccine

Varicella zoster virus (VZV) vaccine is also a live-attenuated viral vaccine and is therefore contraindicated in dialysis patients on immunosuppressive medication and status post RTx [102]. Because of the significant risk for morbidity and mortality from varicella zoster infection posttransplant, there have been several studies to evaluate the immunogenicity of this vaccine in children with kidney failure and on dialysis. Early studies using the previously recommended single immunization with VZV vaccine in children with chronic kidney failure and on dialysis demonstrated seroconversion rates of 85–88%, compared to a rate of 99% in healthy children [103, 104]. Subsequently, two multicenter, prospective studies evaluated antibody levels after a two-dose regimen of VZV vaccine in children with pre-dialysis CKD and on dialysis [105, 106]. Both studies revealed that nearly all patients seroconverted after the second dose of vaccine, with a 98% seroconversion rate in one study and 100% in the other [105, 106]. Unfortunately, very few infants were included in these studies, and thus seroconversion rates in infants and toddlers on dialysis after either a one- or two-dose regimen are not known. Given these data, it is reasonable to consider measuring antibody levels prior to RTx and to provide supplemental vaccination if positive antibody titers are not demonstrated. In line with this, two recent studies from Europe showed that pretransplant rate of positive varicella titers was 79.2% and VZV antibodies were measured during dialysis period or pre-RTx preparations as a policy in 15 out of 18 pediatric nephrology centers [80].

Growing experience suggests that MMR and varicella vaccines can be administered at least 1 year after RTx, in clinically stable patients without a recent (within 2 months) rejection episode. Even though these patients are under minimal immunosuppression, the vaccination option should be evaluated on an individual basis [97].

Pneumococcal Vaccine

All children on dialysis should be vaccinated with the 13-valent conjugated pneumococcal vaccine (PCV13) as is recommended for healthy children to decrease the risk of invasive pneumococcal infection [73–75]. Despite adequate antibody response to conjugated vaccine in children and adults on dialysis [107, 108], due to the increased risk for pneumococcal disease in dialysis patients, they should also receive supplemental immunization with the 23-valent polysaccharide vaccine (PPSV23) after the age of 2 to expand serotype coverage [73–76, 109, 110]. In Europe, only 42% of children received a complete vaccination schedule against pneumococcus before RTx [84]. The timing of the supplemental immunization with PPSV23 vaccine varies depending on the age of the patient and the number of previous immunizations with PCV13 (for specific recommendations, see Table 33.1, CDC and ECDC websites [73–75, 109, 110]). Briefly, at least 8 weeks after primary immunization with PCV13, PPSV23 can be given and repeated after 5 years. Revaccination is important as several studies have suggested that although PPSV23 vaccine produces a reasonable antibody response in children on dialysis, there may be a rapid decline in antibody levels [84, 86, 111]. A recent study showed that only 69.4% of patients exhibited a positive vaccination titer against pneumococci serotypes before transplantation [78].

Hepatitis A, Meningococcal, Human Papillomavirus, and Rotavirus Vaccines

Children on dialysis may receive these vaccines as recommended for healthy children with the caveat that the live-attenuated rotavirus vaccine be avoided in children on immunosuppressive therapy. There are currently no data available on response to hepatitis A or rotavirus vaccines in children on dialysis. Because of the low prevalence of hepatitis A infections, its vaccine is not widely applied in Europe [80]. Although meningococcal and HPV vaccines are included in many countries' standard vaccination schedules [73–75, 80], a recent study from Europe showed that only 27.3% and 47.9% of pediatric RTx candidates had vaccination coverage against HPV and meningococcus [78]. Another study from the USA evaluated antibody response to the standard three-dose vaccine series of the HPV in 57 girls aged 9–21 years old with CKD, on dialysis, or with status post Rtx. Seropositivity was 100% in the CKD and dialysis groups, but a less robust response to the vaccine was observed among those with a RTx [112], which highlighted the importance of immunization before transplantation.

Influenza Vaccine

Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications [73, 113]. The influenza vaccine is available either as an inactivated vaccine (IIV) or a live-attenuated vaccine (LAIV). The CDC has a precaution about usage of LAIV in persons with kidney dysfunction, including those on dialysis. Therefore, only the inactivated vaccine should be given to patients on dialysis [73–75, 113]. The composition of the influenza vaccine changes each year based

Table 33.1 Recommended immunization schedule in children with chronic kidney disease and on dialysis

Vaccine	Age	Dose	Schedule	Route of administration	Booster doses
HBV	0–10 years 11–19 years	5 mcg/dose 10 mcg/dose	Three-dose schedule	IM	Postimmunization testing for anti-HBs is recommended for dialysis patients 4–8 weeks after completion of schedule. If immunization completed before, determine anti-HBs at time of diagnosis. If anti-HBs <10 UI/I 4–8 weeks after the last dose of primary vaccination series, repeat the series: 0–10 years: 10 mcg/dose three dose *series* 11–19 years: 20 mcg/dose three dose *series* Annual anti-HBs should be checked; booster doses should be given when anti-HBs <10 mIU/ml
Inactive influenza	6–35 months 3–8 years ≥9 years	0.25 or 0.5 ml[a] 0.5 ml 0.5 ml	Two annual doses in autumn Two annual doses in autumn (two annual doses for the first time immunization <9 years of age, thereafter one annual dose) One dose	IM/SC	Repeat every year during influenza season
Varicella	>12 months	0.5 ml	12 months to 12 years Two doses minimum 3 months apart >12 years two doses minimum 4 weeks apart	SC	Complete the immunization series or check the IgG level for varicella at the time of diagnosis[b]
Hepatitis A	>12 months	0.5 ml	Two doses 6 months apart	IM	Immunization recommendation depends on epidemiology of disease in the region. Complete the immunization series or check the IgG level for hepatitis A at the time of diagnosis
MMR	>12 months (6–9 months under specific circumstances)	0.5 ml	Two doses (min 4 weeks apart)	SC	Timing of doses depends on the epidemiology in the region Complete the immunization series or check the IgG level for MMR at the time of diagnosis[b]
IPV	2, 4, 6, 12–15 months 15 months to 18 years, unvaccinated	0.5 ml 0.5 ml	Four dose series Three doses with an interval of 1–2 months	IM IM	Booster dose between 5 and 10 years of age Revaccination 1 year after the third dose
Diphtheria, tetanus, acellular pertussis (DTaP)-containing vaccines	Min 6 weeks to 6 months	0.5 ml	Three primary dose series	IM	Booster doses at 12–23 months (DTaP-containing vaccines), 4–6 years, and 9–15 years of age (tetanus, reduced diphtheria, acellular pertussis – Tdap) Thereafter, Td 10 years apart

HIB	6 weeks (min) to 59 months	0.5 ml	One to four dose series depending on the age of first vaccination	IM	Complete and check the immunization series
Conjugated meningococcal vaccines (monovalent-A, C, bivalent-CY, quadrivalent– ACYW) MenB	Min 2 months of age >10 years in the USA >2 mo in Europe	0.5 ml	Dose series depends on starting age and the type of conjugate vaccine used (follow manufacturer recommendations)	IM	Follow national immunization recommendations[c]
HPV	As soon as possible from 9 years of age		Two doses 6 months apart (least 5 months apart)	IM	Older age groups ≥15 years three doses (0, 2, 6 months)
Rotavirus	First dose 6–14 weeks 6 days Last dose at 8 months		Two to three doses depending on vaccine with an interval of 4–8 weeks	PO	–
BCG	As soon as possible after birth	0.05 ml (<12 months) 0.1 ml (>12 months)	One dose One dose	ID	Follow the national immunization recommendations
Pneumococcal vaccine					
PCV13	2–23 months 24–71 months with no previous PCV13 6–18 years with no previous PCV13	0.5 ml	Two to four doses for completion of immunization depending on the age of first immunization Two doses of PCV13 One dose of PCV13	IM	
PPSV23	>2 years	0.5 ml	One dose 8 weeks after completion of PCV13 series	IM or SC	Booster dose 5 years later

IM intramuscular, *SC* subcutaneous, *ID* intradermal, *PO* per oral

[a]Dose volume is based on manufacturer

[b]MMR and varicella vaccine administration should be avoided within 4 weeks of organ donation and after renal transplantation

[c]If there is an ongoing risk, booster doses should be given

on the strains of viruses likely to circulate in the upcoming year, and, therefore, this vaccine must be given annually, typically in the fall [113]. Children under the age of 9 years who are receiving the influenza vaccine for the first time should receive two doses, given at least 1 month apart [74, 113].

Because of the significant risk for morbidity and mortality associated with influenza infection in pediatric patients with CKD and dialysis, there have been several studies evaluating vaccine response in this population that reported very good vaccine responses [114, 115]. Although these studies suggest that influenza vaccine produces a reasonable response in pediatric dialysis patients, because of the significant risk for morbidity and mortality from influenza infection in these patients, household contacts should receive vaccination in an effort to decrease the risk for exposure to influenza [73, 74, 113].

Bacille Calmette-Guerin (BCG) Vaccine

Children with CKD may receive BCG vaccine as recommended for healthy children at 2 months. Alternatively, it can be performed before the age of 6, according to PPD test results [73]. There is a significant variation about BCG vaccine administration among European countries [75]. A recent survey showed that BCG vaccine is routinely performed in only five countries (Greece, Lithuania, Poland, Turkey, and the UK), while PPD or Quantiferon test is applied to CKD patients in 12 centers from eight countries [80]. The difference among national immunization programs may be partly due to the low prevalence or eradication of tuberculosis in some European countries, so that health authorities do not recommend BCG vaccine.

Summary

In conclusion, several abnormalities of the immune system have been reported in children with CKD. Given the complexity of the multifactorial processes involved as well as the heterogeneity of the patients studied, it is difficult to elucidate the exact mechanisms leading to the increased risk of infection. In the meantime, in an effort to minimize risk for vaccine-preventable disease, pediatric patients on dialysis should receive all age-appropriate vaccines currently recommended for healthy children according to the standard schedule, with the exception of the avoidance of the live-attenuated influenza vaccine in all dialysis patients and avoidance of the other live vaccines (rotavirus vaccine, MMR, VZV) in CKD and dialysis patients treated with immunosuppressive medications. Because MMR and VZV vaccines are contraindicated posttransplant, every effort to provide immunization prior to the introduction of immunosuppressive medication posttransplantation should be made. Supplemental and/or augmented doses of hepatitis B vaccine should be given as indicated. Additional vaccination against *Streptococcus pneumonia, Neisseria meningitides*, *and HPV* should be performed. Antibody levels should be monitored regularly to evaluate protection.

Practical points around vaccine administration in children with CKD/Dialysis [73, 74, 76, 97, 98]

- Children with CKD/dialysis should receive all the recommended childhood immunizations according to the standard schedule whenever possible. Vaccination in early stages of CKD has better seroconversion rates than late vaccination.
- Inactive vaccines should be given at least 2 weeks prior to transplantation. Live vaccines (MMR and Varicella) should be administered at least four weeks prior to renal transplantation.
    - If an organ becomes available within 4 weeks of receiving MMR vaccine, a clinical decision must be made by weighing the risks of proceeding with transplant and starting immunosuppression in the face of recent live viral vaccine administration, and the efficacy of post-exposure prophylaxis such as IVIG, vs. the risk of remaining on the wait list.
    - For varicella vaccine, using antiviral treatment (usually IV acyclovir) and proceeding with transplant may be considered even if the patient received varicella vaccine within 3-4 weeks.
- Live attenuated influenza vaccine should not be given to CKD/dialysis patients.
- Live vaccines may be given 1 month after discontinuation of steroid therapy, 3 months or more after completion of other immunosuppressive chemotherapy, or 6 months after treatment with anti-B-cell antibodies.
- MMR and varicella vaccines should be administered ≥2 weeks before receipt of a blood product or should be delayed 3–8 months after receipt of the blood product, depending on the type of product.
- MMR and varicella vaccines can be administered at the age of 6 months, if early transplantation is desired. If transplant has not occurred by the age of 12 months, the schedule for the MMR vaccine should be restarted with two doses at a minimal interval of 4 weeks between doses.

Which vaccines cannot be administered simultaneously?

- The immune response to one live-virus vaccine might be impaired if administered within 28 days of another live-virus vaccine. If MMR and varicella vaccines are not administered simultaneously, administration should be separated by 28 day interval.
- PCV13 and PPSV23 should not be administered simultaneously and preference is for PCV13 first, followed by PPSV23.
- Since Men-ACWY decreases seroconversion of PCV13, it should be delayed at least four weeks after completion of PCV series (in those with asplenia).

Which primary/booster vaccinations can be postponed to after transplantation?

- Any of the inactivated virus vaccines can be postponed to post-transplantation period for the sake of timely transplantation, but ideally want to get it done prior for better seroconversion rates.
- Standard age-appropriate inactivated vaccine series should be administered 3 to 6 months after transplantation

For which vaccines should antibodies be measured routinely after vaccinations to verify an adequate immune response?

Ideally, CKD patients or those on dialysis should be tested for seroconversion 1-3 months after complete vaccination series for Hepatitis B (3 doses), varicella (2 doses) and MMR (2 doses). If antibody titers are positive, they can go into renal transplantation. If anti-HBs <10 mIU/ml, an augmented dose series should be administered. If still seronegative for MMR and Varicella, an extra dose may be administered.

References

1. Hauser AB, Stinghen AEM, Kato S, et al. Characteristics and causes of immune dysfunction related to uremia and dialysis. Perit Dial Int. 2008;28(Suppl 3):S183–7.
2. Warady BA, Sullivan EK, Alexander SR. Lessons from the peritoneal dialysis patient database: a report of the North American pediatric renal transplant cooperative study. Kidney Int Suppl. 1996;53:S68–71.
3. Groothoff JW, Gruppen MP, Offringa M, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002;61:621–9.
4. Lin CY, Huang TP. Serial cell-mediated immunological changes in terminal uremic patients on continuous ambulatory peritoneal dialysis therapy. Am J Nephrol. 1988;8:355–62.
5. Deenitchina SS, Ando T, Okuda S, et al. Cellular immunity in hemodialysis patients: a quantitative analysis of immune cell subsets by flow cytometry. Am J Nephrol. 1995;15:57–65.
6. Chatenoud L, Herbelin A, Beaurain G, Descamps-Latscha B. Immune deficiency of the uremic patient. Adv Nephrol Necker Hosp. 1990;19:259–74.
7. Kelly CJ. T cell function in chronic renal failure and dialysis. Blood Purif. 1994;12:36–41.
8. Lewis SL, Kutvirt SG, Cooper CL, Bonner PN, Holmes CJ. Characteristics of peripheral and peritoneal lymphocytes from continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1993;2(13 Suppl):S273–7.
9. Cohen G, Haag-Weber M, Horl WH. Immune dysfunction in uremia. Kidney Int Suppl. 1997;62:S79–82.
10. Lewis SL, Bonner PN, Cooper CL, Holmes CJ. Prospective comparison of blood and peritoneal lymphocytes from continuous ambulatory peritoneal dialysis patients. J Clin Lab Immunol. 1992;37:3–19.
11. Davies SJ, Suassuna J, Ogg CS, Cameron JS. Activation of immunocompetent cells in the peritoneum of patients treated with CAPD. Kidney Int. 1989;36:661–8.
12. Drachman R, Schlesinger M, Shapira H, Drukker A. The immune status of uraemic children/adolescents with chronic renal failure and renal replacement therapy. Pediatr Nephrol. 1989;3:305–8.
13. Hisano S, Miyazaki C, Hatae K, et al. Immune status of children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1992;6:179–81.
14. Bouts AH, Out TA, Schroder CH, et al. Characteristics of peripheral and peritoneal white blood cells in children with chronic renal failure, dialyzed or not. Perit Dial Int. 2000;20:748–56.
15. Aksu N, Keskinoglu A, Erdogan H, Yavascan O, Mir S, Kansoy S. Does immunologic status predict peritonitis in children treated with CAPD? Adv Perit Dial. 1998;14:243–6.
16. Ensari C, Ekim M, Ikinciogullari A, Tumer N, Ensari A. Are uraemic children immunologically compromised? Nephron. 2001;88:379–81.
17. Nairn J, Hodge G, Henning P. Intracellular cytokines in peripheral blood leucocytes in children with chronic renal failure. Pediatr Nephrol. 2006;21:251–6.
18. Albertazzi A, Cappelli P, Di Marco T, Maccarone M, Di Paolo B. The natural history of uremic neuropathy. Contrib Nephrol. 1988;65:130–7.
19. Bouts AH, Davin JC, Krediet RT, et al. Children with chronic renal failure have reduced numbers of memory B cells. Clin Exp Immunol. 2004;137:589–94.
20. Nairn J, Hodge G, Henning P. Changes in leukocyte subsets: clinical implications for children with chronic renal failure. Pediatr Nephrol. 2005;20:190–6.
21. Bouts AHM, Davin JC. Immune function of children on dialysis. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht/Boston/London: Kluwer; 2004. p. 369–82.
22. Lydyard P, Grossi C. Development of the immune system. In: Roitt I, Brostoff J, Male D, editors. Immunology. 5th ed. London: Mosby; 1998. p. 156–70.
23. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. J Am Soc Nephrol. 2002;13:204–12.
24. Raska K Jr, Raskova J, Shea SM, et al. T cell subsets and cellular immunity in end-stage renal disease. Am J Med. 1983;75:734–40.
25. Kurz P, Kohler H, Meuer S, Hutteroth T, Meyer zum Buschenfelde KH. Impaired cellular immune responses in chronic renal failure: evidence for a T cell defect. Kidney Int. 1986;29:1209–14.
26. Descamps-Latscha B, Chatenoud L. T cells and B cells in chronic renal failure. Semin Nephrol. 1996;16:183–91.
27. Descamps-Latscha B. The immune system in end-stage renal disease. Curr Opin Nephrol Hypertens. 1993;2:883–91.
28. Descamps-Latscha B, Jungers P. New molecular aspects of chronic uraemia and dialysis-related immunocompetent cell activation. Nephrol Dial Transplant. 1996;11(Suppl 2):121–4.
29. Beaurain G, Naret C, Marcon L, et al. In vivo T cell preactivation in chronic uremic hemodialyzed and non-hemodialyzed patients. Kidney Int. 1989;36:636–44.
30. Kamata K, Okubo M, Sada M. Immunosuppressive factors in uraemic sera are composed of both dialysable and non-dialysable components. Clin Exp Immunol. 1983;54:277–81.
31. Lim WH, Kireta S, Leedham E, et al. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. Kidney Int. 2007;72:1138–48.
32. Meuer SC, Hauer M, Kurz P, Meyer zum Buschenfelde KH, Kohler H. Selective blockade of the antigen-receptor-mediated pathway of T cell activation in patients with impaired primary immune responses. J Clin Invest. 1987;80:743–9.
33. Tsakolos ND, Theoharides TC, Hendler ED, et al. Immune defects in chronic renal impairment: evi-

dence for defective regulation of lymphocyte response by macrophages from patients with chronic renal impairment on haemodialysis. Clin Exp Immunol. 1986;63:218–27.
34. Girndt M, Sester M, Sester U, Kaul H, Kohler H. Molecular aspects of T- and B-cell function in uremia. Kidney Int Suppl. 2001;78:S206–11.
35. Girndt M, Kohler H, Schiedhelm-Weick E, Meyer zum Buschenfelde KH, Fleischer B. T cell activation defect in hemodialysis patients: evidence for a role of the B7/CD28 pathway. Kidney Int. 1993;44:359–65.
36. Descamps-Latscha B, Herbelin A, Nguyen AT, et al. Balance between IL-1 beta, TNF-alpha, and their specific inhibitors in chronic renal failure and maintenance dialysis. Relationships with activation markers of T cells, B cells, and monocytes. J Immunol. 1995;154:882–92.
37. Caruana RJ, Leffell MS, Lobel SA, Campbell HT, Cheek PL. Chronic T-lymphocyte activation in chronic renal failure: a study of hemodialysis, CAPD and predialysis patients. Int J Artif Organs. 1992;15:93–8.
38. Rabb H, Agosti SJ, Pollard S, Bittle PA, Ramirez G. Activated and regulatory T lymphocyte populations in chronic hemodialysis patients. Am J Kidney Dis. 1994;24:443–52.
39. Sester U, Sester M, Hauk M, Kaul H, Kohler H, Girndt M. T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. Nephrol Dial Transplant. 2000;15:1217–23.
40. George RP, Mehta AK, Perez SD, et al. Premature T cell senescence in Pediatric CKD. J Am Soc Nephrol. 2017;28:359–67.
41. Bouts AHM, Davin JC, Krediet RT, et al. Increased T-cell cytokine production in children with chronic renal failure normalizes after starting dialysis. Blood Purif. 2002;20:516.
42. Zachwieja J, Zaniew M, Runowski D, Lewandowska-Stachowiak M, Stefaniak E, Siwinska A. Abnormal cytokine synthesis as a consequence of increased intracellular oxidative stress in children treated with dialysis. Nephron Clin Pract. 2005;101:c100–8.
43. Descamps-Latscha B, Herbelin A. Long-term dialysis and cellular immunity: a critical survey. Kidney Int Suppl. 1993;41:S135–42.
44. Vanholder R, Ringoir S. Infectious morbidity and defects of phagocytic function in end-stage renal disease: a review. J Am Soc Nephrol. 1993;3:1541–54.
45. Vanholder R, Ringoir S, Dhondt A, Hakim R. Phagocytosis in uremic and hemodialysis patients: a prospective and cross sectional study. Kidney Int. 1991;39:320–7.
46. Braun N. Expression of adhesion molecules and activation markers on lymphocytes and monocytes during hemodialysis. Blood Purif. 1997;15:61–76.
47. Derfalvi B, Nemet K, Szalai C, et al. In vitro effect of human recombinant growth hormone on lymphocyte and granulocyte function of healthy and uremic children. Immunol Lett. 1998;63:41–7.
48. Wasik M, Blaim M, Kolewska D, Janota-Krawczyk E, Tomaszewska-Panczyk M, Sieniawska M. Changes in the phagocytic cells in children treated with continuous ambulatory peritoneal dialysis. Arch Immunol Ther Exp (Warsz). 1997;45:189–94.
49. Sherry B, Dai WW, Lesser ML, Trachtman H. Dysregulated chemokine receptor expression and chemokine-mediated cell trafficking in pediatric patients with ESRD. Clin J Am Soc Nephrol. 2008;3:397–406.
50. Nockher WA, Scherberich JE. Expanded CD14+ CD16+ monocyte subpopulation in patients with acute and chronic infections undergoing hemodialysis. Infect Immun. 1998;66:2782–90.
51. Brauner A, Lu Y, Hallden G, Hylander B, Lundahl J. Difference in the blood monocyte phenotype between uremic patients and healthy controls: its relation to monocyte differentiation into macrophages in the peritoneal cavity. Inflammation. 1998;22:55–66.
52. Carcamo C, Fernandez-Castro M, Selgas R, Jimenez C, Molina S, Vara F. Long-term continuous ambulatory peritoneal dialysis reduces the expression of CD11b, CD14, CD16, and CD64 on peritoneal macrophages. Perit Dial Int. 1996;16:582–9.
53. Ruiz P, Gomez F, Schreiber AD. Impaired function of macrophage Fc gamma receptors in end-stage renal disease. N Engl J Med. 1990;322:717–22.
54. Halma C, Daha MR, Feitsma RI, et al. Does haemodialysis impair macrophage Fc receptor function? Nephrol Dial Transplant. 1992;7:618–22.
55. Bouts AHM. Fcγ receptor expression on phagocytic cells in children with CRF. Perit Dial Int. 2000;20:112.
56. Bouts AHM, Davin JC, Monnens LA, et al. Complement receptors in blood and dialysate of children on peritoneal dialysis. Blood Purif. 2002;20:515.
57. Bouts AH, Krediet RT, Davin JC, et al. IGG and complement receptor expression on peripheral white blood cells in uraemic children. Nephrol Dial Transplant. 2004;19:2296–301.
58. Bouts AH, Davin JC, Krediet RT, et al. IgG and complement receptor expression in children treated by peritoneal dialysis. Pediatr Nephrol. 2005;20:1161–7.
59. Fivush BA, Case B, May MW, et al. Hypogammaglobulinemia in children undergoing continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1989;3:186–8.
60. Bunchman TE. Chronic dialysis in the infant less than 1 year of age. Pediatr Nephrol. 1995;9(Suppl):S18–22.
61. Schroder CH, Bakkeren JA, Weemaes CM, et al. IgG2 deficiency in young children treated with continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int. 1989;9:261–5.
62. Katz A, Kashtan CE, Greenberg LJ, et al. Hypogammaglobulinemia in uremic infants receiving peritoneal dialysis. J Pediatr. 1990;117:258–61.
63. Kemper MJ, Meyer-Jark T, Muller-Wiefel DE. IgG2 deficiency in uremic children is not restricted to peritoneal dialysis treatment. Pediatr Nephrol. 1997;11:684–6.
64. Bouts AHM, Davin JC, Krediet RT, et al. IgG and subclasses in children before and after starting peritoneal dialysis. Immunol Lett. 1997;56:333.

65. Poyrazoglu HM, Dusunsel R, Patiroglu T, et al. Humoral immunity and frequency of peritonitis in chronic peritoneal dialysis patients. Pediatr Nephrol. 2002;17:85–90.
66. Descamps-Latscha B, Herbelin A, Nguyen AT, et al. Immune system dysregulation in uremia. Semin Nephrol. 1994;14:253–60.
67. Preud'homme JL, Hanson LA. IgG subclass deficiency. Immunodefic Rev. 1990;2:129–49.
68. Kuijpers TW, Weening RS, Out TA. IgG subclass deficiencies and recurrent pyogenic infections, unresponsiveness against bacterial polysaccharide antigens. Allergol Immunopathol (Madr). 1992;20:28–34.
69. Oxelius VA. IgG subclass levels in infancy and childhood. Acta Paediatr Scand. 1979;68:23–7.
70. Krediet RT, Koomen GC, Vlug A, et al. IgG subclasses in CAPD patients. Perit Dial Int. 1996;16:288–94.
71. Kuizon B, Melocoton TL, Holloway M, et al. Infectious and catheter-related complications in pediatric patients treated with peritoneal dialysis at a single institution. Pediatr Nephrol. 1995;9(Suppl):S12–7.
72. Lalan S, Dai H, Warady BA. Hypogammaglobulinemia in infants receiving chronic peritoneal dialysis. Pediatr Nephrol. 2017;32:503–9.
73. Advisory Committee on Immunization Practices. Recommended immunization schedule for children and adolescents, United States, 2019. Accessed at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html on 8 Jan 2020.
74. Advisory Committee on Immunization Practices. Recommended child and adolescent immunization schedule by medical condition, United States, 2019. Accessed at https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html on 8 Jan 2020.
75. European Centre for Disease Prevention and Control Network. Accessed at http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx on 8 Jan 2020.
76. Guidelines for Vaccinating Dialysis Patients and Patients with Chronic Kidney Disease. Summarized from Recommendations of the Advisory Committee on Immunization Practices (ACIP); December, 2012. Accessed at https://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf on 8 Jan 2020.
77. Neu AM. Immunizations in children with chronic kidney disease. Pediatr Nephrol. 2012;27:1257–63.
78. Höcker B, Aguilar M, Schnitzler P, et al. Incomplete vaccination coverage in European children with end-stage kidney disease prior to renal transplantation. Pediatr Nephrol. 2018;33(2):341–35.
79. US Renal Data System: USRDS 2013 Annual Data Report: Atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, 2013. https://www.usrds.org/atlas13.aspx.
80. Bakkaloğlu SA, Özdemir Atikel Y, Paglialonga F, et al. Vaccination practices in pediatric dialysis patients across Europe. A European Pediatric Dialysis Working Group and European Society for Pediatric Nephrology Dialysis Working Group Study. Nephron. 2018;138(4):280–6.
81. Neu AM, Warady BA, Furth SL, et al. Antibody levels to diphtheria, tetanus, and rubella in infants vaccinated while on PD: a study of the pediatric peritoneal dialysis study consortium. Adv Perit Dial. 1997;13:297–9.
82. Girndt M, Pietsch M, Kohler H. Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure. Am J Kidney Dis. 1995;26:454–60.
83. Ghio L, Pedrazzi C, Assael BM, et al. Immunity to diphtheria and tetanus in a young population on a dialysis regimen or with a renal transplant. J Pediatr. 1997;130:987–9.
84. Höcker B, Aguilar M, Schnitzler P, et al. Vaccination titres pre- and post-transplant in paediatric renal transplant recipients and the impact of immunosuppressive therapy. Pediatr Nephrol. 2018;33(5):897–910.
85. Neu AM, Lederman HM, Warady BA, et al. Haemophilus influenza type b immunization in infants on peritoneal dialysis. Pediatr Nephrol. 1996;10:84–5.
86. Laube GF, Berger C, Goetschel P, et al. Immunization in children with chronic renal failure. Pediatr Nephrol. 2002;17L:638–42.
87. Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR. 2001;50(RR-05):1–46.
88. Watkins SL, Alexander SR, Brewer ED, et al. Response to recombinant hepatitis B vaccine in children and adolescents with chronic renal failure. Am J Kidney Dis. 2002;40:365–72.
89. Kamath N, Vasudevan A, Iyengar A. Seroconversion following hepatitis B vaccination in children with chronic kidney disease. Saudi J Kidney Dis Transpl. 2019;30(2):334–8.
90. Miller-Handley H, Paulsen G, Hooper DK, et al. Durability of the hepatitis B vaccination in pediatric renal transplant recipients. Clin Transpl. 2018;32(5):e13247.
91. Misurac JM, Van De Voorde RG, Kallash M, et al. Immunogenicity of augmented compared with standard dose hepatitis B vaccine in pediatric patients on dialysis: a Midwest Pediatric Nephrology Consortium Study. Clin J Am Soc Nephrol. 2017;12:772–8.
92. Sheth RD, Peskin MF, Du XL. The duration of hepatitis B vaccine immunity in pediatric dialysis patients. Pediatr Nephrol. 2014;29(10):2029–37.
93. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of poliomyelitis: recommendations for use of only inactivated polio vaccine for routine immunization. Pediatrics. 1999;104:1404–6.
94. Sipilä R, Hortling L, Hovi T. Good seroresponse to enhanced-potency inactivated poliovirus vaccine in patients on chronic dialysis. Nephrol Dial Transplant. 1990;5:352–5.

95. Centers for Disease Control and Prevention. Measles, mumps, and rubella vaccine use and strategies for elimination of measles, rubella and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 58. 1998;47(RR-08):1.
96. General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Timing and spacing of immunobiologics. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html. Last accessed at 31.01.2020.
97. Suresh S, Upton J, Green M, Pham-Huy A, Posfay-Barbe KM, Michaels MG, Top KA, Avitzur Y, Burton C, Chong PP, Danziger-Isakov L, Dipchand AI, Hébert D, Kumar D, Morris SK, Nalli N, Ng VL, Nicholas SK, Robinson JL, Solomon M, Tapiero B, Verma A, Walter JE, Allen UD. Live vaccines after pediatric solid organ transplant: proceedings of a consensus meeting, 2018. Pediatr Transplant. 2019;23(7):e13571.
98. Danziger-Isakov L, Kumar D, AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13563.
99. Schulman SL, Deforest A, Kaiser BA, et al. Response to measles-mumps-rubella vaccine in children on dialysis. Pediatr Nephrol. 1992;6:187–9.
100. Flynn JT, Frisch K, Kershaw DB, et al. Response to early measles-mumps-rubella vaccination in infants with chronic renal failure and/or receiving peritoneal dialysis. Adv Perit Dial. 1999;15:269–72.
101. Kalman S, Bakkaloğlu SA, Ozkaya O, Buyan N, Söylemezoğlu O. Measles: a rare communicable disease in a child with renal transplantation. Pediatr Transplant. 2002;6:432–4.
102. Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1996;45(RR-11):1–36.
103. Broyer M, Boudailliez B. Varicella vaccine in children with chronic renal insufficiency. Postgrad Med J. 1985;61(Suppl 4):103–6.
104. Zamora I, Simon JM, Da Silva ME, et al. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol. 1994;8:190–2.
105. Furth SL, Hogg RJ, Tarver J, et al. Varicella vaccination in children with chronic renal failure: a report of the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol. 2003;18:33–8.
106. Webb NJ, Fitzpatrick MM, Hughes DA, et al. Immunisation against varicella in end stage and pre-end stage renal failure. Arch Dis Child. 2000;82:141–3.
107. Vieira S, Baldacci ER, Carneiro-Sampaio M, et al. Evaluation of antibody response to the heptavalent pneumococcal conjugate vaccine in pediatric chronic kidney disease. Pediatr Nephrol. 2009;24:83–9.
108. Mitra S, Stein GE, Bhupalam S, Havlichek DH. Immunogenicity of 13-valent conjugate pneumococcal vaccine in patients 50 years and older with end-stage renal disease and on dialysis. Clin Vaccine Immunol. 2016;23(11):884–7.
109. Kim DK, Hunter P, Advisory Committee on Immunization Practices. Recommended adult immunization schedule, United States, 2019. Ann Intern Med. 2019;170(3):182–92.
110. Vandecasteele SJ, Ombelet S, Blumental S, Peetermans WE. The ABC of pneumococcal infections and vaccination in patients with chronic kidney disease. Clin Kidney J. 2015;8(3):318–24.
111. Furth SL, Neu AM, Case B, et al. Pneumococcal polysaccharide vaccine in children with chronic renal disease: a prospective study of antibody response and duration. J Pediatr. 1996;128:99–101.
112. Nelson DR, Neu AM, Abraham A, Amaral S, Batisky D, Fadrowski JJ. Immunogenicity of human papillomavirus recombinant vaccine in children with CKD. Clin J Am Soc Nephrol. 2016;11(5):776–84.
113. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 influenza season. MMWR Recomm Rep. 2019;68(No. RR-3):1–21.
114. Furth SL, Neu AM, McColley SA, Case B, Steinhoff M, Fivush B. Immune response to influenza vaccination in children with renal disease. Pediatr Nephrol. 1995;9:566–8.
115. Donmez O, Akaci O, Albayrak N, Altas A. Safety and effectiveness of a 2009 H1N1 vaccine in chronic kidney disease children. Nephron Clin Pract. 2014;128(3–4):341–4.

Neurocognitive Functioning in Pediatric Dialysis

34

Stephen R. Hooper and Erum Aftab Hartung

Introduction

Children and adult survivors of childhood-onset chronic kidney disease (CKD) have a greater frequency of neurodevelopmental and cognitive challenges compared with the general population [1, 2]. The impact of this neurodevelopmental vulnerability persists into adulthood and contributes to clinical manifestations such as a lower intelligence quotient and a lower frequency of postsecondary education compared with the general population [2]. The mechanisms responsible for the brain dysfunction observed with CKD have not been established, although a number of mechanisms have been hypothesized and are discussed below. The goals of this chapter are to explore potential mechanisms leading to brain dysfunction—including renal-brain connections—summarize known neurocognitive and neurologic findings, and consider possible management strategies for neurocognitive dysfunction in children affected by CKD, particularly once they reach end-stage kidney disease (ESKD).

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The Interaction of Brain Development, Kidney Disease, and Dialysis

Brain Development

Brain development is quite rapid during early childhood and, subtler but equally as critical, in later childhood and adolescence. Consequently, expectations for developmental attainment and general cognitive performance change as the child ages. The timing of this rapid neurodevelopmental growth places the developing brain at particular risk from injury or disease during infancy and childhood. Dennis et al. [3] and others [4] have suggested that the degree and severity of insult is likely related to when the insult occurs in the neurodevelopmental sequence and the cognitive reserve of the individual. Studies of other childhood chronic health conditions present from birth or shortly thereafter have found delays in language, motor skills, and overall developmental level [5–8]. In addition, children with early traumatic brain injury have shown deficits in academic achievement, behavior, cognitive, and motor functioning at the time of injury [9, 10], and these deficits persist long past the initial insult [11]. Given the rapid rate of this early neurodevelopmental growth, these deficits may be worse than brain insults obtained in later years [12]. Although there are relatively few studies of the longitudinal impact of CKD in infancy and early childhood, several studies suggest an

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increased risk of developmental delays in children with early-onset chronic kidney disease (CKD) or end-stage kidney disease (ESKD) [13–15] and in children with a longer duration of CKD or dialysis [16–19]. Further research is needed to improve our understanding of how CKD affects the developing brain and how factors such as age of onset, prematurity, disease severity, duration of disease, and treatment modality moderate immediate and downstream neurocognitive outcomes.

Kidney-Brain Connections

Given the above findings from the available pediatric neurocognitive and neurological literature, there is a clear connection between the kidney and brain. These observations generate key questions: How does kidney dysfunction contribute to brain dysfunction or damage? What do we know about possible mechanisms and how can they affect brain structure, brain function, and brain development?

Potential mechanisms of neurocognitive impairment in CKD include metabolic neuronal toxicity, vascular injury, and endothelial dysfunction, all of which are likely interrelated. At its simplest level, CKD may impact the nervous system by not effectively filtering neurotoxic chemicals and metabolites from the bloodstream, leading to metabolic neuronal injury. This mechanism may be most evident when the individual reaches end-stage kidney disease. Alterations in vascular integrity also may be present secondary to the metabolic changes associated with CKD as well as by its comorbidities such as hypertension, anemia, and dyslipidemia. Vascular injury may be further perpetuated by endothelial dysfunction, mediated by chronic inflammation, hypercoagulability, and oxidative stress [20].

In addition to the potential direct effects of kidney dysfunction on the brain, medical management of CKD and ESKD may affect neurocognitive outcomes. Factors such as malnutrition, aluminum intoxication, and psychosocial deprivation have historically contributed to adverse neurocognitive outcomes in children with CKD [21]. More modern treatment protocols may help to mitigate these effects by optimizing nutrition, reducing aluminum exposure by eliminating aluminum-containing phosphate binders and optimizing dialysis water treatment, and paying greater and more consistent attention to children's cognitive, educational, and psychosocial needs during medical treatment. Similarly, improved management of anemia in children with ESKD may also buffer the impact of CKD on the nervous system based, in part, on findings in adults with ESKD [22]. Dialysis itself may also contribute to neurocognitive dysfunction in the long term, as discussed further in the next section.

Metabolic Changes in CKD CKD causes retention of a large number of uremic toxins that differ in their molecular weight, protein binding, and ability to be removed by dialysis [23]. Many of these uremic toxins have known or putative roles in cerebral dysfunction. For example, guanidino compounds, which are known to have proconvulsant properties [24, 25], have been found in elevated levels in the serum, urine, cerebrospinal fluid, and brain tissue of patients with CKD [26–28]. Another pathway known to be altered in CKD is the kynurenine pathway of tryptophan metabolism, which is also implicated in the pathogenesis of various cognitive and neurodegenerative disorders independent of CKD [29]. In one study of adults with stage 4 CKD, higher serum levels of kynurenic acid were associated with lower cognitive functioning, while higher serum levels of indole-3 acetic acid (IAA) were correlated with anxiety and depression [30].

The advent of metabolomic profiling, in which hundreds of compounds can be measured in a single sample, may help to broaden our understanding of the numerous metabolic changes associated with CKD and their relationship to neurocognitive function. In one study of adults on maintenance hemodialysis, metabolic profiling of pre-dialysis plasma samples showed that levels of four metabolites related to phenylalanine, benzoate, and glutamate metabolism were associated with impaired executive function [31].

Imaging methods, such as magnetic resonance spectroscopy (MRS), may also help to deepen our understanding of the relationship between metabolic changes and neurocognitive dysfunction in CKD. For example, in one study of children with stage 1–5 CKD, including children on dialysis, MRS of the brain showed that the intelligence quotient (IQ) correlated negatively with the brain myoinositol/creatine ratio and positively with the N-acetyl aspartate (NAA)/creatine ratio [32]—neurometabolites related to neurotransmission and tissue damage or necrosis, respectively.

Some studies of the effects of dialysis and transplant on neurocognition also support the hypothesis that metabolic changes are at least partially responsible for neurocognitive dysfunction in CKD. In one small study, an electrophysiologic measure of cognitive potential, the P300 latency, was found to be impaired in adults with ESKD and also was found to normalize 3 months after successful kidney transplantation, presumably due to normalization of metabolic processes [33]. In another pilot study, transition of patients from conventional dialysis to nocturnal daily hemodialysis, which improves clearance of uremic toxins, was associated with improved psychomotor efficiency, attention, and working memory [34].

Vascular Integrity Another potentially strong linkage between kidney disease and brain impairment relates to the vascular integrity in both of these organs. Indeed, there are a number of similarities in the vascular supply to both the brain and kidney, with both being low-resistance end organs that manage high volumes of blood flow. Murray [35] and others have argued for a linkage between the kidney and the brain that is based on a model of accelerated vascular cognitive impairment.

Adults with CKD and ESKD are at much higher risk for cerebrovascular complications than the general population. In the 2006 United States Renal Data System Annual Report, the incidence of stroke was 15.1% in hemodialysis patients and 9.6% in CKD patients, compared to only 2.6% in non-CKD Medicare patients [36]. Preliminary evidence also has begun to show significantly higher rates of stroke, even in children with mild to moderate CKD [37]. Although coexisting risk factors, such as hypertension, diabetes, and dyslipidemia, contribute to stroke risk in many adults with CKD, having a glomerular filtration rate (GFR) of <60 mL/min/1.73m^2 has been shown to be independently associated with an increased risk of stroke [38]. Even in adults with CKD, but without a known clinical history of stroke or transient ischemic attacks, magnetic resonance imaging (MRI) studies have revealed a high prevalence of cerebrovascular abnormalities. In a study of more than 1000 adults, Liu et al. [39] found that GFR <60 mL/min/1.73m^2 was associated with an increased prevalence of markers of cerebral small vessel disease (e.g., lacunes, white matter hyperintensities, cerebral microbleeds, enlarged perivascular space) in individuals <60 years old, even after adjustment for comorbidities such as hypertension and diabetes. In nondiabetic adults, aged 30–60 years, with stage 3–4 CKD, Martinez-Vea et al. [40] found that 1/3 had silent cerebral white matter lesions, with vascular nephropathy being the strongest independent risk factor for the presence of these lesions. Similarly, Kobayashi et al. [41] found a high prevalence of silent brain infarction (SBI) in adults with CKD, with hypertensive nephrosclerosis showing a strong association with SBI.

Although the pediatric data are more limited, MRI studies in children with CKD also show evidence of alterations in cerebral vascular integrity. Among children who received a kidney transplant before 5 years of age, Valanne et al. [42] showed a 54% prevalence of ischemic lesions in vascular border zones. Although overt MRI lesions are much less common in children and young adults with milder CKD [43], a study of cerebral blood flow (CBF) using arterial spin-labeled (ASL) MRI showed that individuals aged 8–25 years with CKD had higher global CBF than healthy controls (primarily related to anemia). In addition, white matter CBF was positively correlated with blood pressure in CKD patients but not in healthy controls, suggesting abnormal cerebrovascular autoregulation in individuals with CKD [44]. This study also showed

that regional differences of CBF in the precuneus correlated with executive dysfunction. These findings provide some early mechanistic insights into how hypertension, a known risk factor for decreased neurocognitive performance in children both without [45] and with CKD [46, 47], may contribute to neurocognitive dysfunction.

Other factors that may contribute to impaired cerebral vascular integrity and cognitive impairment include hyperhomocysteinemia, oxidative stress, and inflammation. Hyperhomocysteinemia is common in patients with CKD [48] and may contribute to neurocognitive dysfunction both via endothelial pro-inflammatory effects and via its direct effects on the N-methyl-D-aspartate receptor [49, 50]. Oxidative stress, mediated by alterations in endothelial nitric oxide signaling, also has been linked to brain dysfunction in adults with CKD and in experimental models [51, 52].

The Impact of Dialysis on Kidney-Brain Connections

Chronic Dialysis Although clearance of uremic toxins by dialysis may improve neurocognitive function, chronic dialysis is associated with physiologic changes that may negatively impact brain function. In adults, initiation of hemodialysis (HD) is associated with a higher incidence of dementia-related symptoms when compared to patients initiating peritoneal dialysis (PD), even after adjustment for comorbidities and controlling for factors that influence dialysis modality selection [53]. In a longitudinal study, cognitive function declined faster in adults on dialysis compared to those with CKD, and the decline was faster in patients on HD than patients on PD [54]. Factors contributing to cerebral dysfunction in dialysis may include repeated episodes of cerebral hypoperfusion caused by hypotension and fluid shifts, which can lead to increased risk of brain ischemia and watershed infarcts. In a study using positron emission tomography-computed tomography (PET-CT) in older adults on hemodialysis, global CBF was found to decline significantly during HD (mean decline of 10 ± 15%), and the degree of CBF decline was associated with higher ultrafiltration (UF) volume and UF rate [55]. Although HD is associated with greater degrees of hemodynamic changes compared to PD, the risk of stroke has been shown to increase in older adults within 30 days of initiating either dialysis modality [56], suggesting that cerebral hypoperfusion can occur with both HD and PD.

Even in stable chronic dialysis patients, HD has been shown to be associated with short-term changes in cognitive performance. In studies of adult patients receiving HD, Costa et al. [57] and Dasgupta et al. [58] demonstrated deterioration of cognitive function when comparing performance before HD versus immediately after HD. Murray et al. [59] showed that global cognitive function in adults varies during a dialysis cycle, with worse performance during the HD session and best performance either shortly before or on the day after the session.

As discussed in more detail in the next sections, multiple studies in children receiving chronic dialysis have shown impaired neurocognitive performance in various domains [60–68]. However, there is very little literature examining the extent to which dialysis-related physiologic changes contribute to neurocognitive impairment in children. In their study of children who received a kidney transplant before age 5 years, Valanne et al. [42] described three patients who had marked widening of the cortical and central cerebrospinal fluid spaces on CT scans performed while receiving chronic dialysis; importantly, it was reported that these abnormalities resolved on posttransplant MRI (Fig. 34.1). They postulated that this reversible "pseudoatrophy" was a result of reversible contraction of brain tissue caused by factors such as fluid/electrolyte shifts, hypoalbuminemia, or medications [42]. However, more definitive physiologic studies of the effects of dialysis on the pediatric brain are needed.

Acute Dialysis Dialysis disequilibrium syndrome can arise acutely during or immediately after a dialysis session, most commonly in patients receiving their first HD treatment [69]. Symptoms of dialysis disequilibrium can include headache,

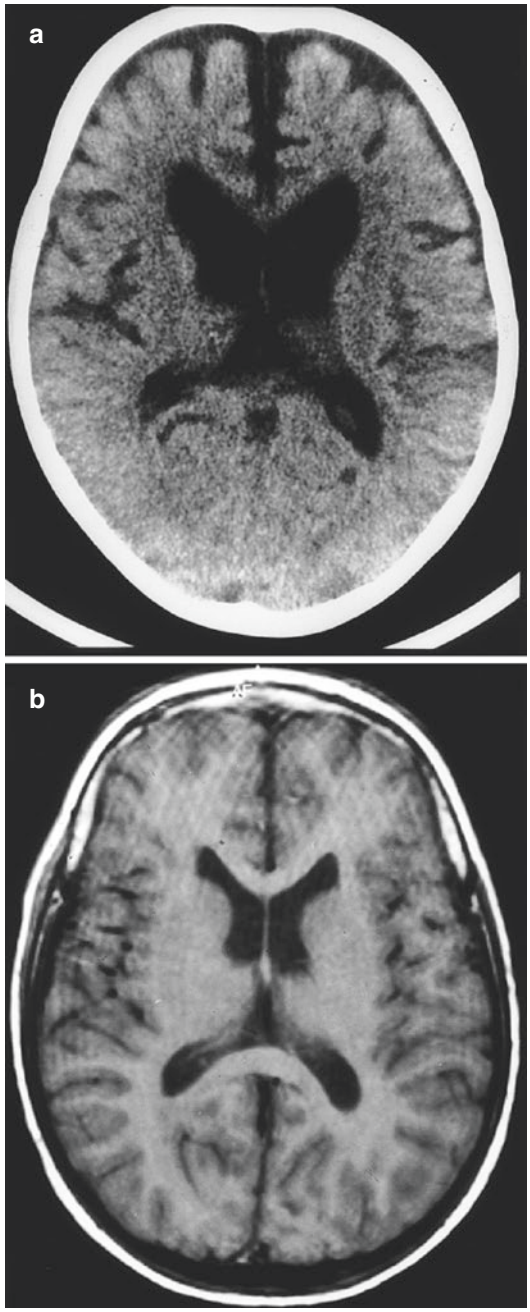

Fig. 34.1 This CT scan presents reversible "pseudoatrophy" in a patient on dialysis. (**a**) shows the presence of larger and misshapen lateral ventricles as well as widening of the subarachnoid spaces in frontal brain regions during dialysis. (**b**) shows an apparent resolution of these abnormalities in the same patient several years posttransplant. (Reprinted with permission from Wiley & Sons)

confusion, nausea, restlessness, and coma. These symptoms are primarily related to cerebral edema and increased intracranial pressure caused by osmotic movement of water into the brain.

There are two hypotheses for the mechanisms responsible for an osmotic gradient between the blood and the brain, namely, the "reverse urea" hypothesis and the "idiogenic osmoles" hypothesis [70]. The "reverse urea" effect is thought to occur because rapid removal of blood urea by dialysis leads to a blood-brain urea gradient, causing osmotic movement of water into the brain [71]. The "idiogenic osmoles" hypothesis arose from animal experiments in which rapid HD was associated with significantly higher brain tissue osmolality compared to the blood, which could not be fully explained by changes in electrolyte or urea concentrations [72]. This led the authors to conclude that the increased brain osmolality was caused by the new formation of organic molecules; however, a subsequent study of rapid HD in another animal model could not confirm the presence of "idiogenic osmoles" [73].

Regardless of the underlying mechanism, the primary method to prevent dialysis disequilibrium is to lower the blood urea concentration slowly, either via slow continuous HD or hemofiltration or by targeting lower urea reduction ratios [69]. Another approach to mitigate dialysis disequilibrium, and perhaps associated neurocognitive impairment, includes increasing blood osmolality by increasing dialysate sodium concentration [74] or by infusing mannitol [75].

Neurocognitive Functioning and Neuroimaging in Pediatric Dialysis

Neurocognitive Functioning in Pediatric Dialysis

Over the past 5 decades, the cognitive function of small cohorts of children receiving various forms of renal replacement therapy (RRT) has

been evaluated. Although informative, results from investigations conducted prior to 1990 were likely significantly influenced by uncontrolled anemia, aluminum exposure, and potentially less stringent nutritional, dialytic, and transplantation services compared with present-day management. Despite the improvement in these treatments [76], even more contemporary findings continue to be plagued by small sample sizes, samples that combined multiple forms of treatments and associated treatment protocols without differentiation, and samples that combine patients with wide age ranges. Further, there is little consistency across the neurocognitive measures used so as to compare one study to the next. These are not research oversights by investigators in the dialysis literature, but rather the result of the challenges of subject ascertainment and the medical needs of the children. A summary of the findings from the available contemporary studies over the past three decades is provided in Table 34.1.

Early studies and overviews of the CKD literature indicated significant concerns for several developmental delays—including gross motor and language functions and other neurological problems (e.g., microcephaly) in both dialyzed and non-dialyzed infants with severe CKD and ESKD [79, 80]. As can be seen in Table 34.1, infants and very young children on dialysis show developmental delays and significantly lower IQ scores compared to healthy children [60–64]. With respect to overall developmental functioning, many children on dialysis have been reported to be in the intellectual disability range. For older children and adolescents, a similar pattern of findings has been present, with overall intellectual functioning being approximately 9–11 points lower than controls [65]. Further, older children and adolescents also have had evidence of poorer abilities in their gross motor, fine-motor coordination, visuomotor skills, short-term memory, verbal abilities, and attention [66–68, 81]. More specifically, memory impairments are particularly noteworthy relative to the healthy control populations, and this impairment is greatest with dialysis-dependent ESKD [68].

A variety of executive function problems also have been reported, with particular concerns noted for problems in working memory, initiation, and sustaining capabilities [68]. Significant problems also have been reported in academic achievement across reading, spelling, and math areas, increased school absences, more frequent grade retentions, and the presence of formal learning disabilities [82, 83]. Unfortunately, we have a paucity of information regarding the impact of CKD and dialysis on specific language functions, overall motor skills, and adaptive behavior in children.

In contrast, several studies have not uncovered significant differences between children with ESKD and controls in the areas of memory, selected executive functions, academic achievement, or self-assessment of health-related quality of life [65, 66, 68, 84]. Furthermore, follow-up studies of children who have received kidney transplants, typically following some time on dialysis, generally have shown relative improvements in overall cognitive functioning. For instance, attention appears to be most severely affected with dialysis-dependent ESKD but reportedly improves after transplantation [15, 21, 81]. Qvist et al. [85] reported low average to average IQ in school-age children who received transplants before age 5 years, with as many as a quarter of the children continuing to show some type of neurocognitive impairment several years posttransplant. Improvements in both verbal and nonverbal IQ have been consistently reported following kidney transplantation [60, 86–88], with about a 10–12-point improvement in IQ being demonstrated at least one month or more posttransplant. Significant improvements also have been observed in processing speed, reaction time, and working memory [81]. Nevertheless, having ESKD in childhood does not appear to bode well for individuals as they move into older childhood or adulthood, with findings suggesting lower verbal and nonverbal intellectual capacities [2], lower academic achievement, and the presence of metacognitive executive dysfunctions [15]. Shorter duration of dialysis in childhood and older age at the time of renal replacement therapies—including transplant—also have been related to better outcomes [2, 15, 89].

Table 34.1 Summary of neurocognitive outcome studies in children and adolescents with ESKD and/or receiving renal replacement therapy

Study	Study population	Neurocognitive outcomes
Davis et al. (1990)	37 children, 25 males and 12 females, undergoing primary transplant evaluation; 20 on dialysis at pretransplant evaluation; 17 with conservative management; mean age at transplant was 17.6 months	Bayley Mental Developmental Index mean was 77 at pretransplant and 91 at posttransplant. Bayley Psychomotor Developmental Index was about 69 at pretransplant and about 86 at posttransplant. Early transplant improved both motor and cognitive developmental status in infants
Fennell et al. (1990)	56 children with CKD; 29 receiving dialysis or transplant and 27 receiving conservative management; 56 age-, race-, and gender-matched health controls; average age = 13.4 yrs	Patients with CKD performed more poorly than controls on visuomotor skills, short-term memory, and verbal abilities. No differences between groups on measures of attention. No differentiation of different types of renal replacement therapies
Lawry et al. (1994)	24 children with CKD, 9 receiving dialysis, 13 receiving transplant, and 2 CKD	Patients receiving transplant performed better on academic achievement tests of written language. They also showed better school performance in English compared to dialysis patients
Hulstijn-Dirkmaat et al. (1995)	31 children, 18 males and 13 females; mean age = 2.5 yrs; 16 receiving HD and 15 CKD	The overall sample was delayed when compared to normal expectations with a Bayley Index of 78.5. Those receiving HD performed evenly more poorly when compared to the CKD group, with scores reflecting intellectual disabilities (Bayley mean = 67.6)
Mendley and Zelko (1999)	9 children, 5 males and 4 females; 5 were receiving PD, 3 HD, and 1 conservative treatment; mean age at pretransplant was 14.2 yrs	Transplant patients significantly improved in reaction time, working memory, and attention posttransplant
Warady et al. (1999)	28 children who started PD < 3 months of age; 24 received transplant at about 2.1 yrs. of age	At 1 year of age, 79% were in average range on developmental testing; 4% were in the below average range of development. At approximately 4 yrs. of age, the percentages remained stable. At approximately 5 yrs. of age, nearly all children were attending school full time and in age-designated classrooms
Ledermann et al. (2000)	20 infants, ranging from birth to 12 months, in long-term peritoneal dialysis	Small head circumference approaching microcephaly, with increased head growth over time. There were 16 survivors, with 14 showing normal development post RRT
Brouhard et al. (2000)	124 subjects: 62 ESRD subjects on dialysis (26) or transplant (36) and 62 sibling controls; mean age was 13.8 yrs	Patients with ESRD performed significantly lower than controls on IQ, academic achievement (reading, spelling, and math). Increased time on dialysis was associated with lower scores
Crocker et al. (2002)	4 children with congenital (n = 13) or acquired (n = 11) ESRD; 15 dialysis and 9 CKD; no CNS syndromes and no suspected CNS medication effects	Neuropsychological testing showed no group differences in IQ, academic achievement, or short-term memory. The congenital ESRD group performed significantly worse on tasks of fine-motor coordination, long-term memory
Bawden et al. (2004)	44 children, 22 on dialysis or awaiting transplant and 22 sibling controls	Children with ESRD exhibited lower IQs of approximately 9–11 points across both verbal and nonverbal abilities than their sibling controls. Significant differences also were noted in fine-motor coordination and visuoconstructive abilities; however, the groups were commensurate in their academic achievement, memory, ratings of behavior, and self-esteem. Overall neurocognitive functioning was deemed more favorable than expected for children with ESRD

(continued)

Table 34.1 (continued)

Study	Study population	Neurocognitive outcomes
Eijsermans et al. (2004)	10 children, 8 males and 2 females, with chronic renal failure with HD for at least 1 month; mean age = 12.3 yrs	Presence of significant gross motor problems in the majority of children on dialysis, with only 1 participant showing fine-motor problems. No concerns were noted in self-assessments of health-related quality of life
Gipson et al. (2006)	20 children with CKD, ages 7.5–19 yrs. (Mean = 13.4), with 12 receiving dialysis and 8 conservative therapy; 18 healthy controls	Intellectual function for the CKD group was within the low average to average range (M = 89.32) and significantly lower than the controls (M = 112.18). After controlling for IQ, the CKD group performed significantly lower than the controls on all memory functions. The CKD group also was significantly lower on some executive functions (initiation, sustaining) but performed similarly to controls on other executive functions (inhibition, set shifting)
Duquette et al. (2007)	30 children with CKD, including 15 receiving dialysis; 41 healthy controls	Compared to healthy controls, children with CKD experienced more grade retentions, school absences, and lower achievement skills in math and reading. They also satisfied criteria for a low achievement definition of learning disabilities more so than the controls

Note. Table adapted from Moodalbail and Hooper [77] and Gipson and Hooper [78]

Neuroimaging Findings in Pediatric Dialysis

In addition to neurocognitive function, the impact of CKD has been demonstrated in various neuroimaging and electroencephalographic (EEG) procedures, as noted above. From the approximately 15 or so neuroimaging studies that have been conducted to date, structural analyses via magnetic resonance imaging (MRI) and computerized tomography (CT) have documented the presence of a variety of anomalies including chronic infarct lesions, ischemic watershed zone white matter lesions, early signs of cerebral vascular disease as demarcated by deep white matter hyperintensities and white matter lesions, and cerebral atrophy [90]; however, virtually none of the childhood studies have isolated children on dialysis, or various forms of dialysis, in their descriptions, with the work by Valanne et al. [42] being the one exception thus far.

Electrical conduction dysfunction has also been reported, with EEG abnormalities being reported in 42% of a pediatric cohort with CKD from infancy, and it has been associated with poorer kidney function and severity of anemia in adults [21, 42, 91]. Hurkx et al. [92] found no differences in auditory pathway nerve conduction between children with CKD and children undergoing PD. For the entire combined sample, high inter-peak latencies were found in the somatosensory cortex and were attributed to decreased cortical conduction via the thalamus. Brainstem conduction was normal for the combined group, with no differences noted between those with CKD and those receiving PD; however, delayed conduction was noted in the thalamocortical region for children less than 30 months of age for the combined sample, perhaps being secondary to delayed myelination in very young children with CKD. In addition to specific conduction abnormalities, children with CKD may be at risk for generalized conduction abnormalities which manifest as a seizure disorder as reported in 0% to 20% of children with CKD [92, 93]. The application of these findings to children receiving dialysis, though, remains unknown at present.

Management of Cognitive Dysfunction in Children on Dialysis

Given the chronic nature of ESKD and its associated neurodevelopmental challenges, it is likely that children and adolescents with ESKD are in need of a variety of management strate-

gies. This is true regardless of their treatment modality. There are various medical complications that many of these children experience that interfere with day-to-day functioning (e.g., school absences, medication compliance issues, etc.), and they likely will experience frequent challenges in the school and preschool settings secondary to their cognitive dysfunction and kidney-related medical complications. For example, there are high rates of low birth weight and prematurity in the CKD population, with rates as high as 18%, and these factors can influence brain development and associated cognitive functioning along with the kidney disease. Similarly, there are concomitant high rates of seizure disorders in children with kidney disease, with these rates ranging from approximately 7% to 18% for children on dialysis [85, 94], particularly those receiving HD [95]. These rates increase during dialysis to 29% for children who have had a prior history of seizures. Further, with respect to the presence of seizures pre-dialysis or the manifestations of seizures during dialysis, it is important for the pediatric nephrologist to understand potential adjustments to the anticonvulsant medications that might be required, particularly during the dialysis process, so as to lessen the chance of seizure occurrence [96]. Taken together with these (and other) medical management strategies, the management of the cognitive dysfunction in pediatric ESKD also requires significant attention by the pediatric nephrologist and the interdisciplinary health-care team.

Although there are no evidence-based educational management strategies or interventions explicitly linked to CKD, there are a number of empirically based interventions that have a demonstrated track record in working with children with learning and developmental difficulties. In addition to the necessary medical interventions detailed across many of the chapters in this text, management of the neurodevelopmental challenges also should be considered and implemented via a developmental framework; that is, these should be considered with the developmental level of the child in mind for their most efficacious applicability to a pediatric dialysis population, and they should be discussed routinely with the family by the interdisciplinary team of professionals caring for the child [97].

Early Intervention

The infant, toddler, and preschool periods of development are critical to the growth of the child. This time period, encompassing birth to approximately 5 years of age, is a remarkable time of development. It is the time when gross motor skills evolve into crawling, walking, running, jumping, and skipping. It is also the time when fine-motor skills evolve into grasping a snack with the rake of a hand to scribbling with a crayon to eventual adaptive skills and other important functions such as dressing and writing. This time period is critical in terms of the ongoing development of cognitive abilities, preacademic skills, and increasingly complex social interactions [98]. As such, these first 5 years of life are at least as important as any other 5-year span in an individual's life and perhaps can influence outcomes across the life span [13, 99].

The quality of neurodevelopmental outcomes also may be dependent on the type and quality of the early intervention services that they receive. The accumulating evidence suggests that the results of early efforts to remediate or attenuate a child's deficits can be successful. Although more evidence exists to support the benefits of early intervention for children at environmental risk [98], research that supports services for young children with biological impairments, such as those receiving dialysis, is also growing. For example, Black et al. [100] examined the influence of home visiting on infants with failure to thrive syndrome using a standardized home intervention curriculum that focused on maternal sensitivity, parent-infant relationships, and child development. This group was compared with a group of typical infants and with a group of other infants with failure to thrive who did not receive home intervention, but were seen in a medical clinic for routine care. At 8-year follow-up, children in the typical growth group were taller and heavier and had better arithmetic scores than the

clinic-only group. The home intervention group had intermediate results. There were no group differences in IQ, reading, or mother-reported behavior problems; however, children in the home intervention group had fewer teacher-reported problems and better work habits than the clinic-only group. How such a program would impact the developmental trajectory of young children with ESKD receiving dialysis remains to be determined; however, such an intervention may be quite applicable to the young dialysis population.

Additionally, it is important to note that there are a number of early intervention programs designed to improve specific developmental areas, such as motor functions, language abilities, and social-emotional skills in the early years [98]. It is suspected that young children with ESKD will respond positively to these types of early intervention approaches and programs. In the meantime, it will be important for pediatric nephrologists to be aware of such programs in their communities, or at least the early intervention programs and professionals, so as to work with their families and local developmental experts in providing the early intervention services that might be necessary for the preschool child with ESKD and receiving dialysis.

School Age

Despite many medical advances in pediatric nephrology, children with CKD are at risk for school-based challenges and failures. Further investigation is needed to potentially improve academic outcomes for this population through hospital-based intervention and special education planning. Although high rates of neurocognitive impairment have been reported, observational studies of school placements have revealed that most children with CKD attend regular education settings with or without special education and that their overall achievement skills are not overly impaired [101]. However, children with ESKD do show increased rates of school difficulties across all subject areas, and they experience increase rates of school absenteeism and grade retentions as shown in Table 34.1. Additional research is needed to better understand the special education and general learning needs of children with ESKD. There are, however, a variety of evidence-based instructional strategies that are likely applicable to children with ESKD.

Specifically, the interventions that have been developed for various aspects of reading have a clear scientific foundation with numerous studies demonstrating their effectiveness for children with reading disorders. For example, there is a preponderance of evidence to indicate the importance of explicit instruction in the alphabetic principle and phonological processing as critical components to reading intervention for children with reading recognition problems. Indeed, the National Reading Panel [102] showed the effects to be large in magnitude. Similarly, repeated reading interventions have been shown to improve reading fluency [103], and the development and use of strategies have been employed to improve reading comprehension [104]. Similar efforts have shown positive outcomes in the areas of mathematics [105] and written language [106, 107]. Another area that has evolved for children with various neurological and neurodevelopmental disorders is cognitive rehabilitation therapy; however, such computer-based treatments have not been applied to children with CKD or ESKD. The presence of neurocognitive difficulties in this population of children raises the potential for the use of these computer-based treatment strategies, particularly with respect to their applicability to the home, school, and clinic settings [108].

Adolescence and Adult Transition

In addition to many of the treatments available for school-age children, adolescents with ESKD face many barriers during their transition to early adulthood. The transition to adulthood is an important period in human development that requires an individual to increase his/her level of autonomy, find gainful employment, and build social relationships. Childhood-onset CKD/ESKD and the associated medical complications can prevent many adolescents from making this transition and facing these developmental challenges successfully [109]. Improvement of the

current survival rates for adolescents with ESKD of 80% at 10 years must be coupled with successful transition expectations [110, 111].

To date, intervention research geared toward the medical and psychosocial barriers that impede transition to adulthood is in development, and intervention research geared toward understanding the cognitive barriers to transition remains nonexistent. Over 8 years ago, Bell et al. [112] noted the importance of the possible interaction between cognitive functioning and successful health-care transition for adolescents and emerging adults with end-stage kidney disease. They asserted the importance of the cognitive/developmental level of the patient as a key factor in successful transition, along with a host of other factors including available health resources, family functioning, and the need for family education about the challenges of health-care transition. Further, Bell et al. discussed the importance of collaboration and clear communication between the pediatric and adult health-care teams in the transition process, and this will be especially important for the adult nephrologist assuming the care of an emerging young adult receiving dialysis.

In spite of minimal response-to-intervention research within this population, several possibilities exist that might prove instrumental in smoothing the transition for adolescents with ESKD. In addition to the special education issues noted above, Icard et al. [113] examined specific transition issues including vocational rehabilitation services and mental health needs and stressed the need for the development of evidence-based transition programs that would facilitate the movement from late adolescence into adulthood [110]. The issue of medical transition also is critical to this population, particularly given the importance of medication adherence [114] and the treatment of the associated medical needs that will continue into adulthood.

Conclusions and Directions

This chapter outlined the neurodevelopmental challenges of children with ESKD, with a particular focus on the effects of dialysis on the brain. While it appears that nearly every neurocognitive function can be affected by ESKD and dialysis, the literature is compromised by a variety of methodological issues including small sample sizes, samples of convenience, highly heterogeneous samples (e.g., wide age ranges, different ages of treatment), heterogeneous treatments, and lack of consistency of measurement across studies [77]. Future studies clearly need to address these methodological issues in order to provide a clearer picture of the neurocognitive outcomes in children receiving dialysis.

Despite these methodological problems, it does appear that children receiving dialysis demonstrated significantly lower IQ when compared to controls, and they show a variety of other neurocognitive and learning difficulties as well. Children receiving hemodialysis may be at particular risk for showing neurocognitive impairments and higher rates of seizures, although this will require additional study, especially the possibility that there could be improvement post-transplant. Findings from the available literature also suggest that shorter durations of dialysis and early kidney transplant hold potential for lessening the degree of neurocognitive impairments. The application of developmentally appropriate interventions to optimize their cognitive trajectory and opportunities for independence as adults also is important, particularly as children move closer to ESKD and the possibility of renal replacement therapies. At a minimum, utilization of a multidisciplinary or interdisciplinary team model would be important to assist in managing the shifting developmental needs of the individual with ESKD and his/her family from a life course perspective, with ongoing neurodevelopmental surveillance being a critical component of that approach. Using a multidisciplinary and scientifically rigorous approach, we anticipate the coming decade to provide opportunities to progress from quantifying the developmental challenges to identifying the underlying mechanisms and associated evidence-based interventions for the cognitive dysfunction demonstrated in children requiring dialysis and other renal replacement therapies.

References

1. Gipson DS, Duquette PJ, Icard PF, Hooper SR. The central nervous system in childhood chronic kidney disease. Pediatr Nephrol. 2007;22:1703–10.
2. Groothoff JW, Grootenhuis M, Dommerholt A, Gruppen MP, Offringa M, Heymans HS. Impaired cognition and schooling in adults with end stage renal disease since childhood. Arch Dis Child. 2002;87:380–5.
3. Dennis M, Spiegler BJ, Juranek JJ, Bigler ED, Snead OC, Fletcher JM. Age, plasticity, and homeostasis in childhood brain disorders. Neurosci Biobehav Rev. 2013;37(10 Pt 2):2760–73.
4. Moser JJ, Veale PM, McAllister DL, Archer DP. A systematic review and quantitative analysis of neurocognitive outcomes in children with four chronic illnesses. Pediatr Anesth. 2013;23:1084–96.
5. Antonini TN, Dreyer WJ, Caudle SE. Neurodevelopmental functioning in children being evaluated for heart transplant prior to 2 years of age. Child Neuropsychol. 2018;24(1):46–60.
6. Hogan AM, Kirkham FJ, Prengler M, Telfer P, Lane R, Vargha-Khadem F, et al. An exploratory study of physiological correlates of neurodevelopmental delay in infants with sickle cell anaemia. Br J Haematol. 2006;132(1):99–107.
7. Caudle SE, Katzenstein JM, Karpen S, McLin V. Developmental assessment of infants with biliary atresia. J Pediatr Gastroenterol Nutr. 2012;55(4):384–9.
8. Compas BE, Jaser SS, Reeslund K, Patel N, Yarboi J. Neurocognitive deficits in children with chronic health conditions. Am Psychol. 2017;72(4):326–38.
9. Keenan HT, Hooper SR, Wetherington CE, Nocera M, Runyan DK. Neurodevelopmental consequences of early traumatic brain injury in 3-year-old children. Pediatrics. 2007;119(3):e616–23.
10. Gagner C, Landry-Roy C, Bernier A, Gravel J, Beauchamp MH. Behavioral consequences of mild traumatic brain injury in preschoolers. Psychol Med. 2018;48(09):1551–9.
11. Garcia D, Hungerford GM, Bagner DM. Topical review: negative behavioral and cognitive outcomes following traumatic brain injury in early childhood. J Pediatr Psychol. 2015;40(4):391–7.
12. Anderson VA, Spencer-Smith MM, Coleman L, Anderson PJ, Greenham M, Jacobs R, et al. Predicting neurocognitive and behavioural outcome after early brain insult. Dev Med Child Neurol. 2014;56(4):329–36.
13. Geary DF, Haka-Ikse K. Neurodevelopmental progress of young children with chronic renal disease. Pediatrics. 1989;84(1):68–72.
14. Hooper SR, Gerson AC, Johnson RJ, Mendley SR, Shinnar S, Lande MB, et al. Neurocognitive, social-behavioral, and adaptive functioning in preschool children with mild to moderate kidney disease. J Dev Behav Pediatr. 2016;37(3):231–8.
15. Johnson RJ, Warady BA. Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy. Pediatr Nephrol. 2013;28(8):1283–91.
16. Mendley SR, Matheson MB, Shinnar S, Lande MB, Gerson AC, Butler RW, et al. Duration of chronic kidney disease reduces attention and executive function in pediatric patients. Kidney Int. 2014;87(4):800–6.
17. Slickers J, Duquette P, Hooper S, Gipson D. Clinical predictors of neurocognitive deficits in children with chronic kidney disease. Pediatr Nephrol. 2007;22(4):565–72.
18. Molnar-Varga M, Novak M, Szabo AJ, Kelen K, Streja E, Remport A, et al. Neurocognitive functions of pediatric kidney transplant recipients. Pediatr Nephrol. 2016;31(9):1531–8.
19. Hartmann H, Hawellek N, Wedekin M, Vogel C, Das AM, Balonwu K, et al. Early kidney transplantation improves neurocognitive outcome in patients with severe congenital chronic kidney disease. Transpl Int. 2015;28:429–36.
20. Bugnicourt J-M, Godefroy O, Chillon J-M, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol. 2013;24:353–63.
21. Elzouki A, Carroll J, Butinar D, Moosa A. Improved neurological outcome in children with chronic renal disease from infancy. Pediatr Nephrol. 1994;8(2):205–10.
22. Pickett JL, Theberge DC, Brown WS, Schweitzer SU, Nissenson AR. Normalizing hematocrit in dialysis patients improves brain function. Am J Kidney Dis. 1999;33:1122–30.
23. Watanabe K, Watanabe T, Nakayama M. Cerebrorenal interactions: impact of uremic toxins on cognitive function. Neurotoxicology. 2014;44:184–93.
24. D'Hooge R, Pei YQ, Marescau B, De Deyn PP. Convulsive action and toxicity of uremic guanidino compounds: behavioral assessment and relation to brain concentration in adult mice. J Neurol Sci. 1992;112(1–2):96–105.
25. De Deyn PP, Vanholder R, Eloot S, Glorieux G. Guanidino compounds as uremic (neuro) toxins. Semin Dial. 2009;22(4):340–5.
26. Marescau B, Nagels G, Possemiers I, De Broe ME, Becaus I, Billiouw JM, et al. Guanidino compounds in serum and urine of nondialyzed patients with chronic renal insufficiency. Metabolism. 1997;46(9):1024–31.
27. De Deyn PP, Marescau B, Cuykens JJ, Van Gorp L, Lowenthal A, De Potter WP. Guanidino compounds in serum and cerebrospinal fluid of non-dialyzed patients with renal insufficiency. Clin Chim Acta. 1987;167(1):81–8.
28. De Deyn PP, Marescau B, D'Hooge R, Possemiers I, Nagler J, Mahler C. Guanidino compound levels in brain regions of non-dialyzed uremic patients. Neurochem Int. 1995;27:227–37.
29. Schwarcz R, Stone TW. The kynurenine pathway and the brain: challenges, controversies and promises. Neuropharmacology. 2017;112(Pt B):237–47.

30. Karu N, McKercher C, Nichols DS, Davies N, Shellie RA, Hilder EF, et al. Tryptophan metabolism, its relation to inflammation and stress markers and association with psychological and cognitive functioning: Tasmanian Chronic Kidney Disease pilot study. BMC Nephrol. 2016;17(1):171.
31. Kurella Tamura M, Chertow GM, Depner TA, Nissenson AR, Schiller B, Mehta RL, et al. Metabolic profiling of impaired cognitive function in patients receiving dialysis. J Am Soc Nephrol. 2016;27(12):3780–7.
32. Youssef DM, Mohamed AH, Kamel Attia WM, Mohammad FF, El Fatah NRA, Elshal AS. Cerebral metabolic alterations and cognitive dysfunction in children with chronic kidney disease using Magnetic Resonance Spectroscopy and Wechsler intelligence scale. Nephrology (Carlton). 2017;23(8):771–7.
33. Chhabra YK, Sood S, Rathi O, Mahajan S. Effect of renal transplantation on cognitive function in hemodialysis patients: a longitudinal study. Int Urol Nephrol. 2017;49(11):2071–8.
34. Jassal SV, Devins GM, Chan CT, Bozanovic R, Rourke S. Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: a longitudinal pilot study. Kidney Int. 2006;70(5):956–62.
35. Murray AM. The brain and the kidney connection: a model of accelerated vascular cognitive impairment. Neurology. 2009;73(12):916–7.
36. United States Renal Data System 2006 Annual Report. Morbidity & mortality. Neuroepidemiology: incident & prevalent stroke [Internet]. https://www.usrds.org/2006/pdf/06_morb_morte_06.pdf.
37. Kupferman JC, Matheson MB, Lande MB, Flynn JT, Furth S, Warady BA, Hooper SR. Increased history of ischemic stroke and decreased neurocognitive performance in children with chronic kidney disease. Pediatr Nephrol. 2020;35(7):1315−1321.
38. Lee M, Saver JL, Chang K-H, Liao H-W, Chang S-C, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ. 2010;341(sep30 1):c4249.
39. Liu B, Lau KK, Li L, Lovelock C, Liu M, Kuker W, et al. Age-specific associations of renal impairment with magnetic resonance imaging markers of cerebral small vessel disease in transient ischemic attack and stroke. Stroke. 2018;49(4):899–904.
40. Martinez-Vea A, Salvadó E, Bardají A, Gutierrez C, Ramos A, García C, et al. Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD. Am J Kidney Dis. 2006;47(2):241–50.
41. Kobayashi M, Hirawa N, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, et al. Relationship between silent brain infarction and chronic kidney disease. Nephrol Dial Transplant. 2009;24(1):201–7.
42. Valanne L, Qvist E, Jalanko H, Holmberg C, Pihko H. Neuroradiologic findings in children with renal transplantation under 5 years of age. Pediatr Transplant. 2004;8(1):44–51.
43. Hartung EA, Erus G, Jawad AF, Laney N, Doshi JJ, Hooper SR, et al. Brain magnetic resonance imaging findings in children and young adults with CKD. Am J Kidney Dis. 2018;72(3):349–59.
44. Liu H-S, Hartung EA, Jawad AF, Ware JB, Laney N, Port AM, et al. Regional cerebral blood flow in children and young adults with chronic kidney disease. Radiology. 2018;288(3):849–58.
45. Lande MB, Kupferman JC, Adams HR. Neurocognitive alterations in hypertensive children and adolescents. J Clin Hypertens (Greenwich). 2012;14(6):353–9.
46. Lande MB, Gerson AC, Hooper SR, Cox C, Matheson M, Mendley SR, et al. Casual blood pressure and neurocognitive function in children with chronic kidney disease: a report of the children with chronic kidney disease cohort study. Clin J Am Soc Nephrol. 2011;6:1831–7.
47. Ruebner RL, Laney N, Kim JY, Hartung EA, Hooper SR, Radcliffe J, et al. Neurocognitive dysfunction in children, adolescents, and young adults with CKD. Am J Kidney Dis. 2016;67:567–75.
48. Cianciolo G, De Pascalis A, Di Lullo L, Ronco C, Zannini C, La Manna G. Folic acid and homocysteine in chronic kidney disease and cardiovascular disease progression: which comes first? Cardiorenal Med. 2017;7(4):255–66.
49. Bertsch T, Mielke O, Höly S, Zimmer W, Casarin W, Aufenanger J, et al. Homocysteine in cerebrovascular disease: an independent risk factor for subcortical vascular encephalopathy. Clin Chem Lab Med. 2001;39(8):721–4.
50. Lipton SA, Kim WK, Choi YB, Kumar S, D'Emilia DM, Rayudu PV, et al. Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A. 1997;94(11):5923–8.
51. Kielstein H, Suntharalingam M, Perthel R, Song R, Schneider SM, Martens-Lobenhoffer J, et al. Role of the endogenous nitric oxide inhibitor asymmetric dimethylarginine (ADMA) and brain-derived neurotrophic factor (BDNF) in depression and behavioural changes: clinical and preclinical data in chronic kidney disease. Nephrol Dial Transplant. 2015;30(10):1699–705.
52. Askari H, Abazari MF, Ghoraeian P, Torabinejad S, Nouri Aleagha M, Mirfallah Nassiri R, et al. Ameliorative effects of hydrogen sulfide (NaHS) on chronic kidney disease-induced brain dysfunction in rats: implication on role of nitric oxide (NO) signaling. Metab Brain Dis. 2018;33(6):1945–54.
53. Wolfgram DF, Szabo A, Murray AM, Whittle J. Risk of dementia in peritoneal dialysis patients compared with hemodialysis patients. Perit Dial Int. 2015;35(2):189–98.
54. Iyasere O, Okai D, Brown E. Cognitive function and advanced kidney disease: longitudinal trends and impact on decision-making. Clin Kidney J. 2017;10(1):sfw128.
55. Polinder-Bos HA, García DV, Kuipers J, Elting JWJ, Aries MJH, Krijnen WP, et al. Hemodialysis induces

an acute decline in cerebral blood flow in elderly patients. J Am Soc Nephrol. 2018;29(4):1317–25.
56. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. J Am Soc Nephrol. 2013;24:1166–73.
57. Costa AS, Tiffin-Richards FE, Holschbach B, Frank RD, Vassiliadou A, Krüger T, et al. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. Am J Kidney Dis. 2014;64(3):434–42.
58. Dasgupta I, Patel M, Mohammed N, Baharani J, Subramanian T, Thomas GN, et al. Cognitive function declines significantly during haemodialysis in a majority of patients: a call for further research. Blood Purif. 2018;45(4):347–55.
59. Murray AM, Pederson SL, Tupper DE, Hochhalter AK, Miller WA, Li Q, et al. Acute variation in cognitive function in hemodialysis patients: a cohort study with repeated measures. Am J Kidney Dis. 2007;50(2):270–8.
60. Davis ID, Chang PN, Nevins TE. Successful renal transplantation accelerates development in young uremic children. Pediatrics. 1990;86:594–600.
61. Hulstijn-Dirkmaat GM, Damhuis IH, Jetten ML, Koster AM, Schroder CH. The cognitive development of pre-school children treated for chronic renal failure. Pediatr Nephrol. 1995;9:464–9.
62. Ledermann SE, Scanes ME, Fernando ON, Duffy PG, Madden SJ, Trompeter RS. Long-term outcome of peritoneal dialysis in infants. J Pediatr. 2000;136:24–9.
63. Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialyzed in infancy. Child Care Health Dev. 2003;29(1):55–61.
64. Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol. 1999;13:759–65.
65. Bawden HN, Acott P, Carter J, Lirenman D, MacDonald GW, McAllister M, McDonnell MC, Shea S, Crocker J. Neuropsychological functioning in end-stage renal disease. Arch Dis Child. 2004;89:644–7.
66. Eijsermans RM, Creemers DG, Helders PJ, Schroder CH. Motor performance, exercise tolerance, and health-related quality of life in children on dialysis. Pediatr Nephrol. 2004;19:1262–6.
67. Fennell RS, Fennell EB, Carter RL, Mings EL, Klausner AB, Hurst JR. Association between renal function and cognition in childhood chronic renal failure. Pediatr Nephrol. 1990;4:16–20.
68. Gipson DS, Hooper SR, Duquette PJ, Wetherington CE, Stellwagen KK, Jenkins TL, Ferris ME. Memory and executive functions in pediatric chronic kidney disease. Child Neuropsychol. 2006;12:391–405.
69. Zepeda-Orozco D, Quigley R. Dialysis disequilibrium syndrome. Pediatr Nephrol. 2012;27(12):2205–11.
70. Silver SM, Sterns RH, Halperin ML. Brain swelling after dialysis: old urea or new osmoles? Am J Kidney Dis. 1996;28(1):1–13.
71. Silver SM, DeSimone JA, Smith DA, Sterns RH. Dialysis disequilibrium syndrome (DDS) in the rat: role of the “reverse urea effect”. Kidney Int. 1992;42(1):161–6.
72. Arieff AI, Massry SG, Barrientos A, Kleeman CR. Brain water and electrolyte metabolism in uremia: effects of slow and rapid hemodialysis. Kidney Int. 1973;4(3):177–87.
73. Silver SM. Cerebral edema after rapid dialysis is not caused by an increase in brain organic osmolytes. J Am Soc Nephrol. 1995;6(6):1600–6.
74. Port FK, Johnson WJ, Klass DW. Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Kidney Int. 1973;3(5):327–33.
75. Rodrigo F, Shideman J, McHugh R, Buselmeier T, Kjellstrand C. Osmolality changes during hemodialysis. Natural history, clinical correlations, and influence of dialysate glucose and intravenous mannitol. Ann Intern Med. 1977;86(5):554–61.
76. Rees L, Schaefer F, Schmitt CP, Shraff R, Warady BA. Chronic dialysis in children and adolescents: challenges and outcomes. Lancet Child Adolesc Health. 2017;1:68–77.
77. Moodalbail DG, Hooper SR. Neurocognitive functioning in children undergoing dialysis. In: Nissenson AR, Fine RN, editors. Handbook of dialysis therapy. 5th ed. Philadelphia: Elsevier; 2017. p. 955–64.
78. Gipson DS, Hooper SR. Neurocognitive complications and management in pediatric kidney disease. In: Warady BA, Schaefer F, Alexander SR, editors. Pediatric dialysis. 2nd ed. New York: Springer; 2012.
79. Polinsky MS, Kaiser BA, Stover JB, Frankenfield M, Baluarte HJ. Neurologic development of children with severe chronic renal failure from infancy. Pediatr Nephrol. 1987;1:157–65.
80. Rotundo A, Nevins TE, Lipton M, Lockman LA, Mauer SM, Michael AF. Progressive encephalopathy in children with chronic renal insufficiency in infancy. Kidney Int. 1982;21:486–91.
81. Mendley SR, Zelko FA. Improvement in specific aspects of neurocognitive performance in children after renal transplantation. Kidney Int. 1999;56:318–23.
82. Brouhard BH, Donaldson LA, Lawry KW, McGowan KR, Drotar D, Davis I, Rose S, Cohn RA, Tejani A. Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplant. 2000;4:261–7.
83. Duquette PJ, Hooper SR, Wetherington CE, Icard PF, Gipson DS. Brief report: intellectual and academic functioning in pediatric chronic kidney disease. J Pediatr Psychol. 2007;32:1011–7.
84. Crocker JFS, Acott PD, Carter JEJ, Lirenman DS, MacDonald GW, McAllister M, McDonnell MC, Shea S, Bawden HN. Neuropsychological outcome in children with acquired or congenital renal disease. Pediatr Nephrol. 2002;17:908–12.

85. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, Sainio K, Ronnholm K, Jalanko H, Holmberg C. Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant. 2002;6:53–62.
86. Falger J, Latal B, Landolt MA, Lehmann P, Neuhaus TJ, Laube GF. Outcome after renal transplantation. Part I: intellectual and motor performance. Pediatr Nephrol. 2008;23:1339–45.
87. Icard P, Hooper SR, Gipson DS, Ferris ME. Cognitive improvement in children with CKD after transplant. Pediatr Transplant. 2010;14:887–90.
88. Rasbury WC, Fennell RS, Fennell EB, Morris MK. Cognitive functioning in children with end stage renal disease pre- and post-dialysis session. Int J Pediatr Nephrol. 1986;7:45–50.
89. Popel J, Joffe R, Acton BV, Bond G, Joffe AR, Midgley J, Robertson CMT, Sauve RS, Morgan C. Neurocognitive and functional outcomes at 5 years of age after renal transplant in early childhood. Pediatr Nephrol. 2019;34:889.
90. Moodabail DG, Reiser KA, Detre JA, Schultz RT, Herrington JD, Davatzikos C, Doshi JJ, Erus G, Liu HS, Radcliffe J, Furth SL, Hooper SR. Systematic review of structural and functional neuroimaging findings in children and adults with CKD. Clin J Am Soc Nephrol. 2013;8:1429–48.
91. Nichols SL, Press GA, Schneider JA, Trauner DA. Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. Pediatr Neurol. 1990;6:379–81.
92. Hurkx W, Hulstijn D, Pasman J, Rotteveel J, Visco Y, Schroder C. Evoked potentials in children with chronic renal failure, treated conservatively or by continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1995;9:325–8.
93. Teschan PE, Ginn HE, Bourne JR, Ward JW, Hamel B, Nunnally JC, Musso M, Vaughn WK. Quantitative indices of clinical uremia. Kidney Int. 1979;15:676–97.
94. Albaramki JH, Al-Ammouri IA, Akl KF. Neurological and cardiac complications in a cohort of children with end-stage renal disease. Saudi J Kidney Dis Transpl. 2016;27:507–11.
95. Glenn CM, Astley SJ, Watkins SL. Dialysis-associated seizures in children and adolescents. Pediatr Nephrol. 1992;6:182–6.
96. Porto I, John EG, Heilliczer J. Removal of phenobarbital during continuous cycling peritoneal dialysis in a child. Pharmacotherapy. 1997;17:832–5.
97. Sanderson KR, Warady BA. End-stage kidney disease in infancy: an educational review. Pediatr Nephrol. 2020;35(2):229–40.
98. Hooper SR, Umansky W, editors. Young children with special needs. 6th ed. Columbus: Pearson/Prentice-Hall; 2014.
99. Coulthard MG, Crosier J. Outcome of reaching end stage renal failure in children under 2 years of age. Arch Dis Child. 2002;87:511–7.
100. Black MM, Dubowitz H, Krishnakumar A, Starr RH Jr. Early intervention and recovery among children with failure to thrive: follow-up at age 8. Pediatrics. 2007;120:59–69.
101. Harshman LA, Johnson RE, Kogon A, Matheson M, Shinnar S, Mendley S, Gerson A, Warady BA, Furth SR, Hooper SR. Academic achievement outcomes in children with mild to moderate chronic kidney disease: a report from the CKiD cohort. J Pediatr Nephrol. 2019;34(4):689–96.
102. National Reading Panel. Report of the National Reading Panel. Teaching children to read: an evidence-based assessment of the scientific research literature on reading and its implications for reading instruction (NIH Publication No. 00–4754). Washington, DC: U.S. Government Printing Office; 2000.
103. Wexler J, Vaughn S, Edmonds M, Reutebuch DK. A synthesis of fluency interventions for secondary struggling readers. Read Writ. 2008;21:317–47.
104. Solis M, Ciullo S, Vaughn S, Pyle N, Hassaram B, Leroux A. Reading comprehension interventions for middle school students with learning disabilities. J. Learning Dis. 2012;45:327–40. https://doi.org/10.1177/0022219411402691.
105. Baker S, Gersten R, Lee D. A synthesis of empirical research on teaching mathematics to low-achieving students. Elem Sch J. 2002;103:51–73.
106. Hooper SR, Wakely MB, de Kruif REL, Swartz CW. Aptitude-treatment interactions revisited: effect of a meta-cognitive intervention on subtypes of written expression in elementary school students. Dev Neuropsychol. 2006;29:217–41.
107. Graham S, Harris KR. Almost 30 years of writing research: making sense of it all with the wrath of Khan. Learn Disabil Res Pract. 2009;24:58–68.
108. Javalkar K, Ferris ME, Cuttance J, Hooper SR. Cognitive remediation in pediatric CKD: rationale, programmatic approaches, and potential applicability. Pediatr Nephrol. 2017;32:2027–35.
109. Ferris ME, Gipson DS, Kimmel PL, Eggers PW. Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America. Pediatr Nephrol. 2006;21:1020–6.
110. McDonald SP, Craig JC. Australian and New Zealand Paediatric Nephrology Association long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350:2654–62.
111. Grootenhuis MA, Stam H, Last BF, Groothoff JW. The impact of delayed development on the quality of life of adults with end-stage renal disease since childhood. Pediatr Nephrol. 2006;21:538–44.
112. Bell LE, Ferris ME, Fenton N, Hooper SR. Health care transition for adolescents with CKD-the journey from pediatric to adult care. Adv Chronic Kidney Dis. 2011;18:384–90.
113. Icard PF, Hower SJ, Kuchenreuther AR, Hooper SR, Gipson DS. The transition from childhood to adult-

hood with ESRD: educational and social challenges. Clin Nephrol. 2008;69:1–7.
114. Foster BJ, Pai ALH, Zelikovsky N, Amaral S, Bell L, Dharnidharka VR, Herbert D, Holly C, Knauper B, Matsell D, Phan V, Rogers R, Smith JM, Zhao H, Furth SL. A randomized trial of a multicomponent intervention to promote medication adherence: the Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT). Am J Kidney Dis. 2018;72:30–41.

35

Psychosocial Adjustment and Adherence to Prescribed Medical Care of Children and Adolescents on Dialysis

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Abbreviations

BFST	Behavioral Family Systems Therapy
CBCL	Child Behavior Checklist
CBT	Cognitive-behavioral therapy
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
DBT	Dialectical Behavior Therapy
ESKD	End-stage kidney disease
HD	Hemodialysis
PD	Peritoneal dialysis
PTSD	Post-traumatic stress disorder

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Psychosocial Adjustment

Children receiving dialysis and their families are faced with complex treatment regimens and uncertainty regarding the future of their health. Additional factors unique to dialysis include treatment demands causing a disruption to typical routines, unknown dialysis treatment duration before receiving a kidney transplant (if eligible), and knowledge that they will likely have to return to dialysis at some point in the future. Thus, it is not surprising that children and their families may have challenges related to emotional and behavioral adjustment. Since children and adolescents exist within a family system, it is important to consider the impact that dialysis has on parents and caregivers, as their function can, in turn, influence the child. Given that emotional health can influence disease outcomes, it is important to understand how dialysis care impacts the child and family as a whole. Table 35.1 provides a summary of relevant factors.

Child Adjustment

There are some children who experience a relatively smooth adjustment to dialysis. However, there are others who find the process stressful, resulting in emotional and behavioral difficulties. Contributing factors to adjustment may include

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Table 35.1 Psychological issues experienced by children on dialysis and their families

Child	Symptoms of depression and anxiety Behavior problems, including hyperactivity Lower self-esteem related to changes in physical appearance School problems Peer and social problems
Family	Symptoms of depression and anxiety Increased stress Poor sleep Lack of social support Disruption to family life/activities Siblings feel left out

the child's age, history of traumatic medical experiences, urgency (expected progression from chronic kidney disease care versus emergency initiation of dialysis), and support network.

Emotional Adjustment Internalizing symptoms are prevalent among children and adolescents undergoing dialysis. Pediatric dialysis patients have been found to have higher rates of internalizing symptoms [5], specifically depressive symptoms [50], than either kidney transplant patients or healthy comparison groups. In a sample of 67 patients undergoing either hemodialysis (HD) or peritoneal dialysis (PD), over half reported the presence of depressive symptoms, with 10% reporting high symptoms and 43% reporting low symptoms [38]. However, a different study found that children on dialysis were less likely to be depressed compared with children at earlier stages of CKD [52]. Bakr et al. [8] studied 19 children on hemodialysis and found that the prevalence of psychiatric disorders in their sample was 52.6%, with adjustment disorders and depression most common. Consistent with other studies, the patients on dialysis had higher rates of psychiatric disorders than a comparison group of pre-dialysis patients. In a group of children diagnosed with end-stage kidney disease (ESKD) early in life, either on dialysis or with a kidney transplant at the time of assessment, 50% scored in the borderline to impaired range on a measure of overall psychological adjustment [54].

Behavioral Adjustment Studies that have assessed externalizing symptoms in this population are not as prevalent as studies of internalizing symptoms or disorders, but a small number suggest a higher rate of externalizing symptoms (i.e., disruptive or noncompliant behavior, hyperactivity) in children on dialysis versus a normative population. One study found that 26.3% of a dialysis sample scored above the clinical cutoff in the clinical range for externalizing symptoms on the Child Behavior Checklist (CBCL; [5]). Marciano et al. [55] examined a group of 136 children with chronic kidney disease (CKD) who were pre-dialysis, on dialysis, or received a transplant. On an assessment of overall emotional-behavioral functioning, children with CKD had significantly more parent-reported symptoms across domains (emotional problems, behavioral problems, hyperactivity, and peer problems) compared to a healthy control group. The prevalence of emotional and behavioral disorders was 57.5%; however, in those who reported poor quality of life, the rate increased to 77.8%.

Social Adjustment The demands of dialysis place a significant social burden on children and families. School attendance declines, opportunities for social activities and peer relationships decrease, participation in extracurricular activities is limited, and increased dependence on parents and other adults (i.e., healthcare staff) may adversely influence development of self-esteem and self-efficacy. Managing ESKD is an endeavor filled with uncertainty and lifestyle restrictions related to the demands of treatment. Children on dialysis are challenged to adjust to a range of significant stressors, in a situation that simultaneously limits social and emotional resources that enable active coping. In other words, when it comes to adjustment and coping, they are expected to do a lot, often with very little. For example, in one study of emotional functioning, the patients who reported the most depressive symptoms also reported very little to no peer social support [38].

One domain of social adjustment that is particularly challenging for patients on dialysis is adjusting to changes in physical appearance. Comorbidities of ESKD and treatment side

effects can significantly alter or influence the physical appearance of patients, which in turn may impact their quality of life and social-emotional adjustment. Patients with short stature, a CKD-related comorbidity, report lower self-esteem compared to normative population data [71]. One study examining 483 children with CKD found that height gains and growth hormone use were associated with improved physical and social functioning [3]. Girls with ESKD report more concerns about their physical appearance [60], and one study indicated that both low and high levels of depressive symptoms were associated with less satisfaction with physical appearance [38].

Demands of treatment limit school attendance and academic achievement. In a group of 136 pre-dialysis, dialysis, and transplant patients, 34.6% reported failing and repeating a grade in school, with over half reporting that this was because of medical treatment [55].

The social effects of pediatric dialysis and transplant are long term. Adult survivors of pediatric ESKD have lower rates of employment, fewer offspring, and lower income than the general population, as well as diminished physical and health-related quality of life [82]. In a 30-year follow-up study, Tjaden et al. [80, 81] found that comorbidities, return to dialysis, short stature, and fewer achieved milestones related to autonomy were associated with adverse outcomes, such as unemployment and lower educational achievement. There was some evidence that this group of patients experienced some "catchup" over time in terms of living with a partner and completing higher education; however, the number who were unable to work for medical reasons also increased.

A recent examination of outcomes deemed most important for patients with CKD indicated that patients valued outcomes that directly affected their lifestyle; maintaining a sense of normalcy was a priority [36]. Alternative dialysis modalities that present with fewer lifestyle restrictions may offer opportunities to improve social-emotional development and quality of life. There is evidence that pediatric patients prefer home HD, because it offers greater flexibility and freedom to live a "normal" life, versus in-center HD which requires patients to be at the hospital multiple days per week [83]. Home nocturnal HD and even in-center nocturnal HD also offer flexibility and have been shown to improve school attendance and quality of life and reduce some aspects of treatment burden, such as dietary and fluid restrictions [30, 41].

Parent and Family Adjustment

The impact of childhood chronic illness, such as ESKD requiring dialysis, understandably extends beyond the patient to one's caregivers and family system [47]. Parents of children receiving dialysis treatment often juggle many demands, including dialysis treatment time and travel burdens, diet restrictions for their child, financial and employment strains, and fears associated with their child's life-threatening condition, among many others. In addition, some parents may be considering or undergoing living kidney donor evaluations, navigating both caregiver and patient roles themselves. Across the pediatric chronic illness literature, parental mental health and stress has been shown to be associated with child psychological and physical health outcomes [16]. Thus, it is critically important that parental mental health be assessed, monitored, and intervened upon via family-centered care to promote optimal outcomes for both patients and their families [49].

Parent Psychological Adjustment A number of studies have examined parental psychological adjustment in families of children receiving dialysis treatment. Many of these studies have been qualitative in nature (see [2] for review). In a study of 32 parents of children with ESKD (38% of sample receiving dialysis), 27% of the total sample reported clinically significant depressive symptoms, whereas 34% reported anxiety symptoms above the scale's cutoff [26]. Similar rates of depression (28%) were endorsed among a sample of 32 parents of children receiving PD treatment [86]. In a more recent study by Zelikovsky and colleagues [96] (2007; 30% of sample receiving dialysis), mothers experienced

greater depressive symptoms than fathers, although mean scores for both groups on a standardized depression measure were in the "minimal" range. Among yet another sample of parents of children receiving PD, over half of the sample endorsed clinically significant scores on a global psychological distress screening measure [51].

Rates of depression, anxiety, and sleep problems have been found to be higher in parents of children undergoing PD compared to parents of kidney transplant recipients [7]. Other factors found to be associated with adverse parental psychological outcomes include lower socioeconomic status, larger family size, increased social impairment of child, and lower satisfaction with dialysis care and treatment [25]. Moreover, use of avoidant coping strategies and increased parenting stress associated with a child's renal disease have also been found to significantly predict depressive symptoms in both mothers and fathers [96].

Parent Stress In a qualitative interview-based study of 31 parents of children receiving three times weekly HD, the most common stressors endorsed included health system issues (e.g., long waits for lab draws, insurance challenges, frequent appointments), financial stressors (94%), growth, appearance and development of child (90%), fluid/diet restrictions, educational difficulties for child (87%), lack of social support, and anxiety about child's critical state [13]. These findings were supported by an interview study of 20 parents who discussed stressors related to the (1) hospital environment (e.g., painful procedures, disempowerment, appointment burden), (2) role of a "medicalized parent" (guilt, time-consuming, anger), and (3) disruption of family norms [84]. Similarly, Tsai et al. [86] found that parents of children undergoing dialysis treatment reported lower family incomes and higher unemployment rates compared to national averages.

As such, parents of children receiving dialysis treatment have reported greater stress than parents of children who underwent kidney transplantation, particularly in the area of "daily psychosocial strains" [11, 91]. Avsar et al. [7] found that caregiver burden scores were 2.6 times higher in the dialysis group when compared to parents in the transplant group. Moreover, mothers tend to endorse greater parenting stress than fathers [91, 96]. Given the significance of assessing and understanding parental stress and burden, Parham et al. [64] developed the validated parent-report 60-item Paediatric Renal Caregiver Burden Scale, which can be used with dialysis populations.

Family Adjustment Families of children with ESKD on HD report significantly more disruptions to family life (77%) than families of those with chronic kidney disease not yet receiving dialysis treatment (31%). Similarly, parents in the dialysis group endorsed greater marital strain (65%) than the non-dialysis group [70]. Family adjustment, in turn, impacts the patient's emotional and physical health outcomes. For example, in a study of 41 parents of children receiving dialysis treatment or undergoing transplantation, higher family conflict predicted increased child externalizing symptoms and a higher number of prescription medications. On the contrary, better family cohesion was associated with fewer hospitalizations [78].

Across several studies, the majority of parents of children receiving dialysis also acknowledged the impact of illness on their parenting approaches. For example, parents reported increased protection of or leniency toward their children on dialysis [70]. Others reported restricting the activities of their healthy children to reduce the impact on their child with ESKD and regularly relying on others (e.g., grandparents) to primarily care for healthy siblings [13].

Sibling Adjustment Changes in parenting practices and family functioning may also impact siblings of children undergoing dialysis. In a small study of 15 siblings, 90% endorsed disruption to family routines, 80% noted feeling jealous or left out, and nearly 50% felt they could not openly share their concerns or problems with their parents [9]. Thus, it is important that attention be

paid to the psychosocial needs of siblings as well throughout the dialysis course.

Treatment of Psychosocial Problems

Children and Adolescents Few researchers have formally investigated psychosocial interventions among pediatric dialysis populations. However, given the incidence of emotional and behavioral concerns in children and adolescents undergoing dialysis treatment, mental health treatment may be needed. Thus, screening for psychosocial problems should be conducted to inform referral and treatment. The Centers for Medicare and Medicaid Services (CMS) requires that patient psychosocial screening is completed annually. The type of screening measures used should be determined by mental health professionals at the dialysis center; however, considerations may include quality of life measures, as well as the freely available NIH PROMIS® screening measures.

For patients requiring intervention, cognitive-behavioral therapy (CBT) remains the most empirically supported treatment for child anxiety and depressive disorders [14], even among children with chronic medical conditions. For patients experiencing procedural distress or anxiety related to dressing changes, dialysis access, etc., CBT interventions, distraction, and hypnosis have been shown to be effective [87]. To promote successful health outcomes, some patients may also require intervention specific to pill swallowing. Behavioral approaches, including modeling, shaping, and positive reinforcement, can be utilized to effectively teach children to swallow pills [10, 65]. Important steps can be taken to ameliorate some of the negative impact of ESKD on child adjustment and functioning and promote children's integration of their healthcare needs into their lives more broadly. Qualitative studies have suggested that improving patients' uptake of knowledge about their disease and its treatment, helping them work toward a sense of normalcy, and increasing autonomy and feelings of empowerment may assist children and adolescents with coping and adaptation to their disease [84].

Parents and Caregivers As noted previously, there has been limited research specific to parent or family-based interventions among pediatric dialysis populations; thus, it is helpful to rely on the broader pediatric chronic illness literature. It has been recommended that comprehensive, interdisciplinary care be provided to best support families of pediatric dialysis patients [22]. The interdisciplinary care team may vary from center to center, but could include a social worker to support parents/caregivers, a psychologist to support the patient, and child life specialists to support both the patient and siblings, along with other team members.

Behavioral Family Systems Therapy (BFST), which focuses on improving problem-solving skills, could be utilized to reduce the significant parental stress and burden families report [95]. In addition, Kazak and colleagues developed a 1-day family-based group cognitive-behavioral intervention for parents affected by childhood cancer to decrease parent and family stress and improve family functioning. This intervention, which resulted in sustained reductions in parental anxiety and post-traumatic stress disorder (PTSD; [48]), could be adapted to meet the psychosocial needs of parents of children undergoing dialysis treatment. Although educational and supportive interventions are often offered to parents, a systematic review of three studies determined that there was limited high-quality evidence to support the effectiveness of informational or support-based CKD caregiver interventions [85].

Siblings Parents and caregivers may also report concerns about sibling emotional and behavioral health to dialysis providers. Similar psychoeducation about the benefits of cognitive-behavioral therapy for childhood mental health problems should be provided, along with a recommendation for parents to discuss concerns with the sibling's pediatrician/healthcare provider, who can provide additional screening and referrals. School-based counselors can also be very helpful for promoting sibling coping (particularly since it

may cause undue burden for the family to transport the sibling to a therapy appointment), as well as child life specialists during hospitalizations.

Adherence to Prescribed Medical Regimens

A widely recognized definition of adherence from the World Health Organization [73] describes it as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed upon recommendations from a healthcare provider." Adherence is the preferred term (versus "compliance"), as it suggests collaboration between the child, family, and provider, while the latter term feels directive and implies a power differential between the provider and patient. Across chronic medical conditions that impact children and adolescents, adherence rates are around 50%, meaning that about half of this population is not receiving the recommended treatment [69]. This rate is staggering, particularly since failure to follow prescribed regimens is associated with symptom persistence, faster disease progression [74], unnecessary change or escalation in treatment [58, 59], reduced quality of life [21, 29], increased healthcare costs [57], and death [61].

Unfortunately, the rate of adherence among pediatric dialysis patients remains understudied, particularly when considering the evidence base among adults on dialysis and among children who have received a kidney transplant. This is likely due to several factors including a relatively small pool of children receiving this treatment modality, the complex nature of the regimen (e.g., oral medication, injections, diet, fluid intake), difficulty tracking the combination of treatments being provided in the clinic and in the home setting, and assumptions that patients are following advice to treat end-stage disease. Much of the data we have are from studies conducted in the late 1980s and 1990s [39, 42, 76], suggesting a lack of momentum on understanding how adherence has evolved in this group. According to those studies, rates of nonadherence for dialysis patients ranged between 17% and 43%. A study assessing follow-through with the PD prescription identified that 45% of patients and families were not adherent to at least one treatment element (i.e., number of sessions per month, duration of each session, number of cycles, dialysate volume). Interestingly, families had the most difficulty carrying out the prescribed number of sessions per month and the recommended dialysate volume [12]. Additionally, self-reported data from a sample of families of children with CKD in Guatemala revealed a medication adherence rate of 76% among HD and PD patients, which was lower than the 82% adherence rate in the transplant sample [68]. This stalled research is particularly concerning as medical technologies evolve with different treatment options becoming available. One recent study of adolescents and young adults with CKD (pre-dialysis) documented rates of nonadherence between 35% and 61% [66]. Further, a review published in 2017 concluded that rates of adherence to dietary restrictions among adults who were dialysis-dependent were suboptimal, as adherence fell between 31% and 68% [53].

While some chronic conditions can be managed solely with oral medication or following a certain diet, dialysis often requires a complex combination of prescription medication (taken either multiple times daily, with meals, every other day, weekly), lifestyle changes, and frequent visits to the clinic (multiple times per week for hemodialysis; weekly to monthly for peritoneal dialysis). Not surprisingly, these treatment expectations can interfere with a child's normal activities, particularly in light of the time they already spend receiving dialysis in the clinic or at home. As such, it may not be feasible for children and families to have strict adherence to all of these aspects of care. There are many factors that may result in a patient intentionally or unintentionally missing medication or not following a low phosphorus diet. Additionally, the nature of child and adolescent development makes it challenging for patients in these age groups to fully appreciate the long-term consequences of not following their medical regimen.

Assessment of Adherence

Behaviors that occur outside of the clinic or hospital setting, such as taking medication or restricting fluid intake, can be difficult to assess. Since these behaviors cannot be directly observed on every occasion that medication or fluid is to be administered, clinicians often rely on the child or family's report or their own interpretation of how adherent they are. However, factors such as relying on memory over a period of weeks to months, fear of disappointing or upsetting the medical team, and confusion about how the regimen is to be carried out can all affect what a patient reports about his or her adherence. Despite this, several strategies have been developed to estimate an individual's degree of adherence. Popular methods include self-report (e.g., "How many times did you take your medication last week?"), provider estimates (e.g., "Do I think my patient is taking his/her medication?"), pharmacy refill data, monitoring blood levels (e.g., checking phosphorus levels as an indicator of adherence to dietary restrictions or administration of phosphate binders), and electronic monitoring (e.g., using a special pill bottle that tracks each opening). Since each method has advantages and disadvantages and cannot guarantee a perfect assessment, it is recommended that providers combine one or more of these methods to get the most comprehensive view of the patient's behavior. A recent study by Pruette et al. [66] evaluated the additive benefit of adherence assessment tools among children with chronic kidney disease and warned of the inaccuracies of relying solely on medical provider assessment.

Factors Associated with Adherence

In an effort to better understand adherence, past research has focused on child and family characteristics that correlate with this behavior. While several theories of adherence exist, the *Pediatric Self-Management Model* [58, 59] presents a helpful framework for understanding various levels of influence on adherence. The model identifies four categories of influence: (1) individual (e.g., gender, cognitive ability, health beliefs), (2) family (e.g., income, parental involvement in the regimen), (3) healthcare system (e.g., availability of healthcare resources, communication between patient and provider), and (4) community (e.g., peer support, school-based accommodations). Within each category, there are factors that are modifiable (i.e., can be changed, such as knowledge about the treatment regimen) and nonmodifiable (i.e., cannot be changed, such as the child's age). Understanding these factors is crucial as it can help identify children and families who may be at risk for adherence difficulties, as well as inform the development or use of existing interventions to promote adherence. It is interesting to note that research examining influences on adherence in the pediatric dialysis population has lagged behind other chronic conditions commonly occurring in childhood. One study reported barriers of pill burden, poor taste of the medication, difficulty remembering the medication schedule, and being tired of living with a chronic medical condition, with patients receiving HD endorsing more obstacles to adherence than those on PD [75]. The following is a summary of existing research with children and adolescents receiving dialysis (see Fig. 35.1 for an overview). The content is supplemented with research from pediatric kidney transplantation, other common chronic medical conditions, or adult dialysis as past research of children on dialysis has not targeted each of these domains.

Individual Factors Across pediatric chronic illness populations, being an adolescent or young adult is a risk factor for poor adherence due to multiple biological, psychological, and relational changes that occur during this period. Consistent with the broader literature, older age was associated with higher phosphorus levels in a study of HD and PD patients, suggesting that older children and teenagers were less likely to take phosphate binders with each meal [79]. Additionally, adolescents and young adults are at highest risk for graft loss after kidney transplantation which is attributed to problems with medication adherence during this developmental period [27, 72, 88]. In one study, nonadherence to the PD pre-

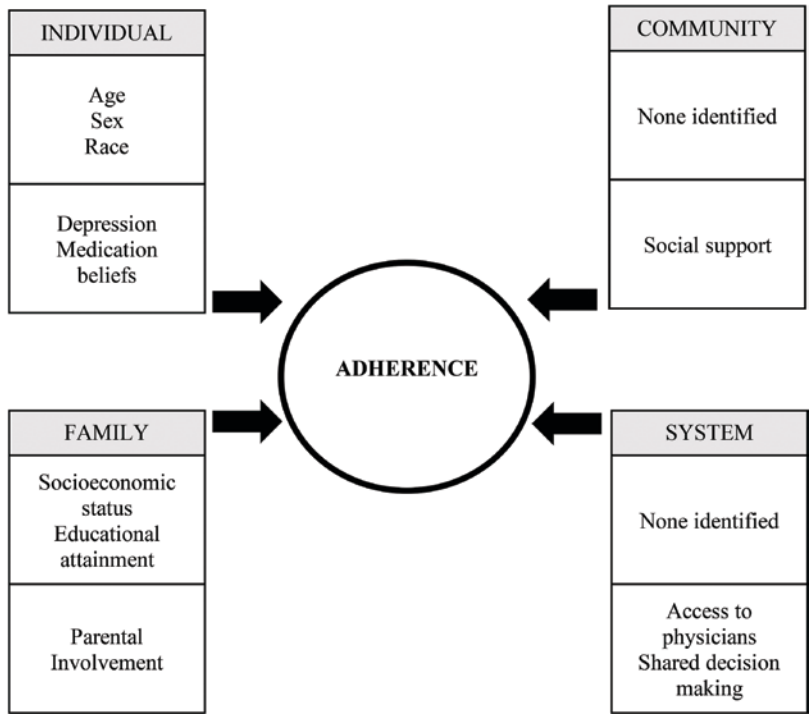

Fig. 35.1 Factors related to poor adherence in pediatric dialysis and CKD. Modifiable factors in top box and nonmodifiable factors in bottom box

scription was more common among patients who were male and of Black race [12]. A study of young adults (16–30 years old) receiving renal replacement therapy found that patients who identified as Black or Asian had poorer adherence [35]. Though symptoms of anxiety or depression have been linked with greater adherence difficulties in other pediatric populations, a study by Simoni et al. [76] failed to detect an association between mood and treatment adherence in 23 pediatric dialysis patients. However, in a different study, there was a moderate correlation between depressive symptoms and nonadherence to recommendations for blood pressure management (adherence to fluid restrictions and antihypertensive medication) among a sample of 118 adults receiving chronic HD [46]. Additionally, a sample of young adults receiving kidney replacement therapy (HD, PD, or transplant) identified psychological comorbidity as being a risk factor for worse adherence [35].

A review of the literature did not identify any studies assessing the relationship between a child's cognitive functioning and adherence. This is both surprising and concerning given that poor kidney function is known to negatively impact executive functioning (e.g., attention, memory, organization) which are critical abilities for managing the complex dialysis regimen [31]. While there were no identified studies examining how patient perspectives impact dialysis adherence in children, beliefs about the relative unimportance of phosphate binders were associated with adult patients on dialysis deliberately choosing not to take the medication [92].

Family Factors Given the complexity of the dialysis regimen, family members are almost always involved in supporting the pediatric dialysis patient. For very young children or children with significant developmental delays, parents or caregivers take on most of the responsibility for ensuring the patient follows his or her medical plan. As the child develops, the manner in which the family supports him or her can change. Generally, parental support is thought to be a protective factor, as children whose parents remain closely involved have better rates of adherence [45]. Among young adults receiving renal

replacement therapy (dialysis or transplant), residing with parents was associated with higher medication adherence [35]. Family socioeconomic factors can also influence adherence. A study of children with CKD in Guatemala found that higher educational attainment among mothers and greater family income were associated with better medication adherence, which was assessed via self-report [68]. However, one study involving children with CKD or ESKD and their parents failed to detect an association between caregiver functional word reading literacy and adherence to their child's medications, diet, or medical appointments [67].

Healthcare System Factors To our knowledge, no studies have examined the impact of healthcare system factors, such as insurance coverage or patient-provider communication, on adherence in pediatric dialysis. However, there was evidence of a positive association between physician access satisfaction and adherence among a sample of young adults with ESKD [35]. These factors are thought to be less directly related to adherence, but still having an indirect influence on patient behavior. There is some evidence of an association between shared decision-making practices and greater adherence across different chronic medical conditions [44]. Additionally, a study of children with asthma found that families who were asked to provide input regarding the treatment regimen had higher adherence to prescribed medications 1 month later [77].

Community Factors There were not any studies identified that assessed the impact of community-level variables on treatment adherence in pediatric dialysis. However, social support is thought to be a potentially modifiable correlate of adherence. In a 2004 meta-analysis by DiMatteo, practical social support emerged as a strong predictor of adherence, noting that the risk of being nonadherent was nearly double for patients without practical social support relative to those who had the resource. Additionally, in a large empirical study examining adults with ESKD, perceived social support had a positive relationship with treatment adherence [90].

The Impact of Treatment Adherence on Health and Other Outcomes

It is well documented that not following treatment recommendations can result in greater morbidity and mortality for children diagnosed with an advanced- or end-stage disease. For example, failing to follow fluid restrictions while on HD can result in volume overload which has cascading effects of hypertension and cardiac problems [89]. However, there is a lack of research investigating the impact of poor adherence on health outcomes, such as with the example above, in pediatric dialysis patients. In a sample of adults on continuous ambulatory PD, poor adherence to the exchange procedure (e.g., not flushing the tubing system, failing to wash hands) was associated with a greater number of peritonitis episodes [56]. Additionally, a study evaluating self-reported adherence to growth hormone in a large sample of children with CKD found that there was an association between nonadherence and poorer growth velocity [1]. There is a larger evidence base for the impact of nonadherence once a child has received a kidney transplant, demonstrating a higher risk of rejection episodes and graft loss [15].

Another consequence of poor adherence is how it affects decision-making for physicians. For example, if a provider notices that a child has elevated blood pressure despite prescribing an antihypertensive medication, they may increase the dose or add a second medication in an attempt to get adequate control. This places children at risk for side effects (if they start taking all of the medication) or other health problems associated with a higher dose. While this has not been studied in dialysis, nonadherence has resulted in unnecessary medication changes in children with epilepsy [58, 59]. Situations like this can also result in unnecessary expenditures. Treatment for nonadherence and related complications is extremely costly as shown in research with other chronic illness populations. In fact, it is estimated that up to $300 billion is spent per year to treat problems related to poor adherence [19, 20]. To our knowledge, there have not been any studies evaluating the financial cost of nonadherence in pediatric dialysis.

Interventions to Promote Adherence

The last edition of this text noted a dearth of intervention studies to improve adherence among dialysis patients, despite the need for such interventions [62]. Very little has been published since that time, even though pediatric patients on dialysis report many barriers to adherence [75], and nonadherence is associated with poorer health outcomes [1] as noted above. Hommel et al. [40] provided a summary of the research on adherence interventions in pediatric psychology broadly and refer readers to a number of meta-analyses of the effectiveness of adherence interventions [17, 33, 63]. In addition, Rapoff [69] provides a comprehensive review and how-to manual with regard to implementation of adherence interventions.

There are many opportunities to address gaps in adherence for children receiving dialysis. In addition to dialysis itself, dialysis patients take medications, often have fluid and dietary restrictions, require routine injections, and may have other prescribed treatments depending on their underlying conditions (e.g., schedule of self-catheterization). Commonly reported barriers to adherence include high pill number burden, aversive taste of medications, difficulty remembering the medication schedule, treatment fatigue, and concern for side effects [75]. Intervention strategies include educational strategies, behavioral strategies, and family-based and multicomponent interventions.

Educational strategies provide knowledge with the assumption that increased understanding will facilitate adherence, and certainly patients and parents must understand the treatment regimen in order to implement it. It is important to consider the patient and family's health literacy when providing education. Strategies such as the teach-back method, which asks the family to "teach back" the information to the provider, can be used to confirm the family's understanding of the information conveyed [4]. Educational strategies may also focus on information to assist patients with managing or ameliorating side effects of treatments, which in turn may promote adherence. Education is believed to be necessary, but not sufficient, to sustain or improve adherence [69] and thus is typically paired with other interventions when the objective is to improve a patient's adherence.

Behavioral strategies include organizational and self-management techniques, including reminders from parents or caregivers, placing medication in a convenient location, and use of a pill box [43]. In addition, reminders delivered by smartphones or other electronic devices are commonly used. Behavioral strategies also include parental monitoring or checking, followed by either positive reinforcement of adherence or consequences for nonadherence, with studies demonstrating that parental monitoring is associated with better adherence [24, 43]. Pill-swallowing difficulties are not uncommon and can be addressed with behavioral strategies as well [6, 10].

Interventions may focus more broadly on the family. In a sample of 45 kidney transplant patients, family efficacy and flexibility were associated with better adherence; thus, the authors suggest family-based interventions might be beneficial to reduce barriers to and promote adherence [34]. In a smaller sample of 13 transplant recipients, increased parent stress, dysfunctional parent-child interactions, and child behavior problems were associated with nonadherence, again suggesting that family-based interventions may promote adherence [32]. A meta-analysis of adherence outcomes in pediatric solid organ transplant more broadly concluded that greater parental distress, child behavior problems, and poor family cohesion correlated with poorer adherence, lending additional support to the suggestion that family-based interventions have the potential to improve adherence [18].

While intervention studies with dialysis patients specifically are rare, studies that focus on chronic health conditions with many similarities to ESKD (e.g., high treatment burden, chronicity of disease, adherence linked to health outcomes) may provide helpful information. One study that included dialysis patients was a feasibility study of Dialectical Behavior Therapy (DBT) to improve adherence among adolescents with CKD [37]. Four of the seven participants were receiving dialysis. Results of this small pilot study showed promising results for improved adherence post-treatment suggesting that DBT could be a helpful treatment avenue for this population. Studies examining the effect of family systems-

based interventions, tailored to pediatric conditions such as diabetes and asthma, have demonstrated improved adherence, reduced family conflict, and improved communication [23, 94]. Foster et al. [28] described a multicomponent intervention for kidney transplant patients that resulted in improved adherence for those in the intervention arm compared to patients in the control group. This intervention used reminder strategies; electronic monitoring; review of adherence data at 3-month intervals, with coaching; and action-focused problem-solving.

Due to the increasing accessibility of mobile devices, there has been a focus on using technology to promote adherence. Wu and Hommel [93] provide an overview of how technology can be used to promote adherence for pediatric populations, which would apply to dialysis patients. Some studies have shown improved adherence with text messaging reminders; however, those improvements are not typically sustained once the reminders are removed. Additionally, electronic monitors applied to pill bottles or injectable drugs can be used to provide feedback on adherence to help families identify patterns of missing doses. Table 35.2 provides an overview of adherence interventions.

Table 35.2 Adherence interventions

Educational	Education about health condition(s) Education about treatment regimen Education about managing side effects
Organizational	Use of pill box Designated location for medications Setting an alarm or text message reminders Use of calendar to track appointments and tasks
Behavioral	Daily logs of adherence, barriers, and facilitators of adherence Establishing associations between routine tasks (e.g., brushing teeth) and healthcare tasks Positive reinforcement of adherence behaviors or behaviors aimed at improving adherence Parental monitoring of adherence Teaching and use of problem-solving strategies to overcome barriers to adherence

Modified from Pai and Ingerski [62]

Summary and Directions for Future Research

Children who undergo dialysis and their families are at risk for emotional, behavioral, and social problems, though some may have protective factors that buffer against these challenges (e.g., younger age, strong family support network). Unfortunately, adjustment difficulties can make the already challenging dialysis regimen (e.g., treatment times, medication, fluid and dietary restrictions) even more difficult, sometimes resulting in less than perfect adherence. It is well documented among adults with ESKD that poor adherence to medication, site care, and other lifestyle factors can contribute to morbidity and mortality; however, there are fewer studies targeting children. Evidence-based behavioral interventions to overcome barriers and ultimately improve adherence exist and could prove beneficial for this patient population.

Within the past 5 years, there has been limited published research to advance our knowledge of the psychological impact of dialysis on children and families. It is possible that research is challenging in this population due to the relatively low number of patients at a single center. While information from adult studies can be helpful to inform hypotheses, children should be considered unique from adults given developmental factors, influence of parental involvement, and so on. The field would likely benefit from more collaboration across dialysis centers to increase the pool of research participants. Additionally, longitudinal research has the benefit of following children across the course of dialysis to determine how adjustment can change with time, medical complications, etc.

Relative to kidney transplant recipients, there are few studies examining the impact of nonadherence on health outcomes when patients are at the dialysis stage of treatment. Further, there is a lack of published studies evaluating adherence promotion interventions designed for pediatric dialysis patients, suggesting that the field would benefit from studying if existing evidence-based treatments are just as useful in this population. Another interesting direction for research is to identify how the provision of behavioral inter-

vention can result in a financial cost offset of treatment required for nonadherence-related medical complications. Additionally, use of emerging technology may help with more accurate monitoring and promotion of the health behaviors expected while a patient receives dialysis. For example, smart water bottles are now widely available and can be used to track a patient's adherence to fluid restrictions and be used as an intervention to help patients self-monitor their water consumption.

Implications for Clinical Practice and Psychosocial Care

It is evident that children receiving dialysis are at risk for emotional and behavioral adjustment issues. Ideally, all children receiving chronic dialysis would receive comprehensive care that addresses their medical and psychosocial needs. This is particularly important as the psychological status can impact the child's overall health, as well as their ability to engage with the recommended regimen to manage their symptoms and prevent serious complications. Further, improving adherence behaviors in pediatric dialysis patients is critical as poor adherence could result in deferral or denial for kidney transplantation. Mental health practitioners and behavioral specialists have the necessary background to assess and treat emotional problems, support behavior change related to adherence, and provide general support for family members who experience significant life disruption when their child's disease is advanced enough to require dialysis. Children receiving HD, in particular, are considered a captive audience given the amount of time spent physically in clinic or hospital. There is also a push for dissemination and implementation of evidence-based treatments into clinical practice. There is promising evidence for the delivery of behavioral interventions by frontline healthcare providers (physicians, registered nurses), which would reduce barriers to accessing additional mental healthcare specialists.

References

1. Akchurin OM, Schneider MF, Mulqueen L, Brooks ER, Langman CB, Greenbaum LA, et al. Medication adherence and growth in children with CKD. Clin J Am Soc Nephrol. 2014;9:1519–25.
2. Aldridge MD. How do families adjust to having a child with chronic kidney failure? A systematic review. Nephrol Nurs J. 2008;35(2):157–63.
3. Al-Uzri A, Matheson M, Gipson DS, Medley SR, Hooper SR, Yadin O, et al. The impact of short stature on health-related quality of life in children with chronic kidney disease. J Pedatr. 2013;163:736–41.
4. American Medical Association Foundation and American Medical Association. Health literacy and patient safety: help patients understand. Chicago: AMA Foundation; 2007.
5. Amr M, Bakr A, El Gilany AH, Hammad A, El-Refaey A, El-Mougy A. Multi-method assessment of behavior adjustment in children with chronic kidney disease. Pediatr Nephrol. 2009;24:341–7.
6. Anderson CM, Ruggiero KJ, Adams CD. The use of functional assessment to facilitate treatment adherence: a case of a child with HIV and pill refusal. Cognitive Behav Prac. 2000;7:282–7.
7. Avsar U, Avsar UZ, Cansever Z, Set T, Cankaya E, Kaya A, et al. Psychological and emotional status, and caregiver burden in caregivers of patients with peritoneal dialysis compared with caregivers of patients with renal transplantation. Transplant Proc. 2013;45(3):883–6.
8. Bakr A, Amr M, Sarhan A, Hammad A, Ragab M, El-Refaey A, et al. Psychiatric disorders in children with chronic renal failure. Pediatr Nephrol. 2007;22:128–31.
9. Batte S, Watson AR, Amess K. The effects of chronic renal failure on siblings. Pediatr Nephrol. 2006;21(2):246–50.
10. Blount RL, Dahlquist LM, Baer RA, Wuori DF. A brief, effective method for teaching children to swallow pills. Behav Ther. 1984;15(4):381–7.
11. Brownbridge G, Fielding DM. Psychosocial adjustment to end-stage renal failure: comparing haemodialysis, continuous ambulatory peritoneal dialysis and transplantation. Pediatr Nephrol. 1991;5(5):612–6.
12. Chua AN, Warady BA. Adherence of pediatric patients to automated peritoneal dialysis. Pediatr Nephrol. 2011;26:789–93.
13. Cimete G. Stress factors and coping strategies of parents with children treated by hemodialysis: a qualitative study. J Pediatr Nurs. 2002;17(4):297–306.
14. Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Adolesc Psychiatry. 2004;43(8):930–59.

15. Connelly J, Pilch N, Oliver M, Jordan C, Fleming J, Meadows H, et al. Prediction of medication non-adherence and associated outcomes in pediatric kidney transplant recipients. Pediatr Transplant. 2015;19:555–62.
16. Cousino MK, Hazen RA. Parenting stress among caregivers of children with chronic illness: a systematic review. J Pediatr Psychol. 2013;38(8):809–28.
17. Dean AJ, Walters J, Hall A. A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. Arch Dis Child. 2010;95:717–23.
18. Dew MA, Dabbs AD, Myaskovsky L, Shyu S, Shellmer DA, DiMartini AF, et al. Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. Transplantation. 2009;88(5):736–46.
19. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol. 2004a;23(2):207–18.
20. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004b;42:200–9.
21. Drotar D, Bonner MS. Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. J Dev Behav Pediatr. 2009;30:574–82.
22. Drotar D, Ganofsky MA, Makker S, DeMaio D. A family-oriented supportive approach to dialysis and renal transplantation in children. In: Levy NB, editor. Psychonephrology 1. Boston: Springer; 1981. p. 79–91.
23. Duncan CL, Hogan MB, Tien KJ, Graves MM, Chorney JM, Zettler MD, et al. Efficacy of a parent-youth teamwork intervention to promote adherence in pediatric asthma. J Pediatr Psychol. 2013;38:617–28.
24. Ellis DA, Podolski C, Frey M, Naar-King S, Wang B, Moltz K. The role of parental monitoring in adolescent health outcomes: impact on regimen adherence in youth with type 1 diabetes. J Pediatr Psychol. 2007;32:907–17.
25. Fielding D, Brownbridge G. Factors related to psychosocial adjustment in children with end-stage renal failure. Pediatr Nephrol. 1999;13(9):766–70.
26. Fielding D, Moore B, Dewey M, Ashley P, McKendrick T, Pinkerton P. Children with end-stage renal failure: psychological effects on patients, siblings and parents. J Psychosom Res. 1985;29(5):457–65.
27. Foster B, Dahhou M, Zhang X, Platt RW, Samuel SM, Hanley JA. Association between age and graft failure rates in young kidney transplant recipients. Transplantation. 2011;98:1237–43.
28. Foster BJ, Pai ALH, Zelikovsky N, Amaral S, Bell L, Dharnidharka VR, et al. A randomized trial of a multicomponent intervention to promote medication adherence: the Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT). Am J Kidney Dis. 2018;72(1):30–41.
29. Fredericks EM, Magee JC, Opipari-Arrigan L, Shieck V, Well A, Lopez MJ. Adherence and health-related quality of life in adolescent liver transplant recipients. Pediatr Transplant. 2008;12:289–99.
30. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147:383–7.
31. Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB, et al. Neurocognitive outcomes in children with chronic kidney disease: current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev. 2006;12:208–15.
32. Gerson AC, Furth SL, Neu AM, Fivush BA. Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. Pediatr Transplant. 2004;8:543–50.
33. Graves MM, Roberts MC, Rapoff M, Boyer A. The efficacy of adherence interventions for chronically ill children: a meta-analytic review. J Pediatr Psychol. 2010;35:368–82.
34. Guilfoyle SM, Goebel JW, Pai ALH. Efficacy and flexibility impact perceived adherence barriers in pediatric kidney post-transplantation. Fam Syst Health. 2011;29(1):44–54.
35. Hamilton AJ, Caskey FJ, Casula A, Inward CD, Ben-Shlomo Y. Associations with wellbeing and medication adherence in young adults receiving kidney replacement therapy. Clin J Am Soc Nephrol. 2018;13:1669–79.
36. Hanson CS, Gutman T, Craig JC, Bernays S, Raman G, Zhang Y, et al. Identifying important outcomes for young people with CKD and their caregivers: a nominal group technique study. Am J Kidney Dis. 2019;74(1):82–94.
37. Hashim BL, Vadnais M, Miller AL. Improving adherence in adolescent chronic kidney disease: a dialectical behavior therapy (DBT) feasibility trial. Clin Pract Pediatr Psychol. 2013;1(4):369–79.
38. Hernandez EG, Loza R, Vargas H, Jara MF. Depressive symptomatology in children and adolescents with chronic renal insufficiency undergoing chronic dialysis. Int J Nephrol. 2011;2011:1–7.
39. Hesse UJ, Roth B, Knuppertz G, Wienand P, von Lilien T. Control of patient compliance in outpatient steroid treatment of nephrologic disease and renal transplant recipients. Transplant Proc. 1990;22(4):1405–6.
40. Hommel KA, Ramsey RR, Rich KL, Ryan JL. Adherence to pediatric treatment regimens. In: Roberts MC, Steele RG, editors. Handbook of pediatric psychology. 5th ed. New York: Guilford; 2017. p. 119–33.
41. Hoppe A, von Puttkamer C, Linke U, Kahler C, Booss M, Braunauer-Kolbert R, et al. A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr. 2011;158:95–9.
42. Hudson J, Fielding D, Jones S, McKendrick T. Adherence to medical regime and related factors in youngsters in dialysis. Br J Clin Psychol. 1987;26:61–2.
43. Ingerski L, Perrazo L, Goebel J, Pai ALH. Family strategies for achieving medication adherence in pediatric kidney transplantation. Nurs Res. 2011;60(3):190–6.
44. Joosten EAG, DeFuentes-Merillas L, de Weert GH, Sensky T, van der Staak CPF, de Jong CAJ. Systematic

review of the effects of shared decision-making on patient satisfaction, treatment adherence, and health status. Psychother Psychosom. 2008;77:219–26.
45. Kahana SY, Frazier TW, Drotar D. Preliminary quantitative investigation of predictors of treatment nonadherence in pediatric transplantation: a brief report. Pediatr Transplant. 2008;12:656–60.
46. Kauric-Klein Z. Depression and medication adherence in patients on hemodialysis. Curr Hypertens Rev. 2017;13(2):138–43.
47. Kazak AE. Families of chronically ill children: a systems and social-ecological model of adaptation and challenge. J Consult Clin Psychol. 1989;57(1):25.
48. Kazak AE, Simms S, Barakat L, Hobbie W, Foley B, Golomb V, et al. Surviving Cancer Competently Intervention Program (SCCIP): a cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. Fam Process. 1999;38(2):176–91.
49. Kazak AE, Simms S, Rourke MT. Family systems practice in pediatric psychology. J Pediatr Psychol. 2002;27(2):133–43.
50. Kilicoglu AG, Bahali K, Canpolat N, Bilgic A, Mutlu C, Yalcin O, et al. Impact of end-stage renal disease on psychological status and quality of life. Pediatr Int. 2016;58:1316–21.
51. Kiliś-Pstrusińska K, Wasilewska A, Medyńska A, Bałasz-Chmielewska I, Grenda R, Kluska-Jóźwiak A, et al. Psychosocial aspects of children and families of children treated with automated peritoneal dialysis. Pediatr Nephrol. 2013;28(11):2157–67.
52. Kogon AJ, Stoep AV, Weiss NS, Smith J, Flynn JT, McCauley E. Depression and its associated factors in pediatric chronic kidney disease. Pediatr Nephrol. 2013;28(9):1855–61.
53. Lambert K, Mullan J, Mansfield K. An integrative review of the methodology and findings regarding dietary adherence in end stage kidney disease. BMC Nephrol. 2017;18(1):318.
54. Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Tompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev. 2003;29(1):55–61.
55. Marciano RC, Soares CM, Diniz JS, Lima EM, Silva JM, Canhestro MR, et al. Behavioral disorders and low quality of life in children and adolescents with chronic kidney disease. Pediatr Nephrol. 2011;26(2):281–90.
56. Mawar S, Gupta S, Mahajan S. Non-compliance to the continuous ambulatory peritoneal dialysis procedures increases the risk of peritonitis. Int Urol Nephrol. 2012;44:1243–9.
57. McGrady ME, Hommel KA. Medication adherence and health care utilization in pediatric chronic illness: a systematic review. Pediatrics. 2013;132:730–40.
58. Modi AC, Pai AL, Hommel KA, Hood KK, Cortina S, Hilliard ME, et al. Pediatric self-management: a framework for research, practice, and policy. Pediatrics. 2012a;129(2):1–13.
59. Modi AC, Wu YP, Guilfoyle SM, Glauser TA. Uninformed clinical decisions resulting from lack of adherence assessment in children with new-onset epilepsy. Epilepsy Behav. 2012b;25:481–4.
60. Neul SK, Minard CG, Currier H, Goldstein SL. Health-related quality of life functioning over a 2-year period in children with end-stage renal disease. Pediatr Nephrol. 2013;28:285–93.
61. Oliva M, Singh TP, Gauvreau K, VanderPluym CJ, Bastardi HJ, Almond CS. Impact of medication non-adherence on survival after pediatric heart transplantation in the USA. J Heart Lung Transplant. 2013;32:881–8.
62. Pai ALH, Ingerski LM. Psychosocial adjustment and adherence of children and adolescents on dialysis. In: Warady BA, Schaefer F, Alexander SR, editors. Pediatric dialysis. 2nd ed. New York: Springer; 2012. p. 593–605.
63. Pai ALH, McGrady ME. Systematic review and meta-analysis of psychological interventions to promote treatment adherence in children, adolescents, and young adults with chronic illness. J Pediatr Psychol. 2014;39:918–31.
64. Parham R, Jacyna N, Hothi D, Marks SD, Holttum S, Camic P. Development of a measure of caregiver burden in paediatric chronic kidney disease: the Paediatric Renal Caregiver Burden Scale. J Health Psychol. 2016;21(2):193–205.
65. Patel A, Jacobsen L, Jhaveri R, Bradford KK. Effectiveness of pediatric pill swallowing interventions: a systematic review. Pediatrics. 2015;135(5):883–9.
66. Pruette CS, Coburn SS, Eaton CK, Brady TM, Tuchman S, Mendley S, et al. Does a multimethod approach improve identification for medication nonadherence in adolescents with chronic kidney disease? Pedatr Nephrol. 2019;34:97–105.
67. Rak EC, Hooper SR, Belsante MJ, Burnett O, Layton B, Tauer D, et al. Caregiver word reading literacy and health outcomes among children treated in a pediatric nephrology practice. Clin Kidney J. 2016;9(3):510–5.
68. Ramay BM, Ceron A, Mendez-Alburez LP, Lou-Meda R. Factors associated to acceptable treatment adherence among children with chronic kidney disease in Guatemala. PLoS One. 2017;12(10):e0186644.
69. Rapoff MA. Adherence to pediatric medical regimens. New York: Springer; 2010.
70. Reynolds JM, Garralda ME, Jameson RA, Postlethwaite RJ. How parents and families cope with chronic renal failure. Arch Dis Child. 1988;63(7):821–6.
71. Riano-Galan I, Malaga S, Rajmil L, Ariceta G, Navarro M, Loris C, et al. Quality of life of adolescents with end-stage renal disease and kidney transplant. Pediatr Nephrol. 2009;24:1561–8.
72. Ritchie AG, Clayton PA, McDonald SP, Kennedy SE. Age-specific risk of renal graft loss from late acute rejection or non-compliance in the adolescent and young adult period. Nephrology. 2018;23:585–91.

73. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
74. Shemesh E, Annunziato RA, Yehuda R, Shneider BL, Newcorn JH, Hutson C, et al. Childhood abuse, nonadherence, and medical outcome in pediatric liver transplant recipients. J Am Acad Child Adoles Psychiatry. 2007;46(10):1280–9.
75. Silverstein DM, Fletcher A, Moylan K. Barriers to medication adherence and its relationship with outcomes in pediatric dialysis patients. Pediatr Nephrol. 2014;29:1425–30.
76. Simoni JM, Asarnow JR, Munford PF, Koprowski CM, Belin TR, Salusky IB. Psychological distress and treatment adherence among children on dialysis. Pedatr Nephrol. 1997;11(5):604–6.
77. Sleath B, Carpenter DM, Slota C, Williams D, Tudor G, Yeatts K, et al. Communication during pediatric asthma visits and self-reported asthma medication adherence. Pediatrics. 2012;130(4):627–33.
78. Soliday E, Kool E, Lande MB. Family environment, child behavior, and medical indicators in children with kidney disease. Child Psychiatry Hum Dev. 2001;31(4):279–95.
79. Taylor JM, Oladitan L, Degnan A, Henderson S, Dai H, Warady BA. Psychosocial factors that create barriers to managing serum phosphorus levels in pediatric dialysis patients: a retrospective analysis. J Ren Nutr. 2016;26(4):270–5.
80. Tjaden LA, Grootenhuis MA, Noordzij M, Groothoff JW. Health-related quality of life in patients with pediatric onset of end-stage renal disease: state of the art and recommendations for clinical practice. Pediatr Nephrol. 2016a;31:1579–91.
81. Tjaden LA, Maurice-Stam H, Grootenhuis MA, Jager KJ, Groothoff JW. Impact of renal replacement therapy in childhood on long-term socioprofessional outcomes: a 30-year follow-up study. J Pediatr. 2016b;171:189–95.
82. Tjaden LA, Vogelzang J, Jager KJ, van Stralen KJ, Maurice-Stam H, Grootenhuis MA, et al. Long-term quality of life and social outcome of childhood end-stage renal disease. J Pediatr. 2014;165:336–42.
83. Tong A, Henning P, Wong G, McTaggart S, Mackie F, Carroll RP, et al. Experiences and perspectives of adolescents and young adults with advanced CKD. Am J Kidney Dis. 2013;61:375–84.
84. Tong A, Lowe A, Sainsbury P, Craig JC. Parental perspectives on caring for a child with chronic kidney disease: an in-depth interview study. Child Care Health Dev. 2010;36(4):549–57.
85. Tong A, Sainsbury P, Craig JC. Support interventions for caregivers of people with chronic kidney disease: a systematic review. Nephrol Dial Transplant. 2008;23(12):3960–5.
86. Tsai TC, Liu SI, Tsai JD, Chou LH. Psychosocial effects on caregivers for children on chronic peritoneal dialysis. Kidney Int. 2006;70(11):1983–7.
87. Uman LS, Chambers CT, McGrath PJ, Kisely S. A systematic review of randomized controlled trials examining psychological interventions for needle-related procedural pain and distress in children and adolescents: an abbreviated Cochrane review. J Pediatr Psychol. 2008;33(8):842–54.
88. Van Arendonk KJ, James NT, Boyarksy BJ, Garonzik-Wang JM, Orandi BJ, Magee JC, et al. Age at graft loss after pediatric kidney transplantation: exploring the high-risk age window. Clin J Am Soc Nephrol. 2013;8(6):1019–26.
89. Van Buren PN, Inrig JK. Hypertension and hemodialysis: pathophysiology and outcome in adult and pediatric populations. Pediatr Nephrol. 2012;27(3):339–50.
90. Varghese SA. Social support: an important factor for treatment adherence and health-related quality of life of patients with end-stage renal disease. J Soc Serv Res. 2018;44(1):1–18.
91. Wiedebusch S, Konrad M, Foppe H, Reichwald-Klugger E, Schaefer F, Schreiber V, et al. Health-related quality of life, psychosocial strains, and coping in parents of children with chronic renal failure. Pediatr Nephrol. 2010;25(8):1477–85.
92. Wileman V, Chilcot J, Norton S, Hughes L, Wellsted D, Farrington K. Choosing not to take phosphate binders: the role of dialysis patients' medication beliefs. Nephron Clin Pract. 2011;119:205–13.
93. Wu YP, Hommel KA. Using technology to assess and promote adherence to medical regimens in pediatric chronic illness. J Pediatr. 2014;164(4):922–7.
94. Wysocki T, Harris MA, Buckloh LM, Mertlich D, Lochrie AS, Mauras N, et al. Randomized trial of behavioral family systems therapy for diabetes: maintenance of effects on diabetes outcomes in adolescents. Diabetes Care. 2007;30:555–60.
95. Wysocki T, Harris MA, Buckloh LM, Mertlich D, Lochrie AS, Taylor A, et al. Effects of behavioral family systems therapy for diabetes on adolescents' family relationships, treatment adherence, and metabolic control. J Pediatr Psychol. 2005;31(9):928–38.
96. Zelikovsky N, Schast A. P, Jean-Francois D. Parent stress and coping: Waiting for a child to receive a kidney transplant. Journal of Clinical Psychology in Medical Settings. 2007;14(4):320–29.

Part VI

Drugs and Dialysis

36

Drug Administration and Pharmacogenomics in Children Receiving Acute or Chronic Renal Replacement Therapy

Bridget L. Blowey, J. Steven Leeder, and Douglas L. Blowey

Introduction

The prescription of a safe and effective dose of a medication for a child receiving dialysis can be a complicated task as both renal failure and dialysis can modify the absorption, distribution, metabolism, elimination, and action of a drug. A safe and effective dosing regimen is one that delivers the appropriate drug in the optimal manner, producing the desired pharmacological response while minimizing the undesirable effects. Achieving the goal of successful drug therapy requires a clear understanding of the therapeutic goal coupled with an appreciation of the factors governing drug disposition and action. Failure to clearly identify the therapeutic goal or to account for the changes in drug disposition or effectiveness associated with renal failure and the performance of dialysis can culminate in drug toxicity or inadequate treatment.

Basic Concepts of Drug Disposition

The desired and undesired effects of a drug generally correlate with the concentration of free (unbound) drug at the site of action. Factors that determine drug concentration at the site of action are the rate and extent of absorption, distribution, biotransformation (i.e., metabolism), and elimination. The characteristics of these processes are unique for each drug, and individual variations are influenced by genetic, environmental, physiological, and developmental factors [1].

Absorption

Under most circumstances, a drug must reach the systemic circulation in order to exert a biological effect. Drug administered orally, intramuscularly, rectally, subcutaneously, topically, or directly into the peritoneum must cross membranes to gain access to the systemic circulation. As a prerequisite to absorption, a drug must be released from the dosage form (e.g., tablet, capsule, transcutaneous patch) and be present at the site of absorption in an aqueous solution. Most drugs

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are either weak acids or weak bases that in an aqueous solution exist as either an ionized (charged) or nonionized (uncharged) moiety. The most common mechanism of drug absorption is passive diffusion of the nonionized drug moiety. Less common mechanisms of drug absorption include convective transport, active transport, facilitated transport, ion-pair transport, and endocytosis. The extent to which a drug is nonionized is determined by the drug's pKa (i.e., dissociation constant) and the pH at the site of absorption (e.g., stomach, small bowel, skin, peritoneal cavity). For example, the oral absorption of ketoconazole is enhanced by the stomach's acidic environment that promotes the formation of the more readily absorbed nonionized drug compound [2]. In this example, the coadministration of drugs that reduce gastric acid (e.g., proton pump inhibitors, antacids) may shift the equilibrium in favor of the poorly absorbed ionized form of ketoconazole resulting in decreased ketoconazole absorption with the potential for subtherapeutic serum concentrations [3].

Distribution

Following the absorption or direct infusion of a drug into the systemic circulation, drug distributes or equilibrates with tissue reservoirs. The extent of drug partitioning among tissues depends on the drug's pKa, the degree of binding to plasma proteins and tissue constituents, tissue blood flow, and the partitioning of drug to fat. The relationship between the plasma drug concentration that theoretically exists at time zero (C_0) and the fraction of the administered dose reaching the systemic circulation defines the volume of distribution (Vd):

$$\mathrm{Vd} = \frac{\mathrm{Dose} \times \mathrm{fraction\ absorbed}}{\mathrm{Drug\ plasma\ concentration}\left(C_0\right)} \tag{36.1}$$

The volume of distribution, generally expressed as liters or liters/kg, is a hypothetical value with no true anatomical correlate that relates the plasma drug concentration to the total amount of drug in the body and serves as a guide in determining whether a drug is distributed primarily within the systemic circulation or extravascular sites (e.g., fat, muscle). A large volume of distribution implies that the majority of drug present in the body resides outside the vascular space, whereas a small volume of distribution suggests that most of the drug is present within the vascular compartment. For example, digoxin binds more strongly to tissue sites outside the vascular space (e.g., muscle) and consequently has a large volume of distribution (16 L/kg). At the other extreme, phenytoin has a small volume of distribution (0.7 L/kg) because it is highly bound to albumin (90–95% protein binding) and is contained within the vascular and extracellular fluid compartments. Disease-related changes in tissue or protein binding or changes in the volume of a compartment (e.g., extracellular fluid volume expansion with edema) can alter the disposition and biological effect of a drug [4].

In some clinical situations, immediate therapeutic drug concentrations are desired, and a loading dose is prescribed to saturate the sites of distribution. A simple rearrangement of Eq. 36.1 shows that the Vd determines the size of the loading dose:

$$\mathrm{Loading\ dose}\left(\mathrm{mg/kg}\right) = \mathrm{desired\ concentration}\left(\mathrm{mg/L}\right) \times \mathrm{Vd}\left(\mathrm{L/kg}\right) \tag{36.2}$$

Biotransformation/Elimination

The total amount of drug eliminated from the body consists of the amount eliminated by the kidneys plus the amount eliminated by biotransformation (i.e., metabolism) and other pathways of elimination such as lung, skin, gastrointestinal, and dialysis-related losses. The rate of drug elimination, or drug clearance, does not indicate how much drug is being removed from the body but, rather, the volume of blood or plasma that would need to be completely freed of drug per unit of

time to account for the amount eliminated. Drug clearance is additive such that the total (systemic) drug clearance is equal to the sum of the clearances by each individual pathway:

$$Cl_{systemic} = Cl_{renal} + Cl_{hepatic} + Cl_{dialysis} + Cl_{other} \quad (36.3)$$

The processes responsible for drug elimination and metabolism usually require that the drug be present within the systemic circulation. Drug partitioned outside the vascular space must return to the vascular space (redistribute) in order to be excreted or metabolized. Therefore, while dialysis may effectively clear drug that is present in the plasma, the fraction of the total drug removed from the body by dialysis may be small when the majority of the drug resides outside the vascular space (e.g., large Vd).

Biotransformation is the enzymatic conversion of a drug to a new chemical moiety. The new drug product (i.e., drug metabolite) is usually an inactive compound that is more easily eliminated from the body. In some cases, metabolites may be generated that have significant pharmacological activity [5, 6], toxic properties [7], and be eliminated differently than the parent drug. Most tissues, including the kidney, possess the ability to biotransform drugs. Quantitatively, the liver and gastrointestinal tract are the most important organs of drug metabolism. Although there are many different types of enzymes capable of carrying out drug biotransformation, the cytochromes P450 (CYP) are the most important in the metabolism of therapeutic drugs. There is great interindividual variability in the biological activity of CYPs because of genetic, environmental, physiological, and developmental factors [8, 9].

The kidney is the most important organ for drug and drug metabolite elimination. Other pathways of drug excretion include biliary, salivary, mammary, sweat, lungs, and intestinal. Renal drug excretion occurs through the combined processes of glomerular filtration, tubular secretion, and tubular reabsorption. Unless limited by size or charge, drug and drug metabolites not bound to plasma proteins are freely filtered through the glomeruli at a rate equal to the glomerular filtration rate (GFR). The active renal tubular secretion of drug and drug metabolites in the proximal tubule can contribute substantially to renal drug elimination. Other drugs or endogenous substrates that employ the same nonspecific transport system may inhibit the renal tubular uptake and secretion of drugs. A clinically relevant example of competitive inhibition of tubular secretion is the coadministration of probenecid and cidofovir [10, 11]. Probenecid inhibits the renal tubular uptake of cidofovir and protects the kidney from cidofovir nephrotoxicity. Reabsorption is the passive diffusion of the nonionized drug from the filtrate back into the renal tubular cell. Basic urine (e.g., urine pH >7.5) favors the ionized form of acidic drugs and limits reabsorption. This concept is used clinically when urine alkalinization is used to enhance the elimination of salicylates in overdose situations [12].

Alteration of Drug Disposition in Renal Failure and Dialysis

For many drugs and drug metabolites, the kidney is the primary pathway of elimination, and any reduction in renal function will decrease the kidney's ability to eliminate drug from the body. Although a reduced capacity to eliminate drug stands out as the most important change in drug disposition associated with renal failure, clinically significant alterations may occur in other determinants of drug disposition including drug absorption, distribution, and metabolism [4, 13, 14] (Table 36.1).

The impact of renal failure on drug disposition is largely determined by the relative contribution of renal drug clearance to systemic drug clearance (Eq. 36.3). When renal drug clearance accounts for more than 25% of systemic drug clearance, it is likely that drug will accumulate to higher and potentially toxic serum drug concentrations with renal failure unless the dosing regimen is modified (Fig. 36.1). In contrast, modification of the dosing regimen is generally not required for drugs that are predominately eliminated by extrarenal pathways unless there

Table 36.1 Possible changes in drug disposition associated with renal failure

PK parameter	Effect	Proposed mechanism
Absorption	↓	Edema of GI tract, uremic nausea/vomiting, delayed gastric emptying Drug interaction – phosphate binders, H2 blockers Altered GI pH
Distribution	↑	Increased unbound drug fraction Hypoalbuminemia (nephrosis, malnutrition) Uremic changes in albumin structure; expansion of extracellular, intracellular, and/or total body water spaces
Metabolism	↓	Inhibition of CYP 450 metabolism (liver, intestine, kidney) Drug interaction Direct inhibition by "uremic" milieu
	↑	Induced CYP 450 metabolism
Excretion	↓	Decreased GFR Decreased tubular secretion Increased tubular reabsorption

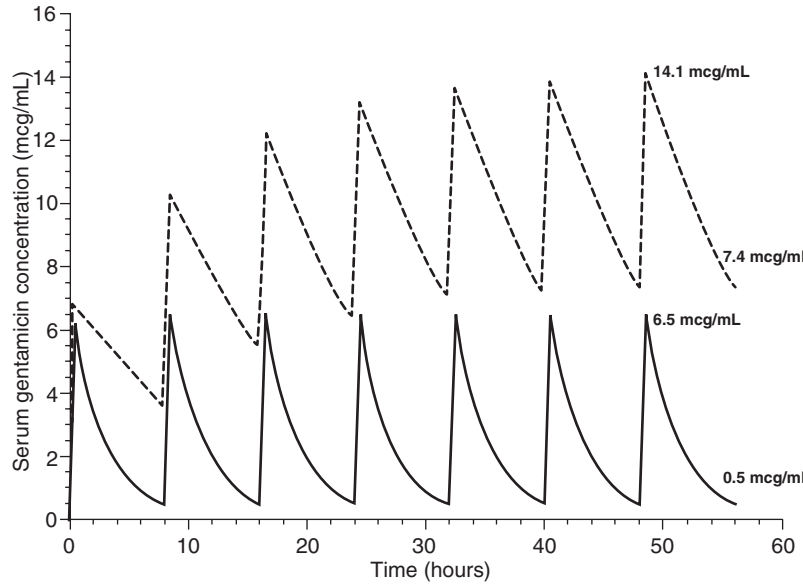

Fig. 36.1 Serum concentration – time profile for a child receiving intravenous gentamicin (2.5 mg/kg IV every 8 h). The solid line depicts the profile in a child with normal renal function. The dashed line depicts the gentamicin accumulation that occurs when dosing adjustments are not made in a child with a GFR measuring 15 mL/min/1.73 m^2

are clinically significant changes in drug absorption, distribution, or metabolism (Table 36.1). Importantly, even though the disposition of the parent drug may be unchanged in renal failure, drugs undergoing extensive biotransformation may have pharmacologically active metabolites that are eliminated by the kidney and accumulate in renal failure [5–7]. An example is the enhanced central nervous system toxicity of the opioid analgesic meperidine in individuals with renal failure. While meperidine biotransformation proceeds unaltered in renal failure, the active and central nervous system toxic metabolite normeperidine is eliminated by the kidneys and accumulates with repeated dosing with an increased risk of seizures in patients with renal failure [7].

The impact of dialysis on drug disposition is determined largely by the extent of drug removal by the dialysis procedure. During dialysis, systemic drug clearance encompasses renal, hepatic, and other intrinsic clearance pathways plus the additional clearance provided by dialysis (Eq. 36.3). In general, drug removal is considered clinically significant when more than 25% of the administered dose is removed by dialysis. Failure to recognize the extent of drug removal and provide supplemental dosing can result in underdosing and therapeutic compromise.

Drug elimination during dialysis occurs by both diffusion and convection. The contribution of each process to the dialysis clearance of a drug varies among the different dialysis modalities. Diffusion is the movement of drug across a dialyzer membrane or peritoneal membrane from a higher to lower drug concentration. While drug usually moves from the blood compartment to the dialysis fluid, drug can be absorbed from the dialysis fluid into the systemic circulation when the drug concentration of the dialysis fluid exceeds the serum concentration. This is the mechanism by which potentially therapeutic serum drug concentrations are achieved with intraperitoneal dosing. Convection is the movement of drug across the dialyzer membrane or peritoneal membrane that occurs when drug is "trapped" within the flow of ultrafiltrate.

Dialysis removes only free drug from the body as drug bound to plasma proteins and other cellular constituents result in drug complexes that are too big and do not cross the dialyzer membrane or peritoneal membrane. The efficiency of drug removal (e.g., amount of drug removed per unit time) is greatest for hemodialysis, followed by continuous renal replacement therapies (CRRT), and least by peritoneal dialysis. Although drug removal by CRRT and peritoneal dialysis is less efficient than hemodialysis, the total drug removal may be equivalent to hemodialysis as CRRT and peritoneal dialysis are usually performed for a longer duration of time.

Hemodialysis

In hemodialysis, blood flows through a parallel series of synthetic capillaries contained in a plastic shell (dialyzer), while dialysis fluid flows in the opposite direction outside the blood-filled capillaries. As blood flows along the length of the capillaries, unbound solutes (e.g., drugs) diffuse across the membrane from the blood into the dialysis fluid. Depending on the need for fluid removal, ultrafiltration and convective drug removal occur, but diffusion is the most important factor influencing solute loss. The elimination of a drug during hemodialysis is dependent upon the size of the drug, protein binding, and dialyzer properties. The blood flow rate, dialyzer surface area, and membrane characteristics are dialyzer factors that impact drug elimination. During hemodialysis, the dialysis flow rate is rapid (e.g., 600 ml/min) and does not limit drug diffusion as the concentration gradient between blood within the dialyzer capillaries and dialysis fluid is continuously refreshed. A dialyzer with a larger surface area and a more porous membrane will increase drug clearance [15]. As technology has advanced, the newer synthetic membranes can be manufactured with larger pore size (e.g., high flux) that may allow for greater clearance of larger molecules than with the traditional membranes. Published drug clearance data should be viewed with caution as the reported clearance values may not be representative of the newer more porous membranes used in current practice. For example, vancomycin is a relatively large drug, and earlier reports suggested that vancomycin removal by hemodialysis was minimal. With the use of high-flux dialyzers (e.g., more porous membranes), the removal of vancomycin during dialysis is much greater than previously noted [16].

Dialysis drug clearance (Cl_d) can be calculated by measuring the prefilter (arterial (C_a)) and postfilter (venous (C_v)) serum drug concentration and the rate of blood flow through the filter (Q_b):

$$Cl_d = \left[\frac{(C_a - C_v)}{C_a}\right] \times Q_b \qquad (36.4)$$

Equation 36.4 can be corrected for protein binding and hematocrit when appropriate [1]. The equation can be further adapted to account for drug removal that occurs with ultrafiltration by measuring the ultrafiltration rate (Q_{uf}):

$$Cl_d = \left[\frac{(C_a - C_v)}{C_a}\right] \times Q_b + \left[\left(\frac{C_v}{C_a}\right) \times Q_{uf}\right] \qquad (36.5)$$

The drug clearance by hemodialysis is considered significant when the dialysis procedure accounts for more than 25% of systemic drug clearance. However, drug clearance of less than 25% may be clinically relevant when a drug has a

very narrow therapeutic index – the differences between concentrations associated with effect and those with toxicity.

Continuous Renal Replacement Therapies

The term "continuous renal replacement therapies" (CRRT) incorporates continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CCVHDF). Drug removal during CRRT is governed by the ultrafiltration and dialysis fluid flow rates as well as the same factors identified in hemodialysis, namely, drug size, protein binding, access blood flow, and dialyzer characteristics. During hemofiltration (e.g., CVVH), countercurrent dialysis fluid is not present, and fluid and solute (e.g., drug) removal occur consequent to convection (i.e., solute movement associated with fluid movement). In order to optimize solute removal, large volumes of ultrafiltration are prescribed, and the patient is provided with a large amount of replacement fluids to offset the hemofiltration losses. During continuous hemodialysis (e.g., CVVHD), countercurrent dialysis fluid is present, and most of the drug removal occurs by diffusion. During hemodiafiltration (CVVHDF), solutes are cleared by both convection and diffusion, but diffusion is the predominant process, and the dialysis fluid flow rate is the factor limiting solute (e.g., drug) removal such that increasing the dialysis fluid flow rate can enhance drug clearance [17]. Typical replacement fluid and dialysis flow rates during CRRT are 2000 mL/h/1.73 m^2.

During isolated hemofiltration, the relationship between drug concentration in the ultrafiltrate and the average drug concentration in the plasma calculated from the arterial (C_a) and venous (C_v) concentrations is termed the sieving coefficient:

$$\text{Sieving coefficient} = \frac{\text{Ultrafiltrate drug concentration}}{\left(C_a + C_v\right)/2} \tag{36.6}$$

A sieving coefficient of 1 suggests that the solute is filtered without hindrance through the dialyzer, whereas a sieving coefficient of 0 suggests there is no ultrafiltration of the drug. Most drugs are small enough that if not bound to plasma protein or cellular constituents, they are easily filtered.

When countercurrent dialysis fluid is present (i.e., CVVHD, CVVHDF), the relationship between the drug concentration in the combined dialysate and ultrafiltrate and the average drug concentration in plasma is termed the saturation coefficient (Sa):

$$\text{Saturation coefficient} = \frac{\text{Ultrafiltrate} + \text{dialysate drug concentration}}{\left(C_a + C_v\right)/2} \tag{36.7}$$

Drug clearance during CRRT (Cl_{CRRT}) can be calculated by measuring the sieving (Si) or saturation (Sa) coefficient and the dialysis (Q_d) and ultrafiltration (Q_{uf}) flow rates:

$$Cl_{CRRT} = \text{Si}\left(\text{or Sa}\right) \times \left(Q_d + Q_{uf}\right) \tag{36.8}$$

The drug clearance by CRRT is considered to be significant when the dialysis procedure accounts for more than 25% of systemic drug clearance. Similar to hemodialysis, when a drug has a very narrow therapeutic window, a drug clearance less than 25% may be clinically relevant.

Peritoneal Dialysis

In peritoneal dialysis, the peritoneal membrane serves as a highly vascularized semipermeable membrane separating blood and dialysis fluid. Fresh dialysis fluid is placed into the peritoneal cavity for a predetermined length of time, ranging anywhere from 30 min to 6 h, during which

drug moves across the peritoneal membrane in both directions by way of diffusion and convection. Factors influencing peritoneal drug clearance are characteristics of the peritoneal membrane (transport capacity), dialysis exchange volume (e.g., amount of peritoneal surface area exposed to dialysate), ultrafiltration rate, drug size, and protein binding.

Drug clearance by peritoneal dialysis is more difficult to measure because peritoneal blood flow rates cannot be easily determined. Drug clearance by peritoneal dialysis can be estimated by measuring the amount of drug present in the dialysate along with an estimate of the average serum concentration during the dialysis procedure. A mid-dialysis plasma drug level is used to estimate the average serum drug concentration (Eq. 36.9), or alternatively multiple blood samples can be obtained and an area under the curve (measure of exposure) calculated (Eq. 36.10):

$$\mathrm{Cl}_{\mathrm{pd}} = \frac{\text{Volume of dialysate} \times \text{drug concentration}}{\text{Mid} - \text{dialysis}\, C_{\mathrm{a}} \times \text{time}} \tag{36.9}$$

$$\mathrm{Cl}_{\mathrm{pd}} = \frac{\text{Volume of dialysate} \times \text{drug concentration}}{\mathrm{AUC}_{0-\mathrm{t}}} \tag{36.10}$$

Peritonitis, a common infectious complication of children receiving peritoneal dialysis, is often due to Gram-positive organisms but may also be a result of Gram-negative or fungal infections. In the presence of cloudy dialysis fluid, the empiric administration of intraperitoneal antibiotics is recommended after the appropriate laboratory studies and cultures are completed [18, 19]. Treatment is initiated with an intraperitoneal loading dose that dwells for 3–6 h and is followed by continuous or intermittent maintenance therapy to complete a 14–21-day treatment course. During continuous intraperitoneal maintenance therapy, antibiotic is present in the dialysis fluid of each exchange and ensures that the antibiotic concentration in the dialysis fluid exceeds the minimal inhibitory concentration (MIC) for the infective organisms throughout the treatment course. During intermittent maintenance dosing, serum antibiotic concentrations are maintained by placing a higher dose of antibiotic in the dialysis fluid for a single exchange each day or, in the case of vancomycin and teicoplanin, a single exchange every 5–7 days. During the subsequent antibiotic-free exchanges, antibiotic diffuses from the serum back into the dialysis fluid and accumulates to therapeutic intraperitoneal concentrations. The movement of drug into the peritoneum is dependent on the ratio of the drug in the serum to the dialysate concentration and the time allowed for drug diffusion (e.g., dwell time). The prolonged dwell time employed during continuous ambulatory peritoneal dialysis (CAPD) is usually sufficient to achieve a therapeutic intraperitoneal concentration if the serum drug concentration is adequate. During continuous cycling peritoneal dialysis (CCPD), the dwell times may be too short to allow for adequate movement of drug into the peritoneum resulting in subtherapeutic peritoneal drug concentrations. Whether therapeutic peritoneal antibiotic concentrations are required for the treatment of peritonitis is not known, and intermittent vancomycin and teicoplanin therapy has been used successfully in children receiving peritoneal dialysis [20]. Guidelines for the intraperitoneal dosing of common antibiotics are provided in Table 36.2.

The intraperitoneal administration of a drug is a convenient and acceptable route of administering medications for systemic effect but may not be appropriate for all drugs or all clinical circumstances. It is of great importance to recognize that in the treatment of serious infections outside the peritoneal cavity, intraperitoneal administration is not superior to intravenous therapy as the bioavailability of the intravenous form is always 100%, whereas the bioavailability of intraperitoneal administration may not be consistently predictable. In situations where intraperitoneal administration is required, therapeutic drug monitoring will help ensure that there has been adequate drug absorption.

Table 36.2 Intraperitoneal dosing recommendations for children with peritonitis [18]

Drug	Loading dose (mg/L)	Continuous therapy dosage (mg/L)	Intermittent therapy dosage
Ampicillin		125	
Cefazolin	500	125	20 mg/kg QD
Cefepime	500	125	15 mg/kg QD
Ceftazidime	500	125	20 mg/kg QD
Clindamycin	300	150	
Gentamicin	8	4	Anuric: 0.6 mg/kg QD Non-anuric: 0.75 mg/kg QD
Teicoplanin	400	20	15 mg/kg Q 5–7 D
Tobramycin	8	4	Anuric: 0.6 mg/kg QD Non-anuric: 0.75 mg/kg QD
Vancomycin	1000	25	30 mg/kg with further doses based on TDM

Dosing Strategies in Children with Renal Failure

Given that there is little information on drug disposition in children with renal failure and children receiving dialysis, an individualized systematic approach (Table 36.3), using the available adult and pediatric data on drug disposition in renal failure, is required to design a drug administration regimen that maximizes the effectiveness of therapy while minimizing the potential for adverse effects. The design of a successful therapeutic regimen begins with an estimate of the child's residual renal function and an estimate of the relative contribution of renal elimination to the total drug elimination obtained from the literature. While children receiving dialysis by definition have very poor renal function, it is inappropriate to assume that there is no renal elimination as many children maintain a significant amount of residual renal function. Failure to account for the continued renal elimination of drug may result in insufficient drug dosing and therapeutic failure. Additionally, patients receiving CRRT who require supraphysiologic rates of clearance (i.e., >2000 ml/h/1.73 m^2) may need closer patient-specific therapeutic monitoring to avoid insufficient drug dosing and therapeutic failure.

Table 36.3 Guidelines for drug dosing in children with renal failure

1. Estimate residual renal function
2. Determine percentage of drug eliminated by the kidneys
3. Determine if there are any active/toxic metabolites and route of elimination
4. Calculate the dosage adjustment factor (Q), or review published dosing recommendations
5. Adjust dose size or dosing interval
6. If patient is receiving dialysis, evaluate if supplemental dosing is required
7. Monitor response
8. Therapeutic drug monitoring (when available)

If one assumes that drug protein binding, distribution, and metabolism are not altered to a clinically significant degree in renal failure, an assumption that is likely true for most drugs, then a dosing adjustment factor (Q) can be estimated using the following equation:

$$Q = 1 - \left[\text{Fractional renal elimination} \times \left(1 - \frac{\text{Child's Cl}_{cr}\left(\text{mL / min/ 1.73m}^2\right)}{\text{Normal Cl}_{cr}\left(\text{mL / min/ 1.73m}^2\right)} \right) \right] \tag{36.11}$$

An appropriate dose amount or dosing interval for a child with reduced kidney function is generated by applying the dosing adjustment factor to either the normal dose amount or normal dosing interval. The dosage adjustment factor estimates the changes in elimination associated with renal failure but does not account for any additional clearance by dialysis. If appropriate, supplemen-

tal drug doses or an increased dose amount may be required to replace the dialysis-related drug losses. Whether a change is made in the dose amount or dosing interval depends on the therapeutic goal and relationships between drug concentrations and clinical response and toxicity.

As an example, the bactericidal aminoglycoside antibiotic gentamicin is primarily eliminated unchanged by the kidney (95% renal elimination), and if the dosing regimen is not modified, gentamicin accumulates to toxic blood levels in renal failure (Fig. 36.1). Using Eq. 36.11, the dosing adjustment factor (Q) for a 5-year-old child with a measured creatinine clearance of 12 ml/min/1.73 m^2 is calculated to be 0.15:

$$Q = 1 - \left[0.95 \times \left(1 - \frac{12\left(\text{mL / min/ 1.73m}^2\right)}{120\left(\text{mL / min/ 1.73m}^2\right)} \right) \right] = 0.15 \qquad (36.12)$$

A gentamicin dosing regimen modified for the reduced renal elimination is calculated by applying the dosage adjustment factor (Q) to either the dose amount or dosing interval. When the dosage adjustment factor is applied to the dose amount (multiplied), the modified dose is calculated to be 0.375 mg/kg administered IV every 8 h (0.15 × 2.5 mg/kg/dose). When the dosage adjustment factor is applied to the dosing interval (divided), the modified regimen is calculated to be 2.5 mg/kg administered IV every 53 h (8 h ÷ 0.15). As displayed in Fig. 36.2, both adjustments produce similar mean gentamicin serum levels but very different gentamicin serum peak and trough concentrations. Prolongation of the dosing interval (e.g., 2.5 mg/kg IV every 53 h) results in gentamicin serum peak and trough concentrations that are similar to those observed with normal dosing. In contrast, reduction of the dosage amount administered on a normal schedule (i.e., 0.375 mg/kg IV every 8 h) provides less variation between the serum peak and trough levels. For gentamicin and other aminoglycoside antibiotics, therapeutic peak levels that exceed the MIC90 of the organism are desired, and a prolonged dosing interval regimen is the most appropriate. For other drugs (e.g., antihypertensive agents), large swings in drug concentrations are undesired, and the method of reducing the dosage amount while maintaining the normal dosing interval will provide more consistent serum concentrations.

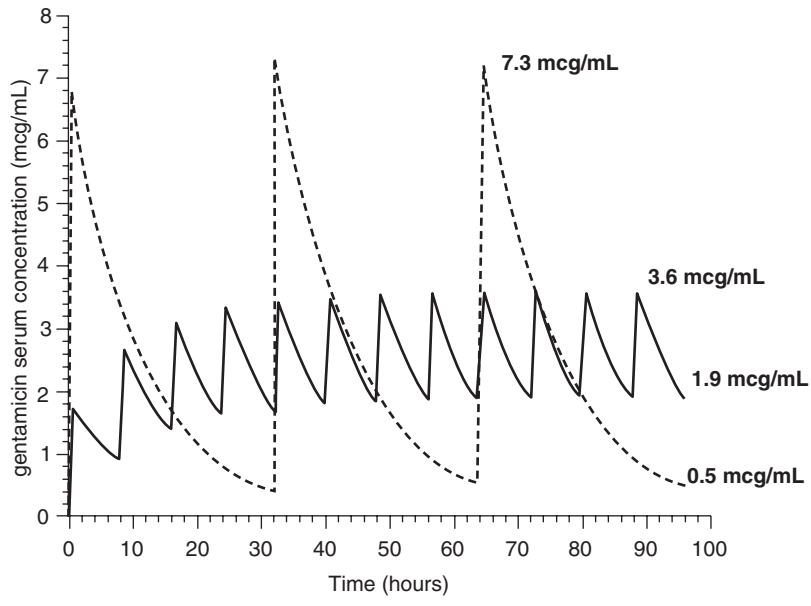

Fig. 36.2 Serum concentration – time profile for a child with a GFR = 15 mL/min/1.73 m^2. The dashed line depicts the profile when the dosing interval is adjusted to 2.5 mg/kg IV every 53 h. The solid line depicts the profile when the dosing interval is unchanged and the dosage amount is reduced (0.375 mg/kg IV every 8 h)

Once the prescribed drug dosing schedule has been adjusted for renal failure, a supplemental dose or dosing adjustment may be required for children receiving dialysis when more than 25% of drug is removed during the dialysis procedure. Supplemental dosing is given to replace the amount of drug removed by dialysis and may be achieved as a partial or full dose administered after hemodialysis or an increase in the dosing amount or frequency in children receiving peritoneal dialysis or CRRT. When possible, routine maintenance drugs should be provided after hemodialysis. Table 36.4 lists some common drugs and notes whether adjustments are needed for renal failure and if supplemental doses are suggested during dialysis.

Table 36.4 Dosing guidelines in renal failure and dialysis for common pediatric therapeutic agents

Drug	Adjustment for renal failure	Supplement for dialysis				Comments
		Hemodialysis	Peritoneal dialysis	CRRT	Sieving coefficient*	
Antibiotic, antiviral, antifungal agents						
Acyclovir [24–30]	Yes	Yes	No	No	0.9	Neurotoxicity
Amantadine [31–33]	Yes	No	No	No		
Amikacin [34–39]	Yes	Yes	Yes	Yes	0.9	TDM
Amoxicillin [40–42]	Yes	Yes	No	Yes	0.7	
Amoxicillin/clavulanic acid [43–45]	Yes	Yes	?	?	(Clav) 1	Consider dosing BID in HD
Amphotericin B [46, 47]	No	No	No	No	0.3	
Amphotericin B lipid complex [48, 49]	No	No	No	No		Dose after hemodialysis
Ampicillin [50–52]	Yes	Yes	No	Yes	0.7	
Azithromycin [32, 53]	No	No	No	No		
Cefaclor [54–56]	Yes	Yes	No	?		
Cefazolin [57–61]	Yes	Yes	Yes	Yes		
Cefepime [62–66]	Yes	Yes	Yes	Yes		Neurotoxicity
Cefixime [67, 68]	Yes	No	No	No		
Cefotaxime [50, 69, 70]	Yes	Yes	No	Yes		
Cefpodoxime [71–73]	Yes	Yes	No	?		
Cefprozil [74]	Yes	Yes	?	?		
Ceftazidime [42, 50, 75–77]	Yes	Yes	No	Yes	0.9	
Ceftriaxone [17, 50, 78, 79]	No	No	No	Yes	0.7	Dose after hemodialysis
Cefuroxime [50, 80–82]	Yes	Yes	No	Yes	0.9	
Cephalexin [32]	Yes	Yes	No	?		
Ciprofloxacin [32, 42, 83–85]	Yes	No	No	No	0.9	
Clindamycin [86]	No	No	No	No		
Co-trimoxazole [87–91]	Yes	Yes	No	Yes		
Erythromycin [32, 50, 92]	Yes	No	No	No		

Table 36.4 (continued)

Drug	Adjustment for renal failure	Supplement for dialysis				Comments
		Hemodialysis	Peritoneal dialysis	CRRT	Sieving coefficient*	
Famciclovir [93, 94]	Yes	No	?	?		Dose after hemodialysis
Fluconazole [42, 95–97]	Yes	Yes	No	Yes	0.8	
Foscarnet [98, 99]	Yes	Yes	?	?		Nephrotoxicity
Ganciclovir [100–104]	Yes	Yes	?	Yes	0.8	Dose after hemodialysis
Gentamicin [105–107]	Yes	Yes	Yes	Yes	0.8	TDM
Imipenem/cilastatin [50, 108–110]	Yes	Yes	No	Yes	1	Seizures
Isoniazid [111–114]	No	No	No	No		TDM dose after hemodialysis
Ketoconazole [115]	No	No	No	No		
Loracarbef [116]	Yes	Yes	?	?		
Meropenem [117–120]	Yes	Yes	?	Yes	0.9	
Metronidazole [32, 42, 50, 121, 122]	Yes	No	No	No	0.9	Dose after hemodialysis
Oxacillin [123]	No	No	No	No	0.02	
Penicillin G [32]	Yes	Yes	No	Yes		
Pentamidine [124, 125]	No	No	No	No		
Piperacillin [126–129]	Yes	Yes	No	Yes	0.8	
Piperacillin/tazo [130, 131]	Yes	Yes	No	?		
Rifampin [32, 111]	No	No	No	No		
Ticarcillin [45, 132, 133]	Yes	Yes	Yes	Yes	0.7	
Tobramycin [134–136]	Yes	Yes	Yes	Yes		TDM
Valacyclovir [137]	Yes	No	No	No		Dose after hemodialysis neurotoxicity
Valganciclovir [138, 139]	Yes	?	?	?		Not recommended in dialysis
Vancomycin [32, 42, 140, 141]	Yes	No	No	No	0.7	TDM
Anticonvulsants						
Carbamazepine [142, 143]	Yes	No	No	No		TDM
Gabapentin [144]	Yes	No	No	No		Dose after hemodialysis
Lamotrigine [145, 146]	Yes	No	?	?		
Levetiracetam [147–153]	Yes	Yes	?	No	1	
Phenobarbital [32, 154]	Yes	Yes	Yes	Yes	0.8	
Phenytoin [32, 155] (Fosphenytoin)	No	?	No	?	0.4	↓ Protein binding TDM – free levels

(continued)

Table 36.4 (continued)

Drug	Adjustment for renal failure	Supplement for dialysis				Comments
		Hemodialysis	Peritoneal dialysis	CRRT	Sieving coefficient*	
Valproic acid [4, 156–159]	No	No	No	No		↓ Protein binding; HD/CRRT may be useful in setting of overdose
Cardiovascular agents						
Aliskiren [160]	No	No	?	?		
Amlodipine [161–163]	No	No	No	?		
Atenolol [164–167]	Yes	Yes	No	?		
Captopril [168–172]	Yes	Yes	No	Yes		
Clonidine [173, 174]	No	No	No	?		
Digoxin [13, 175–178]	Yes	No	No	No	0.8	↓ Vd (adjust loading dose) Avoid K^+ depletion
Enalapril [179, 180]	Yes	Yes	No	Yes		
Esmolol [181, 182]	No	No	No	No		
Fosinopril [183, 184]	Yes	No	No	No		
Labetalol [185, 186]	No	No	No	No		
Lisinopril [172]	Yes	Yes	No	Yes		
Minoxidil [32, 187]	No	No	No	?		
Nifedipine [188–190]	No	No	No	?		
Nadolol [191]	Yes	Yes	No	?		
Metoprolol [32, 167]	No	Yes	?	?		Dose after hemodialysis
Prazosin [192]	No	No	No	?		
Propranolol [193–195]	No	No	No	No		
Immunosuppressive agents						
Daclizumab	No	?	?	?		
Azathioprine [32, 196]	Yes	Yes	?	?		
Cyclosporine [197–199]	No	No	No	No	0.6	TDM, nephrotoxicity
Mycophenolate [200–202]	No	No	No	No	0.02	TDM
Prednisone [203]	No	No	No	No		
Sirolimus	No	?	?	?		TDM
Tacrolimus [204, 205]	No	No	No	No		TDM, nephrotoxicity
Miscellaneous						
Buspirone [206, 207]	Yes	No	?	?		Active metabolites
Cetirizine [208, 209]	Yes	No	?	?		
Diazepam [32]	No	No	?	?		Active metabolites
Enoxaparin [210–212]	Yes	Yes	?	Yes	0.3–0.7	TDM

Table 36.4 (continued)

Drug	Adjustment for renal failure	Supplement for dialysis				Comments
		Hemodialysis	Peritoneal dialysis	CRRT	Sieving coefficient*	
Famotidine [213–215]	Yes	No	No	No	0.7	Active metabolites
Fentanyl [32]	Yes	No	?	?		
Fluoxetine [216–218]	No	No	No	No		
Hydromorphone [219, 220]	Yes	No	?	?		
Imipramine [32, 221]	No	No	No	?		
Lansoprazole [222–224]	No	No	?	?		
Lithium [225–227]	Yes	Yes	No	?		TDM
Loratadine [228]	Yes	No	?	?		
Meperidine [7]	Yes	?	?	?		Seizures, metabolites not recommended
Methadone [32, 229, 230]	Yes	No	?	?		
Methylphenidate	No	?	?	?		
Midazolam [5, 231, 232]	Yes	?	?	?	0.04	Active metabolites
Montelukast	No	?	?	?		
Morphine [6, 32, 233, 234]	Yes	No	?	?		
Omeprazole [235, 236]	No	No	?	?		
Ondansetron	No	?	?	?		
Oxycodone [32]	Yes	?	?	?		Active metabolites
Paroxetine [237]	Yes	?	?	?		
Ranitidine [238–241]	Yes	No	No	?	0.8	Dose after hemodialysis
Sufentanil [229]	No	?	?	?		
Warfarin [32]	No	No	No	?		

*Sieving coefficient may vary based on membrane and should be confirmed with membrane-specific data when available

The determinants of drug disposition and action in children with renal failure and those children receiving dialysis are frequently altered such that changes in the dosing regimen are necessary to avoid toxicity or inadequate treatment. In view of the many factors that can alter both the disposition and action of a given drug, it is important to individualize drug therapy for the known alterations associated with age, kidney failure, and dialysis.

Future Considerations: Pediatric Pharmacogenetics

The application of pharmacogenetic principles to the optimal use of medications in children requires an understanding that the consequences of genetic variation in genes involved in drug disposition and response are superimposed upon variability associated with the processes of growth and development. Changes in end-organ

function, such as ontogeny of renal function early in life as well as renal failure and drug removal by dialysis, represent additional factors that must be considered in the pharmacotherapeutic decision-making process. Nevertheless, there are two factors that should be considered when determining if genetic variation (pharmacogenetics) is likely to be clinically relevant for a particular medication in a given patient. First, pharmacogenetic variation is most relevant when the pathway subject to genetic variation is quantitatively important to the overall clearance of the drug from the body. There are no specific guidelines as to what constitutes "quantitatively important," but pharmacokinetic differences between "poor metabolizers" who have two nonfunctional copies of the gene and "extensive metabolizers," who have two functional copies of the gene, begin to manifest when the polymorphic pathway accounts for at least 50% of the overall clearance. Traditionally, genetic variation has been considered to be increasingly important as the therapeutic index – the difference between concentrations associated with effect and those associated with toxicity – decreases; warfarin is one example of a narrow therapeutic index medication where genetic information is becoming a very useful adjunct to initial dose selection. More recently, however, there is an increasing appreciation for pharmacogenetic variation to impact the use of broad therapeutic index drugs, with the primary concern being lack of efficacy, rather than increased risk of toxicity.

Efforts to assess the relative contributions of ontogeny and genetic variation to overall interindividual variability in drug disposition and response have largely focused on genes involved in hepatic drug biotransformation. For example, cytochrome P450 2D6 (CYP2D6) is one of the best-studied, clinically relevant pharmacogenetic polymorphisms [21]. The CYP2D6 gene locus is highly polymorphic with more than 140 allelic variants with corresponding activity phenotypes ranging from poor metabolizer phenotypes (no functional activity) at one end of the activity spectrum to intermediate, extensive, and ultrarapid metabolizer phenotypes at the other end of the spectrum. From a pediatric perspective, CYP2D6 is not expressed to an appreciable degree in fetal liver, but functional activity appears relatively soon after birth [8]. Thus, for pharmacogenetics to be integrated into pediatric drug therapy, knowledge of ontogeny is essential as the functional consequences of genetic variability will not become fully apparent until the genes are fully expressed. In the case of CYP2D6, a longitudinal phenotyping study was conducted in children over the first year of life using a test dose of the over-the-counter cough suppressant dextromethorphan as a measure of CYP2D6 activity. Measured CYP2D6 activity based on urinary metabolite ratios (phenotype) was concordant with genotype at 2 weeks of age and throughout the following 12 months [22]. Thus, in vivo phenotyping data indicate that genetic variation in CYP2D6 is expected to be a more important determinant of variability in drug disposition than developmental considerations.

The relevance of pharmacogenetics to drug administration in renal failure relates more to ancillary drug therapy than the renally eliminated medications whose clearance is prolonged by renal failure or altered during dialysis. For example, CYP2D6 is important for elimination of many drugs used to manage other conditions in children with renal failure. These medications include selective serotonin reuptake inhibitors, fluoxetine and paroxetine; the selective norepinephrine reuptake inhibitors, atomoxetine and venlafaxine; tricyclic antidepressants, amitriptyline, nortriptyline, and desipramine; antipsychotics, haloperidol, aripiprazole, and risperidone; analgesics, codeine, oxycodone, and tramadol; antihistamines, chlorpheniramine and diphenhydramine; and drugs such as metoclopramide, ondansetron, and promethazine. Genetic variation is also important for other CYPs as well, and two of the most important clinically are CYP2C9 and CYP2C19. Examples of CYP2C9 substrates include phenytoin, warfarin, glipizide, several NSAIDs, and angiotensin receptor blockers, such as losartan, valsartan, and irbesartan. Clinically important CYP2C19 substrates include proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole), clopidogrel, and escitalopram. In most situations, individuals with

two nonfunctional copies of the CYP2C9 or CYP2C19 genes are at increased risk for concentration-dependent side effects. Proton pump inhibitors are an exception as "poor metabolism" is associated with higher systemic exposure of the drugs and thus improved clinical response.

Much less is known about the roles of ontogeny and genetic variation in transporter genes involved in drug elimination by the kidney and how this function is altered in chronic kidney disease. As an example, organic cation transporters (OCTs) in the SLC22A subfamily are primarily expressed on the basolateral membrane of polarized epithelia and mediate the renal secretion of small organic cations. OCT1 (also known as SLC22A1) is expressed at the apical side of proximal and distal renal tubules, whereas OCT2 (SLC22A2) is predominantly expressed on the basolateral surface of proximal renal tubules. In adults, allelic variation in OCT1 and OCT2 is associated with increased renal clearance of metformin. On the other hand, no studies addressing the genetic variation of OCT1 and OCT2 have been conducted in children, but developmental factors appear to be operative. For example, neonates possess very limited ability to eliminate organic cations, but this function increases rapidly during the first few months of life; when standardized for body weight or surface area, it tends to exceed adult levels during the toddler stage.

Most importantly, the application of pharmacogenetics to aid in optimizing drug therapy in children is rapidly gaining momentum but has not yet reached the stage of routine incorporation into clinical decision-making, especially in specialized conditions like chronic renal failure. Although a number of clinical guidelines have been released by the Clinical Pharmacogenetics Implementation Consortium (CPIC) to provide information regarding dosing of medications in the presence of a test result for a given patient, few of those published to date have specific information for children; an exception is the recently released guideline for CYP2D6 and atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) [23]. Nevertheless, pediatric experience across many subspecialty areas continues to accumulate, and a potential role for pharmacogenetics should be anticipated in situations where a medication is associated with a narrow therapeutic index, and when there is considerable variability in the response to a medication, whether lack of efficacy or toxicity.

References

1. Blowey DL. Extracorporeal methods of drug removal. In: Ritschel W, Kearns G, editors. Handbook of basic pharmacokinetics. 7th ed. Washington, DC: American Pharmaceutical Association; 2009. p. 395–407.
2. Miyagawa CI. Hydrochloric acid given with ketoconazole through a jejunostomy tube. Clin Pharm. 2019;3(2):205–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6327144.
3. Blum RA, D'Andrea DT, Florentino BM, Wilton JH, Hilligoss DM, Gardner MJ, et al. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med. 1991;114(9):755–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2012358
4. Bruni J, Wang LH, Marbury TC, Lee CS, Wilder BJ. Protein binding of valproic acid in uremic patients. Neurology. 1980;30(5):557–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6768007
5. Bauer TM, Ritz R, Haberthür C, Ha HR, Hunkeler W, Sleight AJ, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet (London, England). 1995;346(8968):145–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7603229.
6. Ball M, McQuay HJ, Moore RA, Allen MC, Fisher A, Sear J. Renal failure and the use of morphine in intensive care. Lancet (London, England). 1985;1(8432):784–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2858668
7. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidenberg MM. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. Ann Intern Med. 1977;86(6):738–41.
8. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther. 2008;118(2):250–67. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163725808000375
9. Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem. 2008;392(6):1093–108.

Available from: http://link.springer.com/10.1007/s00216-008-2291-6
10. Ortiz A, Justo P, Sanz A, Melero R, Caramelo C, Guerrero MF, et al. Tubular cell apoptosis and cidofovir-induced acute renal failure. Antivir Ther. 2005;10(1):185–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15751777
11. Lacy SA, Hitchcock MJ, Lee WA, Tellier P, Cundy KC. Effect of oral probenecid coadministration on the chronic toxicity and pharmacokinetics of intravenous cidofovir in cynomolgus monkeys. Toxicol Sci. 1998;44(2):97–106. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1096608098924817
12. Prescott LF, Balali-Mood M, Critchley JA, Johnstone AF, Proudfoot AT. Diuresis or urinary alkalinisation for salicylate poisoning? Br Med J. 1982;285(6352):1383–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6291695
13. Paulson MF, Welling PG. Calculation of serum digoxin levels in patients with normal and impaired renal function. J Clin Pharmacol. 1976;16(11–12):660–5.
14. Blowey DL, Kearns GL, Lalkin A. Special considerations in the prescribing of medications for the pediatric CAPD/CCPD patient. In: Fine R, ALexander S, Warady B, editors. CAPD/CCPD in children. Boston: Kluwer Academic Publishers; 1998. p. 229–46.
15. Zhang Y, Zhang L, Abraham S, Apparaju S, Wu T-C, Strong JM, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clin Pharmacol Ther. 2009;85(3):305–11. Available from: http://doi.wiley.com/10.1038/clpt.2008.208
16. DeSoi CA, Sahm DF, Umans JG. Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes. Am J Kidney Dis. 1992 Oct;20(4):354–60.
17. Matzke GR, Frye RF, Joy MS, Palevsky PM. Determinants of ceftriaxone clearance by continuous venovenous hemofiltration and hemodialysis. Pharmacotherapy. 2000;20(6):635–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10853618
18. Warady BA, Bakkaloglu S, Newland J, Cantwell M, Verrina E, Neu A, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(Suppl 2):S32–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22851742
19. Li PK-T, Szeto CC, Piraino B, de Arteaga J, Fan S, Figueiredo AE, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Perit Dial Int. 2016;36(5):481–508. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27282851
20. Schaefer F, Klaus G, Muller-Wiefel DE, Mehls O. Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). J Am Soc Nephrol. 1999 Jan;10(1):136–45.
21. Pharmacogene variation (PharmVar) consortium: CYP2D6. Available from: http://www.pharmvar.org/gene/CYP2D6, accessed January 4, 2021.
22. Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther. 2007;81(4):510–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17301735
23. Brown JT, Bishop JR, Sangkuhl K, Nurmi EL, Mueller DJ, Dinh JC, et al. Clinical pharmacogenetics implementation consortium guideline for cytochrome P450 (*CYP*) *2D6* genotype and atomoxetine therapy. Clin Pharmacol Ther. 2019;106(1):94–102. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1409
24. Boelaert J, Schurgers M, Daneels R, Van Landuyt HW, Weatherley BC. Multiple dose pharmacokinetics of intravenous acyclovir in patients on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother. 1987 Jul;20(1):69–76.
25. Stathoulopoulou F, Almond MK, Dhillon S, Raftery MJ. Clinical pharmacokinetics of oral acyclovir in patients on continuous ambulatory peritoneal dialysis. Nephron. 1996;74(2):337–41.
26. Wagstaff AJ, Faulds D, Goa KL. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1994;47(1):153–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7510619
27. Laskin OL, Longstreth JA, Whelton A, Krasny HC, Keeney RE, Rocco L, et al. Effect of renal failure on the pharmacokinetics of acyclovir. Am J Med. 1982;73(1A):197–201. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7102702
28. Khajehdehi P, Jamal JA, Bastani B. Removal of acyclovir during continuous veno-venous hemodialysis and hemodiafiltration with high-efficiency membranes. Clin Nephrol. 2000;54(4):351–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11076113
29. Bleyzac N, Barou P, Massenavette B, Contamin B, Maire P, Berthier JC, et al. Assessment of acyclovir intraindividual pharmacokinetic variability during continuous hemofiltration, continuous hemodiafiltration, and continuous hemodialysis. Ther Drug Monit. 1999;21(5):520–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10519448
30. Boulieu R, Bastien O, Gaillard S, Flamens C. Pharmacokinetics of acyclovir in patients undergoing continuous venovenous hemodialysis. Ther Drug Monit. 1997;19(6):701–4.
31. Wu MJ, Ing TS, Soung LS, Daugirdas JT, Hano JE, Gandhi VC. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. Clin Nephrol. 1982;17(1):19–23.

32. Olyaei A, De Mattos A, Bennett W. Prescribing drugs in renal disease. In: Brenner B, editor. The kidney. Philadelphia: WB Saunders; 2000. p. 2606–53.
33. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2005;54(RR-8):1–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16086456
34. Chow-Tung E, Lau AH, Vidyasagar D, John EG. Effect of peritoneal dialysis on serum concentrations of three drugs commonly used in pediatric patients. Dev Pharmacol Ther. 1985;8(2):85–95.
35. Lanao JM, Dominguez-Gil A, Tabernero JM, Macias J. Influence of type of dialyzer on the pharmacokinetics of amikacin. Int J Clin Pharmacol Ther Toxicol. 1983;21:197–202.
36. Armendariz E, Chelluri L, Ptachcinski R. Pharmacokinetics of amikacin during continuous veno-venous hemofiltration. Crit Care Med. 1990;18(6):675–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2344762
37. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Lefrant J-Y, et al. Influence of renal replacement modalities on amikacin population pharmacokinetics in critically Ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother. 2016;60(8):4901–9.
38. D'Arcy DM, Casey E, Gowing CM, Donnelly MB, Corrigan OI. An open prospective study of amikacin pharmacokinetics in critically ill patients during treatment with continuous venovenous haemodiafiltration. BMC Pharmacol Toxicol. 2012;13:14.
39. Smeltzer BD, Schwartzman MS, Bertino JS. Amikacin pharmacokinetics during continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1988;32(2):236–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3364945
40. Oe PL, Simonian S, Verhoef J. Pharmacokinetics of the new penicillins. Amoxycillin and flucloxacillin in patients with terminal renal failure undergoing haemodialysis. Chemotherapy. 1973;19(5):279–88.
41. Bouman CSC. Antimicrobial dosing strategies in critically ill patients with acute kidney injury and high-dose continuous veno-venous hemofiltration. Curr Opin Crit Care. 2008;14(6):654–9.
42. Bouman CSC, Van Kan HJM, Koopmans RP, Korevaar JC, Schultz MJ, Vroom MB. Discrepancies between observed and predicted continuous venovenous hemofiltration removal of antimicrobial agents in critically ill patients and the effects on dosing. Intensive Care Med. 2006;32(12):2013–9.
43. Hui K, Patel K, Kong DCM, Kirkpatrick CMJ. Impact of high-flux haemodialysis on the probability of target attainment for oral amoxicillin/clavulanic acid combination therapy. Int J Antimicrob Agents. 2017;50(1):110–3.
44. Slaughter RL, Kohli R, Brass C. Effects of hemodialysis on the pharmacokinetics of amoxicillin/clavulanic acid combination. Ther Drug Monit. 1984;6(4):424–7.
45. Wan WTP, Guerra Valero Y, GYS C, Ordóñez Mejia JL, Wallis SC, Joynt GM, et al. In-vitro adsorption and sieving coefficient of ticarcillin-clavulanate during continuous haemofiltration. Int J Antimicrob Agents. 2019;54(2):261–4.
46. Muther RS, Bennett WM. Peritoneal clearance of amphotericin B and 5-fluorocytosine. West J Med. 1980;133(2):157–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7015695
47. Block ER, Bennett JE, Livoti LG, Klein WJJ, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. Studies in man. Ann Intern Med. 1974;80(5):613–7.
48. Malone ME, Corrigan OI, Kavanagh PV, Gowing C, Donnelly M, D'Arcy DM. Pharmacokinetics of amphotericin B lipid complex in critically ill patients undergoing continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2013;42(4):335–42.
49. Bellmann R, Egger P, Djanani A, Wiedermann CJ. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous venovenous haemofiltration. Int J Antimicrob Agents. 2004;23(1):80–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14732318
50. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. J Antimicrob Chemother. 1995;36(5):773–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8626257
51. Jusko WJ, Lewis GP, Schmitt GW. Ampicillin and hetacillin pharmacokinetics in normal and anephric subjects. Clin Pharmacol Ther. 1973;14:90–9.
52. Golper TA, Pulliam J, Bennett WM. Removal of therapeutic drugs by continuous arteriovenous hemofiltration. Arch Intern Med. 1985;145(9):1651–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4026495
53. Kent JR, Almond MK, Dhillon S. Azithromycin: an assessment of its pharmacokinetics and therapeutic potential in CAPD. Perit Dial Int. 2001;21(4):372–7.
54. Berman SJ, Boughton WH, Sugihara JG, Wong EG, Sato MM, Siemsen AW. Pharmacokinetics of cefaclor in patients with end stage renal disease and during hemodialysis. Antimicrob Agents Chemother. 1978;14(3):281–3.
55. Gartenberg G, Meyers BR, Hirschmann SZ, Srulevitch E. Pharmacokinetics of cefaclor in patients with stable renal impairment, and patients undergoing haemodialysis. J Antimicrob Chemother. 1979;5(4):465–70.
56. Spyker DA, Gober LL, Scheld WM, Sande MA, Bolton WK. Pharmacokinetics of cefaclor in renal failure: effects of multiple doses and hemodialysis. Antimicrob Agents Chemother. 1982;21(2):278–81.
57. Marx MA, Frye RF, Matzke GR, Golper TA. Cefazolin as empiric therapy in hemodialysis-

related infections: efficacy and blood concentrations. Am J Kidney Dis. 1998;32(3):410–4.
58. Manley HJ, Bailie GR, Asher RD, Eisele G, Frye RF. Pharmacokinetics of intermittent intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 2019;19(1):65–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10201343
59. Manley HJ, Bridwell DL, Elwell RJ, Bailie GR. Influence of peritoneal dialysate flow rate on the pharmacokinetics of cefazolin. Perit Dial Int. 2019;23(5):469–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14604200
60. Sowinski KM, Mueller BA, Grabe DW, Manley HJ, Frye RF, Bailie GR, et al. Cefazolin dialytic clearance by high-efficiency and high-flux hemodialyzers. Am J Kidney Dis. 2001;37(4):766–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11273877
61. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC. Cefazolin and cephalexin kinetics in continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther. 1983;33(1):66–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6848301
62. Cronqvist J, Nilsson-Ehle I, Oqvist B, Norrby SR. Pharmacokinetics of cefepime dihydrochloride arginine in subjects with renal impairment. Antimicrob Agents Chemother. 1992;36(12):2676–80.
63. Wong KM, Chan WK, Chan YH, Li CS. Cefepime-related neurotoxicity in a haemodialysis patient. Nephrol Dial Transplant. 1999;14(9):2265–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10489256
64. Barbhaiya RH, Knupp CA, Pfeffer M, Zaccardelli D, Dukes GM, Mattern W, et al. Pharmacokinetics of cefepime in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1992;36(7):1387–91.
65. Carlier M, Taccone FS, Beumier M, Seyler L, Cotton F, Jacobs F, et al. Population pharmacokinetics and dosing simulations of cefepime in septic shock patients receiving continuous renal replacement therapy. Int J Antimicrob Agents. 2015;46(4):413–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0924857915002265
66. Isla A, Gascón AR, Maynar J, Arzuaga A, Toral D, Pedraz JL. Cefepime and continuous renal replacement therapy (CRRT): In vitro permeability of two CRRT membranes and pharmacokinetics in four critically ill patients. Clin Ther. 2005;27(5):599–608.
67. Faulkner RD, Yacobi A, Barone JS, Kaplan SA, Silber BM. Pharmacokinetic profile of cefixime in man. Pediatr Infect Dis J. 1987;6(10):963–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3696837
68. Guay DR, Meatherall RC, Harding GK, Brown GR. Pharmacokinetics of cefixime (CL 284,635; FK 027) in healthy subjects and patients with renal insufficiency. Antimicrob Agents Chemother. 1986;30(3):485–90.
69. Albin H, Demotes-Mainard F, Bouchet J, Vincon G, Martin-Dupont C. Pharmacokinetics of intravenous and intraperitoneal cefotaxime in chronic ambulatory peritoneal dialysis. Clin Pharmacol Ther. 1985;38:285–9.
70. Ings RM, Fillastre JP, Godin M, Leroy A, Humbert G. The pharmacokinetics of cefotaxime and its metabolites in subjects with normal and impaired renal function. Rev Infect Dis. 2019;4(Suppl):S379–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6294787
71. Höffler D, Koeppe P, Corcilius M, Przyklinik A. Cefpodoxime proxetil in patients with end-stage renal failure on hemodialysis. Infection. 2019;18(3):157–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2365467
72. Borin MT, Hughes GS, Kelloway JS, Shapiro BE, Halstenson CE. Disposition of cefpodoxime proxetil in hemodialysis patients. J Clin Pharmacol. 1992;32(11):1038–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1474165
73. Johnson CA, Ateshkadi A, Zimmerman SW, Hughes GS, Craig WA, Carey PM, et al. Pharmacokinetics and ex vivo susceptibility of cefpodoxime proxetil in patients receiving continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1993;37(12):2650–5.
74. Shyu WC, Pittman KA, Wilber RB, Matzke GR, Barbhaiya RH. Pharmacokinetics of cefprozil in healthy subjects and patients with renal impairment. J Clin Pharmacol. 1991;31(4):362–71.
75. Welage LS, Schultz RW, Schentag JJ. Pharmacokinetics of ceftazidime in patients with renal insufficiency. Antimicrob Agents Chemother. 1984;25(2):201–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6370127
76. Nikolaidis P, Tourkantonis A. Effect of hemodialysis on ceftazidime pharmacokinetics. Clin Nephrol. 1985;24(3):142–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3899438
77. Kinowski JM, de la Coussaye JE, Bressolle F, Fabre D, Saissi G, Bouvet O, et al. Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. Antimicrob Agents Chemother. 1993;37(3):464–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8460915
78. Losno Garcia R, Santivanez V, Battilana CA. Single-dose pharmacokinetics of ceftriaxone in patients with end-stage renal disease and hemodialysis. Chemotherapy. 1988;34(4):261–6.
79. Kroh UF, Lennartz H, Edwards DJ, Stoeckel K. Pharmacokinetics of ceftriaxone in patients undergoing continuous veno-venous hemofiltration. J Clin Pharmacol. 1996;36(12):1114–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9013367
80. Konishi K, Suzuki H, Hayashi M, Saruta T. Pharmacokinetics of cefuroxime axetil in patients with normal and impaired renal function. J Antimicrob Chemother. 1993;31(3):413–20.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/8486575
81. Weiss LG, Cars O, Danielson BG, Grahnen A, Wikstrom B. Pharmacokinetics of intravenous cefuroxime during intermittent and continuous arteriovenous hemofiltration. Clin Nephrol. 1988;30(5):282–6.
82. Janssen PKC, Foudraine NA, Burgers DMT, Neef K, Le Noble JLML. Population pharmacokinetics of cefuroxime in critically ill patients receiving continuous venovenous hemofiltration with regional citrate anticoagulation and a phosphate-containing replacement fluid. Ther Drug Monit. 2016;38(6):699–705.
83. Singlas E, Taburet AM, Landru I, Albin H, Ryckelinck JP. Pharmacokinetics of ciprofloxacin tablets in renal failure; influence of haemodialysis. Eur J Clin Pharmacol. 1987;31(5):589–93.
84. Roger C, Wallis SC, Louart B, Lefrant J-Y, Lipman J, Muller L, et al. Comparison of equal doses of continuous venovenous haemofiltration and haemodiafiltration on ciprofloxacin population pharmacokinetics in critically ill patients. J Antimicrob Chemother. 2016;71(6):1643–50.
85. Spooner AM, Deegan C, D'Arcy DM, Gowing CM, Donnelly MB, Corrigan OI. An evaluation of ciprofloxacin pharmacokinetics in critically ill patients undergoing continuous veno-venous haemodiafiltration. BMC Clin Pharmacol. 2011;11:11.
86. Roberts AP, Eastwood JB, Gower PE, Fenton CM, Curtis JR. Serum and plasma concentrations of clindamycin following a single intramuscular injection of clindamycin phosphate in maintenance haemodialysis patients and normal subjects. Eur J Clin Pharmacol. 1978;14(6):435–9.
87. Paap CM, Nahata MC. Clinical use of trimethoprim/sulfamethoxazole during renal dysfunction. DICP. 1989;23(9):646–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2678767
88. Nissenson AR, Wilson C, Holazo A. Pharmacokinetics of intravenous trimethoprim-sulfamethoxazole during hemodialysis. Am J Nephrol. 1987;7(4):270–4.
89. Kesner JM, Yardman-Frank JM, Mercier R-C, Wong CS, Walker SE, Argyres DP, et al. Trimethoprim and sulfamethoxazole transmembrane clearance during modeled continuous renal replacement therapy. Blood Purif. 2014;38(3–4):195–202.
90. Curkovic I, Luthi B, Franzen D, Ceschi A, Rudiger A, Corti N. Trimethoprim/Sulfamethoxazole pharmacokinetics in two patients undergoing continuous venovenous hemodiafiltration. Ann Pharmacother. 2010;44(10):1669–72.
91. Walker SE, Paton TW, Churchill DN, Ojo B, Manuel MA, Wright N. Trimethoprim-sulfamethoxazole pharmacokinetics during continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int. 1989;9(1):51–5.
92. Disse B, Gundert-Remy U, Weber E, Andrassy K, Sietzen W, Lang A. Pharmacokinetics of erythromycin in patients with different degrees of renal impairment. Int J Clin Pharmacol Ther Toxicol. 1986;24(9):460–4.
93. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. Clin Pharmacokinet. 1996;31(1):1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8827396
94. Boike SC, Pue MA, Freed MI, Audet PR, Fairless A, Ilson BE, et al. Pharmacokinetics of famciclovir in subjects with varying degrees of renal impairment. Clin Pharmacol Ther. 1994;55(4):418–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8162668
95. Dudley MN. Clinical pharmacology of fluconazole. Pharmacotherapy. 1990;10(6 (Pt 3)):141S–5S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2075112
96. Nicolau DP, Crowe H, Nightingale CH, Quintiliani R. Effect of continuous arteriovenous hemodiafiltration on the pharmacokinetics of fluconazole. Pharmacotherapy. 2019;14(4):502–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7937290
97. Patel K, Roberts JA, Lipman J, Tett SE, Deldot ME, Kirkpatrick CM. Population pharmacokinetics of fluconazole in critically ill patients receiving continuous venovenous hemodiafiltration: using Monte Carlo simulations to predict doses for specified pharmacodynamic targets. Antimicrob Agents Chemother. 2011;55(12):5868–73. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.00424-11
98. Aweeka FT, Jacobson MA, Martin-Munley S, Hedman A, Schoenfeld P, Omachi R, et al. Effect of renal disease and hemodialysis on foscarnet pharmacokinetics and dosing recommendations. J Acquir Immune Defic Syndr Hum Retrovirol. 1999;20(4):350–7.
99. Alexander AC, Akers A, Matzke GR, Aweeka FT, Fraley DS. Disposition of foscarnet during peritoneal dialysis. Ann Pharmacother. 1996;30(10):1106–9. Available from: http://journals.sagepub.com/doi/10.1177/106002809603001007
100. Combarnous F, Fouque D, Bernard N, Boulieu R, Chossegros P, Laville M, et al. Pharmacokinetics of ganciclovir in a patient undergoing chronic haemodialysis. Eur J Clin Pharmacol. 1994;46(4):379–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7957527
101. Boulieu R, Bastien O, Bleyzac N. Pharmacokinetics of ganciclovir in heart transplant patients undergoing continuous venovenous hemodialysis. Ther Drug Monit. 1993;15(2):105–7.
102. Horvatits T, Kitzberger R, Drolz A, Zauner C, Jäger W, Böhmdorfer M, et al. Pharmacokinetics of ganciclovir during continuous venovenous hemodiafiltration in critically ill patients. Antimicrob Agents Chemother. 2014;58(1):94–101. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.00892-13

103. Gando S, Kameue T, Nanzaki S, Hayakawa T, Nakanishi Y. Pharmacokinetics and clearance of ganciclovir during continuous hemodiafiltration. Crit Care Med. 1998;26(1):184–7.
104. Sommadossi JP, Bevan R, Ling T, Lee F, Mastre B, Chaplin MD, et al. Clinical pharmacokinetics of ganciclovir in patients with normal and impaired renal function. Rev Infect Dis. 2019;10(Suppl 3):S507–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2847287
105. Golper TA, Bennett WM. Drug removal by continuous arteriovenous haemofiltration. A review of the evidence in poisoned patients. Med Toxicol Adverse Drug Exp. 1988;3(5):341–9.
106. Ernest D, Cutler DJ. Gentamicin clearance during continuous arteriovenous hemodiafiltration. Crit Care Med. 1992;20(5):586–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1572182
107. Hamann SR, Oeltgen PR, Shank WA, Blouin RA, Natarajan L. Evaluation of gentamicin pharmacokinetics during peritoneal dialysis. Ther Drug Monit. 1982;4(3):297–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6753255
108. Somani P, Freimer EH, Gross ML, Higgins JTJ. Pharmacokinetics of imipenem-cilastatin in patients with renal insufficiency undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1988;32(4):530–4.
109. Verpooten GA, Verbist L, Buntinx AP, Entwistle LA, Jones KH, De Broe ME. The pharmacokinetics of imipenem (thienamycin-formamidine) and the renal dehydropeptidase inhibitor cilastatin sodium in normal subjects and patients with renal failure. Br J Clin Pharmacol. 1984;18(2):183–93.
110. Tegeder I, Bremer F, Oelkers R, Schobel H, Schüttler J, Brune K, et al. Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. Antimicrob Agents Chemother. 1997;41(12):2640–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9420033
111. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1580–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10228130
112. Ellard GA. Chemotherapy of tuberculosis for patients with renal impairment. Nephron. 1993;64(2):169–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8321347
113. Ahn C, Oh K-H, Kim K, Lee KY, Lee JG, Oh MD, et al. Effect of peritoneal dialysis on plasma and peritoneal fluid concentrations of isoniazid, pyrazinamide, and rifampin. Perit Dial Int. 2019;23(4):362–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12968844
114. Gold CH, Buchanan N, Tringham V, Viljoen M, Strickwold B, Moodley GP. Isoniazid pharmacokinetics in patients in chronic renal failure. Clin Nephrol. 1976;6(2):365–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/954244
115. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. Clin Pharmacokinet. 1988;14(1):13–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3280211
116. Therasse DG, Farlow DS, Davidson RL, Quadracci LJ, Hatcher BL, Cerimele BJ, et al. Effects of renal dysfunction on the pharmacokinetics of loracarbef. Clin Pharmacol Ther. 1993;54(3):311–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8375126
117. Tegeder I, Neumann F, Bremer F, Brune K, Lötsch J, Geisslinger G. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. Clin Pharmacol Ther. 1999;65(1):50–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9951430
118. Giles LJ, Jennings AC, Thomson AH, Creed G, Beale RJ, McLuckie A. Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. Crit Care Med. 2000;28(3):632–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10752806
119. Chimata M, Nagase M, Suzuki Y, Shimomura M, Kakuta S. Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. Antimicrob Agents Chemother. 1993;37(2):229–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8452352
120. Thalhammer F, Hörl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. Clin Pharmacokinet. 2000;39(4):271–9. Available from: http://link.springer.com/10.2165/00003088-200039040-00003
121. Somogyi AA, Kong CB, Gurr FW, Sabto J, Spicer WJ, McLean AJ. Metronidazole pharmacokinetics in patients with acute renal failure. J Antimicrob Chemother. 1984;13(2):183–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6706889
122. Cassey JG, Clark DA, Merrick P, Jones B. Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. Antimicrob Agents Chemother. 1983;24(6):950–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6660863
123. Ruedy J. The effects of peritoneal dialysis on the physiological disposition of oxacillin, ampicillin and tetracycline in patients with renal disease. Can Med Assoc J. 1966;94(6):257–61.
124. Conte JEJ. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. J Infect Dis. 1991;163(1):169–75.
125. Conte JE, Upton RA, Lin ET. Pentamidine pharmacokinetics in patients with AIDS with impaired renal function. J Infect Dis. 1987;156(6):885–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3680992

126. Thompson MI, Russo ME, Matsen JM, Atkin-Thor E. Piperacillin pharmacokinetics in subjects with chronic renal failure. Antimicrob Agents Chemother. 1981;156:885–90.
127. Francke EL, Appel GB, Neu HC. Pharmacokinetics of intravenous piperacillin in patients undergoing chronic hemodialysis. Antimicrob Agents Chemother. 1979;16(6):788–91.
128. Debruyne D, Ryckelynck JP, Hurault De Ligny B, Moulin M. Pharmacokinetics of piperacillin in patients on peritoneal dialysis with and without peritonitis. J Pharm Sci. 1990;79(2):99–102.
129. Awissi DK, Beauchamp A, Hébert E, Lavigne V, Munoz DL, Lebrun G, et al. Pharmacokinetics of an extended 4-hour infusion of piperacillin-tazobactam in critically ill patients undergoing continuous renal replacement therapy. Pharmacotherapy. 2015;35(6):600–7.
130. Mueller SC, Majcher-Peszynska J, Hickstein H, Francke A, Pertschy A, Schulz M, et al. Pharmacokinetics of piperacillin-tazobactam in anuric intensive care patients during continuous venovenous hemodialysis. Antimicrob Agents Chemother. 2002;46(5):1557–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11959598
131. Tamme K, Oselin K, Kipper K, Tasa T, Metsvaht T, Karjagin J, et al. Pharmacokinetics and pharmacodynamics of piperacillin/tazobactam during high volume haemodiafiltration in patients with septic shock. Acta Anaesthesiol Scand. 2016;60(2):230–40. Available from: http://doi.wiley.com/10.1111/aas.12629
132. Parry MF, Neu HC. Pharmacokinetics of ticarcillin in patients with abnormal renal function. J Infect Dis. 1976;133(1):46–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1107435
133. Wise R, Reeves DS, Parker AS. Administration of ticarcillin, a new antipseudomonal antibiotic, in patients undergoing dialysis. Antimicrob Agents Chemother. 1974;5(2):119–20.
134. Lockwood WR, Bower JD. Tobramycin and gentamicin concentrations in the serum of normal and anephric patients. Antimicrob Agents Chemother. 1973;3(1):125–9.
135. Zarowitz BJ, Anandan JV, Dumler F, Jayashankar J, Levin N. Continuous arteriovenous hemofiltration of aminoglycoside antibiotics in critically ill patients. J Clin Pharmacol. 1986;26(8):686–9.
136. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC. Tobramycin kinetics during continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther. 1983;34(1):110–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6861432
137. Smiley ML, Murray A, de Miranda P. Valacyclovir HCl (Valtrex): an acyclovir prodrug with improved pharmacokinetics and better efficacy for treatment of zoster. Adv Exp Med Biol. 1996;394:33–9.
138. Vaudry W, Ettenger R, Jara P, Varela-Fascinetto G, Bouw MR, Ives J, et al. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. Am J Transplant. 2009;9(3):636–43. Available from: http://doi.wiley.com/10.1111/j.1600-6143.2008.02528.x
139. Izzedine H, Mercadal L, Aymard G, Launay-Vacher V, Martinez V, Issad B, et al. Neurotoxicity of valacyclovir in peritoneal dialysis: a pharmacokinetic study. Am J Nephrol. 2001;21(2):162–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11359026
140. Blowey DL, Warady BA, Abdel-Rahman S, Frye RF, Manley HJ. Vancomycin disposition following intraperitoneal administration in children receiving peritoneal dialysis. Perit Dial Int. 2007;27(1):79–85.
141. Moffett BS, Morris J, Munoz F, Arikan AA. Population pharmacokinetic analysis of vancomycin in pediatric continuous renal replacement therapy. Eur J Clin Pharmacol. 2019;75(8):1089–97. Available from: http://link.springer.com/10.1007/s00228-019-02664-7
142. Kandrotas RJ, Oles KS, Gal P, Love JM. Carbamazepine clearance in hemodialysis and hemoperfusion. DICP. 1989;23(2):137–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2728503
143. Lee CS, Wang LH, Marbury TC, Bruni J, Perchalski RJ. Hemodialysis clearance and total body elimination of carbamazepine during chronic hemodialysis. Clin Toxicol. 1980;17(3):429–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7449356
144. Wong MO, Eldon MA, Keane WF, Türck D, Bockbrader HN, Underwood BA, et al. Disposition of gabapentin in anuric subjects on hemodialysis. J Clin Pharmacol. 1995;35(6):622–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7665723
145. Fillastre JP, Taburet AM, Fialaire A, Etienne I, Bidault R, Singlas E. Pharmacokinetics of lamotrigine in patients with renal impairment: influence of haemodialysis. Drugs Exp Clin Res. 1993;19(1):25–32.
146. Garnett WR. Lamotrigine: pharmacokinetics. J Child Neurol. 1997;12(Suppl 1):S10–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9429124
147. Asconapé JJ. Use of antiepileptic drugs in hepatic and renal disease. Handb Clin Neurol. 2014;119:417–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780702040863000278
148. Nei SD, Wittwer ED, Kashani KB, Frazee EN. Levetiracetam pharmacokinetics in a patient receiving continuous venovenous hemofiltration and venoarterial extracorporeal membrane oxygenation. Pharmacotherapy. 2015;35(8):e127–30. Available from: http://doi.wiley.com/10.1002/phar.1615
149. Wieruszewski PM, Kashani KB, Rabinstein AA, Frazee E. Levetiracetam pharmacokinetics in a critically ill anephric patient on intermittent hemodialysis. Neurocrit Care. 2018;28(2):243–6. Available from: http://link.springer.com/10.1007/s12028-017-0441-4
150. Bahte SK, Hiss M, Lichtinghagen R, Kielstein JT. A missed opportunity – consequences of unknown levetiracetam pharmacokinetics in a peritoneal

dialysis patient. BMC Nephrol. 2014;15(1):49. Available from: http://bmcnephrol.biomedcentral.com/articles/10.1186/1471-2369-15-49
151. New AM, Nei SD, Kashani KB, Rabinstein AA, Frazee EN. Levetiracetam pharmacokinetics during continuous venovenous hemofiltration and acute liver dysfunction. Neurocrit Care. 2016;25(1):141–4. Available from: http://link.springer.com/10.1007/s12028-016-0242-1
152. Company-Albir MJ, Ruíz-Ramos J, Solana Altabella A, Marqués-Miñana MR, Vicent C, Poveda JL. Haemodialysis significantly reduces serum levetiracetam levels inducing epileptic seizures: case report. J Clin Pharm Ther. 2017;42(6):774–5. Available from: http://doi.wiley.com/10.1111/jcpt.12568
153. Van Matre ET, Mueller SW, Fish DN, MacLaren R, Cava LF, Neumann RT, et al. Levetiracetam pharmacokinetics in a patient with intracranial hemorrhage undergoing continuous veno-venous hemofiltration. Am J Case Rep. 2017;18:458–62.
154. Porto I, John EG, Heilliczer J. Removal of phenobarbital during continuous cycling peritoneal dialysis in a child. Pharmacotherapy. 1997;17(4):832–5.
155. Czajka PA, Anderson WH, Christoph RA, Banner W. A pharmacokinetic evaluation of peritoneal dialysis for phenytoin intoxication. J Clin Pharmacol. 1980;20(10):565–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7440764
156. Lapierre O, Dubreucq JL, Beauchemin MA, Vinet B. Valproic acid intoxication in a patient with bipolar disorder and chronic uremia. Can J Psychiatry. 1999;44(2):188. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10097841
157. Orr JM, Farrell K, Abbott FS, Ferguson S, Godolphin WJ. The effects of peritoneal dialysis on the single dose and steady state pharmacokinetics of valproic acid in a uremic epileptic child. Eur J Clin Pharmacol. 1983;24(3):387–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6407847
158. Ghannoum M, Laliberte M, Nolin TD, MacTier R, Lavergne V, Hoffman RS, et al. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015;53(5):454–65.
159. Thanacoody RH. Extracorporeal elimination in acute valproic acid poisoning. Clin Toxicol (Phila). 2009;47(7):609–16. Available from: http://www.tandfonline.com/doi/full/10.1080/15563650903167772
160. Khadzhynov D, Slowinski T, Lieker I, Neumayer H-H, Albrecht D, Streefkerk HJ, et al. Pharmacokinetics of aliskiren in patients with end-stage renal disease undergoing haemodialysis. Clin Pharmacokinet. 2012;51(10):661–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23018529
161. Laher MS, Kelly JG, Doyle GD, Carmody M, Donohoe JF, Greb H, et al. Pharmacokinetics of amlodipine in renal impairment. J Cardiovasc Pharmacol. 1988;12(Suppl 7):S60–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2467131
162. Doyle GD, Donohue J, Carmody M, Laher M, Greb H, Volz M. Pharmacokinetics of amlodipine in renal impairment. Eur J Clin Pharmacol. 1989;36(2):205–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2524389
163. Kungys G, Naujoks H, Wanner C. Pharmacokinetics of amlodipine in hypertensive patients undergoing haemodialysis. Eur J Clin Pharmacol. 2003;59(4):291–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12845505
164. Wan SH, Koda RT, Maronde RF. Pharmacokinetics, pharmacology of atenolol and effect of renal disease. Br J Clin Pharmacol. 1979;7(6):569–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/465278
165. Salahudeen AK, Wilkinson R, McAinsh J, Bateman DN. Atenolol pharmacokinetics in patients on continuous ambulatory peritoneal dialysis. Br J Clin Pharmacol. 1984;18(3):457–60.
166. Flouvat B, Decourt S, Aubert P, Potaux L, Domart M, Goupil A, et al. Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. Br J Clin Pharmacol. 1980;9(4):379–85.
167. Tieu A, Velenosi TJ, Kucey AS, Weir MA, Urquhart BL. β-Blocker dialyzability in maintenance hemodialysis patients: a randomized clinical trial. Clin J Am Soc Nephrol. 2018;13(4):604–11. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.07470717
168. Ferguson RK, Rotmensch HH, Vlasses PH. Clinical use of captopril. Illustrative cases. JAMA. 1982;247(15):2117–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7038176
169. Sica DA, Gehr TW, Fernandez A. Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease. Drug Saf. 2000;22(5):350–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10830252
170. Fujimura A, Kajiyama H, Ebihara A, Iwashita K, Nomura Y, Kawahara Y. Pharmacokinetics and pharmacodynamics of captopril in patients undergoing continuous ambulatory peritoneal dialysis. Nephron. 1986;44(4):324–8.
171. Duchin KL, Pierides AM, Heald A, Singhvi SM, Rommel AJ. Elimination kinetics of captopril in patients with renal failure. Kidney Int. 1984;25(6):942–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6381858
172. Hoyer J, Schulte KL, Lenz T. Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. Clin Pharmacokinet. 1993;24(3):230–54.
173. Lowenthal DT, Saris SD, Paran E, Cristal N. The use of transdermal clonidine in the hypertensive patient with chronic renal failure. Clin Nephrol. 1993;39(1):37–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8428406

174. Rosansky SJ, Johnson KL, McConnell J. Use of transdermal clonidine in chronic hemodialysis patients. Clin Nephrol. 1993;39(1):32–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8428405
175. Doherty JE, Flanigan WJ, Perkins WH, Ackerman GL. Studies with tritiated digoxin in anephric human subjects. Circulation. 1967;35(2):298–303. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6022799
176. Iisalo E, Forsström J. Elimination of digoxin during maintenance haemodialysis. Ann Clin Res. 1974;6(4):203–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4429332
177. Pancorbo S, Comty C. Digoxin pharmacokinetics in continuous peritoneal dialysis. Ann Intern Med. 1980;93(4):639. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7436202
178. Benken ST, Lizza BD, Yamout H, Ghossein C. Management of digoxin therapy using pharmacokinetics in a patient undergoing continuous venovenous hemofiltration. Am J Heal Pharm. 2013;70(23):2105–9.
179. Sica DA, Cutler RE, Parmer RJ, Ford NF. Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. Clin Pharmacokinet. 1991;20(5):420–7. Available from: http://link.springer.com/10.2165/00003088-199120050-00006
180. Mason NA. Angiotensin-converting enzyme inhibitors and renal function. DICP. 1990;24(5):496–505. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2188438
181. Lowenthal DT, Porter RS, Saris SD, Bies CM, Slegowski MB, Staudacher A. Clinical pharmacology, pharmacodynamics and interactions with esmolol. Am J Cardiol. 1985;56(11):14F–8F. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2864843
182. Flaherty JF, Wong B, La Follette G, Warnock DG, Hulse JD, Gambertoglio JG. Pharmacokinetics of esmolol and ASL-8123 in renal failure. Clin Pharmacol Ther. 1989;45(3):321–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2563962
183. Gehr TW, Sica DA, Grasela DM, Duchin KL. The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. Eur J Clin Pharmacol. 1993;45(5):431–6.
184. Gehr TW, Sica DA, Grasela DM, Fakhry I, Davis J, Duchin KL. Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. Eur J Clin Pharmacol. 1991;41(2):165–9.
185. Wood AJ, Ferry DG, Bailey RR. Elimination kinetics of labetalol in severe renal failure. Br J Clin Pharmacol. 1982;13(1 Suppl):81S–6S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7093103
186. Halstenson CE, Opsahl JA, Pence TV, Luke DR, Sirgo MA, Plachetka JR, et al. The disposition and dynamics of labetalol in patients on dialysis. Clin Pharmacol Ther. 1986;40(4):462–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3757409
187. Halstenson CE, Opsahl JA, Wright CE, Fleishaker JC, Andreadis NA, Sobieraj J, et al. Disposition of minoxidil in patients with various degrees of renal function. J Clin Pharmacol. 1989;29(9):798–802. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2808745
188. Spital A, Scandling JD. Nifedipine in continuous ambulatory peritoneal dialysis. Arch Intern Med. 1983;143:2025.
189. Kleinbloesem CH, van Brummelen P, Woittiez AJ, Faber H, Breimer DD. Influence of haemodialysis on the pharmacokinetics and haemodynamic effects of nifedipine during continuous intravenous infusion. Clin Pharmacokinet. 1986;11(4):316–22.
190. Martre H, Sari R, Taburet AM, Jacobs C, Singlas E. Haemodialysis does not affect the pharmacokinetics of nifedipine. Br J Clin Pharmacol. 1985;20(2):155–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4041333
191. Herrera J, Vukovich RA, Griffith DL. Elimination of nadolol by patients with renal impairment. Br J Clin Pharmacol. 1979;7(Suppl 2):227S–31S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/37878
192. Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. West J Med. 1992;156(6):633–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1615656
193. Wood AJ, Vestal RE, Spannuth CL, Stone WJ, Wilkinson GR, Shand DG. Propranolol disposition in renal failure. Br J Clin Pharmacol. 1980;10:561–6.
194. Lowenthal DT, Briggs WA, Gibson TP, Nelson H, Cirksena WJ. Pharmacokinetics of oral propranolol in chronic renal disease. Clin Pharmacol Ther. 1974;16(5 Part 1):761–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4426144
195. Bianchetti G, Graziani G, Brancaccio D, Morganti A, Leonetti G, Manfrin M, et al. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin Pharmacokinet. 1976;1(5):373–84.
196. Schusziarra V, Ziekursch V, Schlamp R, Siemensen HC. Pharmacokinetics of azathioprine under haemodialysis. Int J Clin Pharmacol Biopharm. 1976;14(4):298–302. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1002367
197. Follath F, Wenk M, Vozeh S, Thiel G, Brunner F, Loertscher R, et al. Intravenous cyclosporine kinetics in renal failure. Clin Pharmacol Ther. 1983;34(5):638–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6627824
198. Venkataramanan R, Ptachcinski RJ, Burckart GJ, Yang SL, Starzl TE, Van Theil DH. The clearance of cyclosporine by hemodialysis. J Clin Pharmacol. 2019;24(11–12):528–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6392355
199. Munar MY, Doyle IC, Meyer MM. Cyclosporine and vancomycin disposition during continuous venovenous hemodiafiltration. Ann Pharmacother.

1995;29(4):374–7. Available from: http://journals.sagepub.com/doi/10.1177/106002809502900406
200. MacPhee IA, Spreafico S, Bewick M, Davis C, Eastwood JB, Johnston A, et al. Pharmacokinetics of mycophenolate mofetil in patients with end-stage renal failure. Kidney Int. 2000;57(3):1164–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10720968
201. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet. 1998;34(6):429–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9646007
202. Cussonneau X, Bolon-Larger M, Prunet-Spano C, Bastien O, Boulieu R. Evaluation of MPA and MPAG removal by continuous venovenous hemodiafiltration and continuous venovenous hemofiltration. Ther Drug Monit. 2008;30(1):100–2.
203. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet. 1990;19(2):126–46. Available from: http://link.springer.com/10.2165/00003088-199019020-00003
204. Venkataramanan R, Jain A, Warty VS, Abu-Elmagd K, Alessiani M, Lever J, et al. Pharmacokinetics of FK 506 in transplant patients. Transplant Proc. 1991;23(6):2736–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1721261
205. Filler G, Grygas R, Mai I, Stolpe HJ, Greiner C, Bauer S, et al. Pharmacokinetics of tacrolimus (FK 506) in children and adolescents with renal transplants. Nephrol Dial Transplant. 1997;12(8):1668–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9269646
206. Caccia S, Vigano GL, Mingardi G, Garattini S, Gammans RE, Placchi M, et al. Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. Clin Pharmacokinet. 1988;14(3):171–7.
207. Gammans RE, Mayol RF, LaBudde JA. Metabolism and disposition of buspirone. Am J Med. 1986;80(3B):41–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3515929
208. Awni WM, Yeh J, Halstenson CE, Opsahl JA, Chung M, Matzke GR. Effect of haemodialysis on the pharmacokinetics of cetirizine. Eur J Clin Pharmacol. 1990;38(1):67–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1970299
209. Noiri E, Ozawa H, Fujita T, Nakao A. Pharmacokinetics of cetirizine in chronic hemodialysis patients: multiple-dose study. Nephron. 2001;89(1):101–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11528239
210. Buckley MM, Sorkin EM. Enoxaparin. A review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. Drugs. 1992;44(3):465–97.
211. Isla A, Gascon AR, Maynar J, Arzuaga A, Corral E, Martin A, et al. In vitro and in vivo evaluation of enoxaparin removal by continuous renal replacement therapies with acrylonitrile and polysulfone membranes. Clin Ther. 2005;27(9):1444–51.
212. Brophy DF, Carr MEJ, Martin EJ, Venitz J, Gehr TWB. The pharmacokinetics of enoxaparin do not correlate with its pharmacodynamic effect in patients receiving dialysis therapies. J Clin Pharmacol. 2006;46(8):887–94.
213. Lin JH, Chremos AN, Yeh KC, Antonello J, Hessey GA 2nd. Effects of age and chronic renal failure on the urinary excretion kinetics of famotidine in man. Eur J Clin Pharmacol. 1988;34(1):41–6.
214. Saima S, Echizen H, Yoshimoto K, Ishizaki T. Hemofiltrability of H2-receptor antagonist, famotidine, in renal failure patients. J Clin Pharmacol. 1990;30(2):159–62.
215. Gladziwa U, Klotz U, Krishna DR, Schmitt H, Glöckner WM, Mann H. Pharmacokinetics and dynamics of famotidine in patients with renal failure. Br J Clin Pharmacol. 1988;26(3):315–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2902874
216. Aronoff GR, Bergstrom RF, Pottratz ST, Sloan RS, Wolen RL, Lemberger L. Fluoxetine kinetics and protein binding in normal and impaired renal function. Clin Pharmacol Ther. 1984;36(1):138–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6610522
217. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nephrol Dial Transplant. 2012;27(10):3736–45.
218. Blumenfield M, Levy NB, Spinowitz B, Charytan C, Beasley CM, Dubey AK, et al. Fluoxetine in depressed patients on dialysis. Int J Psychiatry Med. 1997;27(1):71–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9565715
219. Perlman R, Giladi H, Brecht K, Ware MA, Hebert TE, Joseph L, et al. Intradialytic clearance of opioids: methadone versus hydromorphone. Pain. 2013;154(12):2794–800. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006396-201312000-00031
220. Davison SN, Mayo PR. Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. J Opioid Manag. 2008;4(6):335–6, 339–344.
221. Bailey RR, Sharman JR, O'Rourke J, Buttimore AL. Haemodialysis and forced diuresis for tricyclic antidepressant poisoning. Br Med J. 1974;4(5938):230–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4422728
222. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet. 1996;31(1):9–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8827397
223. Barradell LB, Faulds D, McTavish D. Lansoprazole. A review of its pharmacodynamic and pharmacoki-

netic properties and its therapeutic efficacy in acid-related disorders. Drugs. 1992;44(2):225–50.
224. Karol MD, Machinist JM, Cavanaugh JM. Pharmacokinetics of lansoprazole in hemodialysis patients. J Clin Pharmacol. 1995;35(8):815–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8522639
225. Clericetti N, Beretta-Piccoli C. Lithium clearance in patients with chronic renal diseases. Clin Nephrol. 1991;36(6):281–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1769139
226. Bjarnason NH, Munkner R, Kampmann JP, Tornoe CW, Ladefoged S, Dalhoff K. Optimizing lithium dosing in hemodialysis. Ther Drug Monit. 2006;28(2):262–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16628141
227. Walcher J, Schoecklmann H, Renders L. Lithium acetate therapy in a maintenance hemodialysis patient. Kidney Blood Press Res. 2004;27(3):200–2. Available from: https://www.karger.com/Article/FullText/79812
228. Matzke GR, Halstenson CE, Opsahl JA, Hilbert J, Perentesis G, Radwanski E, et al. Pharmacokinetics of loratadine in patients with renal insufficiency. J Clin Pharmacol. 1990;30(4):364–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2140371
229. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004;28(5):497–504. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0885392404003355
230. Opdal MS, Arnesen M, Müller LD, Hullstein I, Sayed K, Brørs O, et al. Effects of Hemodialysis on Methadone Pharmacokinetics and QTc. Clin Ther. 2015;37(7):1594–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0149291815002428
231. Kirwan CJ, MacPhee IAM, Lee T, Holt DW, Philips BJ. Acute kidney injury reduces the hepatic metabolism of midazolam in critically ill patients. Intensive Care Med. 2012;38(1):76–84. Available from: http://link.springer.com/10.1007/s00134-011-2360-8
232. Swart EL, De Jongh J, Zuideveld KP, Danhof M, Thijs LG. Population pharmacokinetics of lorazepam and midazolam and their metabolites in intensive care patients on continuous venovenous hemofiltration. Am J Kidney Dis. 2005;45(2):360–71.
233. Portenoy RK, Foley KM, Stulman J, Khan E, Adelhardt J, Layman M, et al. Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: plasma profiles, steady-state concentrations and the consequences of renal failure. Pain. 1991;47(1):13–9.
234. Jamal JA, Joh J, Bastani B. Removal of morphine with the new high-efficiency and high-flux membranes during haemofiltration and haemodialfiltration. Nephrol Dial Transplant. 1998;13(6):1535–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9641188
235. Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, Skånberg I, et al. Pharmacokinetics of [14C]omeprazole in patients with impaired renal function. Clin Pharmacol Ther. 1986;40(3):344–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3742939
236. Howden CW, Payton CD, Meredith PA, Hughes DM, Macdougall AI, Reid JL, et al. Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. Eur J Clin Pharmacol. 1985;28(6):637–40.
237. Doyle GD, Laher M, Kelly JG, Byrne MM, Clarkson A, Zussman BD. The pharmacokinetics of paroxetine in renal impairment. Acta Psychiatr Scand Suppl. 1989;350:89–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2530798
238. McFadyen ML, Folb PI, Miller R, Keeton GR, Marks IN. Pharmacokinetics of ranitidine in patients with chronic renal failure. Eur J Clin Pharmacol. 1983;25(3):347–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6313378
239. Zech PY, Chau NP, Pozet N, Labeeuw M, Hadj-Aissa A. Ranitidine kinetics in chronic renal impairment. Clin Pharmacol Ther. 1983;34(5):667–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6313275
240. Gladziwa U, Krishna DR, Klotz U, Ittel TH, Schunkert H, Glöckner WM, et al. Pharmacokinetics of ranitidine in patients undergoing haemofiltration. Eur J Clin Pharmacol. 1988;35(4):427–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3197752
241. Gladziwa U, Klotz U. Pharmacokinetics and pharmacodynamics of H2-receptor antagonists in patients with renal insufficiency. Clin Pharmacokinet. 1993;24(4):319–32. Available from: http://link.springer.com/10.2165/00003088-199324040-00005

37

Role of Radiological Assessment and Intervention in Pediatric Dialysis

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Abbreviations

ACR	American College of Radiology
CAPD	Continuous ambulatory peritoneal dialysis
CIN	Contrast-induced nephropathy
CT	Computed tomography
ESRD	End-stage renal disease
GBCA	Gadolinium-based contrast agents
Gd	Gadolinium
GFR	Glomerular filtration rate
HD	Hemodialysis
HOCM	High-osmolar contrast media
IOCM	Iso-osmolar contrast media
LOCM	Low-osmolar contrast media
MRI	Magnetic resonance imaging
NSF	Nephrogenic systemic fibrosis
PD	Peritoneal dialysis

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Introduction

The development of acute and chronic dialysis modalities has led to an increasing use of radiological techniques to help initiate the dialysis and to assess the complications of dialysis access [1]. Besides initial assessment of hemodialysis or peritoneal dialysis catheter placement at the correct location, various radiological procedures are used for determining the etiology and location of complications such as catheter malposition, obstruction, or stenosis. More recently, interventional radiology techniques have developed to address issues such as stenosis or obstruction.

In these procedures, contrast media have been widely used [2]. Contrast media facilitate the interpretation of medical imaging by increasing the differences seen between body tissues displayed on the images. Through various mechanisms, contrast media influence a tissue or organ's ability to absorb or reflect energy from electromagnetic radiation or ultrasound. These agents are commonly used with many imaging techniques including conventional radiography/angiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.

There are many types of contrast media with different properties available for use which will be discussed later in this chapter. In order to achieve a high concentration of contrast in the desired tissue, these agents can be administered intra-arterial, intravenous, intrathecal, or directly into a body cavity such as the gastrointestinal or urinary tract.

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However, like any other pharmaceutical agent, adverse events may occur: with iodinated contrast, 0.6% aggregate [3], 0.04% severe adverse events have been reported [4], and with gadolinium-based, 0.01–0.22% aggregate, 0.008% severe [5].

Each year, millions of radiological examinations are performed in patients with the assistance of contrast media. In many cases, these studies are conducted in patients with advanced renal insufficiency or renal failure undergoing dialysis therapy. In patients with renal failure, there are several concerns and issues to consider with regard to the administration of contrast: (1) direct nephrotoxicity to the remaining functional nephrons, (2) extra-renal toxicity due to delayed contrast excretion, (3) the role of dialysis after the administration of contrast media, and (4) the relationship to nephrogenic systemic fibrosis (NSF).

The purpose of this chapter is to give an overview of the radiological assessment and interventions in pediatric dialysis. We also review the classification and renal handling of contrast agents, review their mechanisms for toxicity, and examine the role of dialysis as a means to remove contrast in patients with advanced renal failure or end-stage renal disease (ESRD). We will also review recent data on the use of gadolinium (Gd) in patients with renal failure, especially in the context of NSF. Since studies on these issues in children are lacking, most inferences are extrapolated from adult data. Pharmacological prophylaxis for contrast-induced nephropathy is beyond the scope of this chapter and will not be discussed. Interested readers are referred to a recently published in-depth review and meta-analysis of the available adult data on this controversial topic [6].

Classification of Contrast Media

Contrast agents used in conventional radiology and CT are categorized as positive or negative media depending on their capacity to attenuate the passage of radiation [7]. Positive contrast media are used more commonly and are radiopaque. Barium and iodine can attenuate X-rays 50–1000 times more than soft tissues and are the main components in positive contrast media. Gadolinium-based contrast agents (GBCA) are also considered positive contrast agents. On the other hand, the introduction of air or carbon dioxide (CO_2) will attenuate radiation less than the body soft tissues, due to the lower number of radiation attenuating atoms, and are considered negative contrast agents.

Iodinated Contrast Media

Non-water-soluble contrast agents are used for complex interventional oncology treatments and lymphatic imaging and will not be discussed in this chapter. The most commonly used iodinated contrast agents are water soluble. They are utilized for angiography, CT, and conventional radiography since they can also be administered into the urinary or alimentary tract.

The initial water-soluble contrast agents were mono-iodinated- or di-iodinated-pyridine-based compounds with a high toxicity. Since the 1950s, contrast media are based from a tri-iodinated benzene ring which has lower toxicity. The derivatives are either monomeric or dimeric depending on whether they contain one or two benzene rings [8–10]. Furthermore, their water solubility is achieved in different ways. Ionic contrast media dissociate in water into electrically charged positive and negative ions which are attracted to the negative poles and positive poles of water molecules. Nonionic contrast media are electrically neutral but are water soluble due to their polar hydrophilic hydroxyl groups which are attracted to the electrical poles in the water molecules [10, 11].

The osmolality of contrast media depends upon the number of molecules per volume unit solution and varies significantly depending on the class of the agent. The ratio of a contrast agent is indicative of its osmolality. Hence, the ionic agents which dissociate into two water-soluble particles have a ratio of 1.5 (monomeric; 3 iodine atoms per 2 water-soluble particles) or 3 (dimeric; 6 iodine atoms per 2 water-soluble particles). The nonionic contrast media that do not dissociate in water have a ratio of 3 (monomeric; 3 iodine atoms per 1 water-soluble particle) and 6 (dimeric; 6 iodine atoms per 1 water-soluble particle). Contrast agents with a ratio of 1.5 are

termed high-osmolar contrast media (HOCM), those with a ratio of 3 are low-osmolar contrast media (LOCM), and those with a ratio of 6 are iso-osmolar contrast media (IOCM) [8, 11]. These different characteristics are responsible for the diverse levels of toxicity between the agents. A detailed listing of commercially available iodinated contrast agents and their respective chemical properties can be found in other publications, including the contrast manual from the American College of Radiology (ACR), the definitive document that lists all the latest agents and their osmolarity [12].

Renal Handling of Contrast Media

Overall, iodinated contrast media have a relatively small molecular weight, high water solubility, and minimal protein binding [8, 9, 13, 14]. After intravascular injection they are distributed primarily into the extracellular space, and they rapidly reach equilibrium across the capillary membrane. These molecules do not cross the blood-brain barrier or cellular membranes, so there is virtually no intracellular penetration [15, 16].

Contrast media are not metabolized and are freely filtered through the glomeruli, so the concentration of the agent in the initial filtrate is equal to the plasma concentration [17–19]. There is minimal tubular reabsorption and secretion, so under normal conditions, nearly the totality of the contrast media is eliminated through the kidneys with less than 1% being eliminated through the biliary system [9]. In the tubules, contrast media exert an osmotic force reducing the reabsorption of water and sodium [20, 21]. The result is an increase in the tubular hydrostatic pressure followed by a decrease in the glomerular filtration rate (GFR). These changes are primarily seen with the use of HOCM and are minimized when LOCM and IOCM are employed [22]. However, nonionic dimeric contrast media can cause a prolonged increase in tubular hydrostatic pressure and a more extended decrease in GFR as a result of their increased viscosity [23].

The half-life of these agents is dependent on the GFR and in patients with normal renal function is approximately 1–2 h for each of the four groups of contrast media [24]. In patients with renal insufficiency and renal failure, contrast elimination is significantly delayed with approximately 50% of the injected dose recovered in the urine between 16 and 84 h after administration [24]. In individuals with end-stage renal failure, the plasma concentration of the agent remains elevated for a longer period of time.

Mechanisms for Toxicity of Iodinated Contrast Media

There are two main concerns with the administration of iodinated contrast media in patients with renal failure: (1) the effects of the contrast on the remaining functional nephrons in pre-dialysis and dialysis patients with residual renal function and (2) the extra-renal effects due to prolonged contrast elimination.

The exact mechanisms leading to renal injury after iodinated contrast administration are still incompletely understood. Three proposed and distinct pathways that have gathered the most clinical attention are (1) reduction in renal perfusion leading to ischemia, (2) direct tubular cell toxicity, and (3) increase in oxygen-free radicals or decrease in antioxidant enzyme activity [25, 26].

It is now recognized that the reduction in renal blood flow after contrast media administration is transient and unlikely to result in ischemia. However, a decrease in renal vascular resistance in the cortex without a similar change in the medulla may lead to hypoxic damage in this region. The increased viscosity of IOCM which decreases renal medullary blood flow and partial oxygen pressure is also an important factor. The higher tubular fluid viscosity increases the renal interstitial pressure causing a decrease in medullary blood flow and GFR [27, 28].

Contrast media also have a direct cytotoxic effect on renal tubular cells. Early investigations revealed a marked impairment in cell transport. More recent studies have shown that contrast media alters mitochondrial function and mitochondrial membrane potential and may play a role in DNA fragmentation and apoptosis in tubular cells [29, 30]. In vitro, dimeric contrast media have a greater potential for cytotoxic effects on proximal renal tubular cells than monomeric contrast media [31].

Reactive oxygen species (ROS) also may play an important role in contrast-induced nephropathy (CIN). ROS are known to scavenge nitric oxide and cause cellular damage, but they may also mediate the actions of vasoconstrictors thought to be of importance in the development of CIN [26].

All of the abovementioned pathways may contribute to renal injury. Patients with chronic kidney disease have a higher filtered load of the contrast media per nephron in addition to prolonged tubular exposure of the agent, placing them at increased risk for toxicity. Overall, preexisting renal disease with decreased renal function is one of the most important risk factors for the development of CIN.

The extra-renal side effects of contrast media can be minor (flushing, nausea, vomiting, pruritus, headache, urticaria), intermediate (hypotension, bronchospasm), or severe (seizure, pulmonary edema, cardiac arrest, cardiac arrhythmias). The incidence of adverse reactions is very low, especially with the use of contemporary LOCM agents. Minor adverse reaction rates with LOCM occur at a frequency of 0.2–0.7% of all patients [12]. Serious adverse reactions with LOCM injection are extremely rare, occurring at a frequency of 0.04%.There are several case reports and case series of contrast-related side effects in patients with renal failure which include skin disorders (iododerma), vasculitis, and sialadenitis (also known as iodide mumps) [32–35]. Younathan et al. studied 10 patients with ESRD on chronic hemodialysis (HD) who underwent 11 procedures requiring intravascular administration of LOCM [36]. The investigators did not find significant changes in blood pressure, electrocardiogram, serum osmolality, extracellular fluid volume, or body weight in these patients. None of the patients required emergent dialysis after the administration of contrast. A similar observation was reported by Hamani et al. in eight chronic HD patients after the administration of LOCM [37]. The largest group of 22 dialysis patients who received LOCM was reported by Harasawa et al. The patients were followed for 5 days, and only one developed a localized urticarial reaction [38]. These reports suggest that the risk for extra-renal toxicity in ESRD patients after the administration of contrast is low and that immediate post-procedural dialysis is not necessary.

Dialysis in the Removal of Iodinated Contrast Media

Contrast media have a molecular weight ranging from 700 to 1550 Da and their water solubility, low protein binding, and minimal intracellular penetration allow for efficient removal from blood by HD. Treatment variables such as blood flow rate, membrane surface area, membrane material, additional ultrafiltration, and dialysis time will influence contrast media clearance. Currently, there are multiple published studies evaluating the removal of all classes of iodinated contrast media by HD (Table 37.1) [39–50]. Comparison between these studies is difficult due to variations in contrast media molecules, time period between contrast administration and initiation of dialysis, blood flow rates, membrane type/size, time on dialysis, ultrafiltration rate, and presence of residual renal function. Nevertheless, several important observations can be made from these investigations.

The mean reduction rate of iodine by HD increases with longer dialysis time reaching over 70% at 3 h in most studies [39, 47, 48, 50]. The relationship between contrast media clearance and blood flow rate was addressed by Teraoka et al. These investigators observed that when blood flow rates were set at 100, 150, and 200 mL/min, the clearance of iopromide increased to 45.35 ± 2.54, 53.88 ± 6.46, and 57.61 ± 4.72 mL/min, respectively [46].

A study by Matzkies et al. evaluated the clearance of iopromide using dialyzers with two different membrane materials and sizes [41]. A significant increase in the plasma clearance of iodine was observed when larger dialyzers were used. The clearance was also higher for the polysulfone as compared to the cuprophan dialyzers.

Table 37.1 Hemodialysis removal of contrast media

Study	Contrast agent	Molecular weight (D)	Dialyzer	Contrast clearance (mL/min)	Contrast removal
Kierdorf et al. [40]	Iopromide	791		80	41% in 3 h
Waaler et al. [49]	Iohexol	821	Polycarbonate Cellulose Cuprophan	81 ± 15	72 ± 11% in 4 h
Moon et al. [43]	Iohexol	821	Cuprophan Polysulfone	70.4 ± 24.6	60–90% in 6 h
Ueda et al. [48]	Ioversol	807	Cellulose	114–129	82.5 ± 5.1% at 4 h
Ueda et al. [47]	Iomeprol	777	Cellulose	131.4–133.3	81.4 ± 4.6% at 4 h
Johnsson et al. [50]	Iohexol	821	Cellulose		71% at 3 h 79% at 6 h
Matzkies et al. [42]	Iopromide	791	Haemophan Polyamide	108 ± 1.9 110 ± 1.4	62% at 3 h 58% at 3 h
Horiuchi et al. [39]	Iohexol	821	Cellulose		72.9% at 3 h
Matzkies et al. [41]	Iopromide	791	Cuprophan Polysulfone	87–121 147–162	57–63% at 2 h 60–68% at 2 h
Sterner et al. [45]	Iodixanol Iohexol	1550 821	Low flux	58 ± 11 69 ± 16	
Schindler et al. [44]	Iopromide	791	Hemophan	82 ± 2.3	64% at 4 h
Teraoka et al. [46]	Iopromide	791	Cuprammonium	57.6	

Overall, most studies have reported that high-flux membranes were more efficient than low-flux membranes in the elimination of contrast media [42, 44]. In contrast, one report by Matzkies et al. studied the elimination of iopromide in chronic HD patients using low-flux (haemophan) and high-flux (polyamide) dialyzers and found a comparable difference in the clearance rates for both membranes [42].

The post-dialysis rebound or redistribution of contrast media has been reported in only three studies [42, 45, 50]. One study found no significant rebound when measuring the iodine concentration 1 hour after treatment [41]. However, a study by Johnsson et al. reported an increase in the blood concentration of iohexol at 1 and 24 h as compared to the immediate post-dialysis level [50]. Sterner et al. found similar results [24, 45]. These investigators measured iodine concentrations 2 and 45 min after the conclusion of HD. When using the 45 min post-dialysis plasma level, they reported an 8–10% decrease in clearance, representing what they termed "hemodialysis clearance of extracellular space." The clinical significance of the rebound effect is not known.

Peritoneal dialysis (PD) is relatively ineffective in removing contrast media. A total of ten patients on continuous ambulatory peritoneal dialysis (CAPD) were studied after the administration of iopamidol [51]. CAPD removed an average of 53.6% of the administered dose during the study period using 8 L of dialysate per day. An average of 93% of the total dose was cleared when dialysis and renal clearances were combined. A study by Moon et al. reported three patients who received iohexol [43]. Using 36–60 L of dialysate, 43–72% of the administered dose was removed over 16–18 h. In another group of 14 patients with and without residual renal function, CAPD removed 75% of the administered iomeprol after a period of 4 days [52]. When compared to HD, the clearance of contrast media with PD is slower. However, no adverse events as a result of contrast exposure were reported in any of these studies.

Dialysis as a Strategy to Minimize Contrast-Induced Nephropathy

Post-procedural dialysis to prevent extra-renal complications in patients with ESRD does not seem to be warranted and was addressed in an above section.

Immediate dialysis after the administration of iodinated contrast media has been advocated for patients considered at very high risk for toxicity: ESRD patients on chronic dialysis and those with advanced chronic renal failure as a way to protect residual renal function and avoid further decreases in GFR. Several studies have shown that the administration of HD does not reduce the risk of CIN.

In a prospective, randomized study, Lenhnert et al. evaluated the influence of HD on CIN in 30 patients with chronic renal failure [53]. Both groups received pre-hydration with intravenous 0.9% saline. In addition, the patients randomized to Group 1 received HD for 3 h with a high-flux polysulfone membrane after the administration of iopentol. The rate of CIN was similar for both groups (53% for Group 1 and 40% for Group 2) despite data indicating that HD removed the iopentol effectively.

In a similar study, Sterner et al. reported 32 patients who were randomized to receive either HD plus pre- and post-procedural hydration or hydration alone after an angiographic examination [45]. HD was started within 2 h after the end of contrast administration. The treatment was prescribed for 4 h using low-flux cellulose acetate or cellulose diacetate hemodialyzers. The GFR was determined by iohexol clearance 1 day prior to and 1 week after the procedure. There was no significant difference in the renal iohexol clearance between the groups. The investigators concluded that HD was not effective in preventing CIN in patients with chronic renal failure.

The largest prospective, randomized study of 113 patients addressing this issue reported that the rate of CIN did not differ between the HD and standard hydration alone treatment groups [54]. The same conclusion held true even for the subgroup of patients receiving a larger volume of contrast media. In this study, HD was started at a median of 120 min after the administration of contrast and was prescribed for a mean of 3 h using a high-flux polysulfone dialyzer.

The lack of protection against CIN could be the result of starting HD "late" after contrast administration given the fact that renal injury may occur rapidly. A study by Frank et al. evaluated the influence of simultaneous HD at the time of contrast media administration on renal function [55]. Creatinine clearance was measured prior to 1 and 8 weeks after the procedure. In each of the study groups, the creatinine clearance was not different. Two patients from each study arm developed ESRD requiring subsequent dialysis treatments. With a small sample size of 17 patients, the study failed to demonstrate a protective effect of "early" HD on development of CIN.

More recently, hemofiltration has been reported by Marenzi et al. as a successful strategy for the prevention of CIN [56]. A total of 114 patients were randomized to receive pre-contrast hydration or hemofiltration 4–6 h prior to and 18–24 h after the angiography. CIN occurred in 5% of patients in the hemofiltration group and in 50% of patients in the control group. A follow-up study compared patients receiving hemofiltration after contrast administration to those receiving hemofiltration 6 h prior to and after the procedure [57]. The rate of CIN was significantly less in the pre-/post-hemofiltration group as compared to the post-hemofiltration group (26% vs. 3%). The mechanisms involving the protective effects of hemofiltration remain unclear, and further studies with this form of therapy are needed.

Negative Contrast Media

The negative radiological contrast media are the gases: air, oxygen, nitric oxide (N_2O), or carbon dioxide (CO_2). CO_2 has been used as an intravascular imaging agent for over 30 years and as an alternative to iodinated contrast agents or gadolinium in patients with advanced renal failure. CO_2 has certain unique properties: it is not nephrotoxic, lacks allergic potential, and is eliminated by one pass through the lungs.

Several animal studies have reported the lack of renal toxicity of CO_2. Hawkins et al. evaluated the effects of selective CO_2 injection in the renal arteries of dogs [58]. The investigators found no dose-dependent effect of CO_2 on renal function or renal histology. Palm et al. compared the effects of CO_2 with those of ioxaglate in the rat kidney [59]. The pronounced decrease in medullary blood flow and PO_2 observed after injection of ioxaglate was not present in the animals injected with CO_2. Furthermore, a review of the published literature did not reveal any cases of CIN secondary to CO_2 administration.

CO_2 is indicated for angiography in patients with renal failure. However, it is not recommended to evaluate the cerebral or coronary circulations. Animal studies have suggested but failed to confirm its neurotoxicity [60, 61]. However, widespread ST segment elevation, decrease in coronary flow velocity, and profound global left ventricular dysfunction were documented after administration of small doses of intracoronary carbon dioxide in swines [61].

Overall, CO_2 angiography is well tolerated and can be successfully used in patients with renal failure in order to avoid CIN (for a review, see Ref. [62]).

Ferumoxytol

Ferumoxytol is a superparamagnetic iron oxide particle that is currently Food and Drug Administration (FDA) approved for intravenous iron replacement for treatment of iron deficiency anemia in patients with chronic kidney disease. The FDA label additionally states that ferumoxytol alters MRI studies, and more recently, its use as a contrast agent for MRI has been studied and explored. Ferumoxytol acts as a blood pool agent, as it is a relatively large molecule with a long intravascular half-life of 14–15 hours [63], compared to about 90 seconds for traditional GBCA [64]. Eventually, phagocytic cells, especially macrophages of the reticuloendothelial system, eliminate ferumoxytol from circulation [65]. The ability of ferumoxytol to remain largely in the intravascular space for an extended period of time has important implications in its use as a contrast agent: longer imaging studies can be attained, covering larger anatomical areas. This is in contrast to GBCAs, which have a relatively short intravascular half-life and thus limited time for acquisition of imaging. Ferumoxytol causes strong enhancement on T1-weighted images [66], which allows depiction of vessels while ferumoxytol remains in the intravascular space. In contrast, ultrasound and MRI with GBCA can only cover limited vascular territories. Various studies have shown that ferumoxytol can be used effectively as a contrast agent for ceMRA with comparable quality to GBCA, good visibility of occlusions, and the ability to image large areas of the body. Figure 37.1 shows a coronal T1 image from a ferumoxytol enhanced MRI in a patient with renal failure, depicting fat saturated with ferumoxytol. Figure 37.2 is a 3D reconstructed image from ferumoxytol MRI, demonstrating stenosis and internal jugular veins with collateral venous structures.

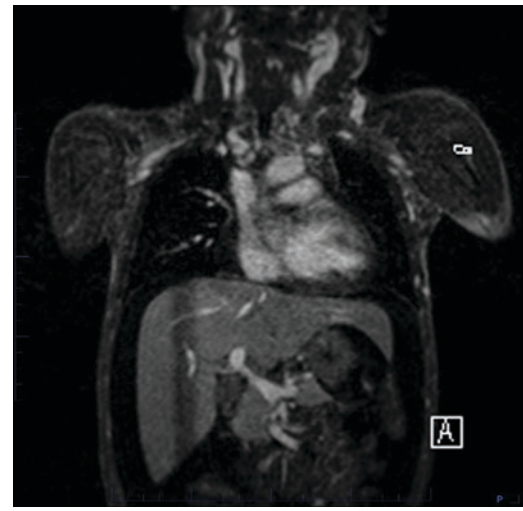

Fig. 37.1 Images from a ferumoxytol-enhanced MRI in a patient with renal failure. Coronal T1 shows fat saturated with ferumoxytol

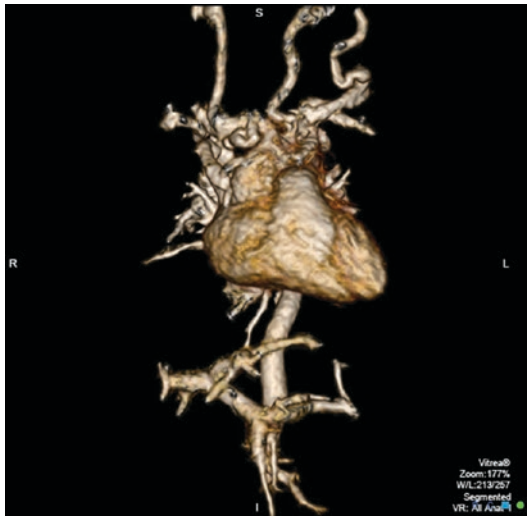

Fig. 37.2 Three-dimensional reconstructed image from ferumoxytol MRI demonstrating stenosis and internal jugular veins with collateral venous structures

Gadolinium

Gadolinium is a rare earth metallic element in the lanthanide series of the periodic table, with an atomic number of 64 and molecular weight of 157.25 Da. This element has the unusual property of possessing seven unpaired electrons in its outer shell, thereby making Gd an ideal "paramagnetic" substance to disturb the relaxation of surrounding water molecule protons and generate contrast in MRI [67]. The GBCA are classified into four main categories based on their biochemical structure (macro-cylic or linear) and their charge (ionic or nonionic). The different properties of each category are important in order to understand their potential for toxicity as a result of liberation of free Gd from its chelate. Overall, macro-cyclic chelates tend to be more stable and have lower dissociation rates.

Renal Handling of Gadolinium

The GBCA have a molecular weight ranging from 500 to 1000 Da, are highly soluble in water, and have low binding to plasma proteins. Hence, after intravenous administration, GBCA distribute into the extracellular space and rapidly equilibrate with the interstitial space. There is no intracellular penetration. These properties account for the small volume of distribution of GBCA (0.26–0.28 L/kg body weight) [68].

Chelated Gd is freely filtered by the glomeruli, is neither secreted nor reabsorbed by the renal tubules, and is eliminated unchanged in the urine. In the presence of normal renal function, GBCA clearance approximates GFR. Their mean half-life is typically under 2 h with 95% of the administered dose eliminated in the first 24 h. In renal failure, the half-life can be prolonged up to 30–120 h. Extra-renal elimination of GBCA is negligible with less than 3% being excreted in the stool [68, 69].

Mechanisms for Toxicity of Gadolinium

Though free Gd^{+} can be toxic, the chelated form of Gd was believed for many years to be nontoxic and generally safe. Only 64 adverse reactions, mostly mild, were reported after 158,439 doses in one study [70] and only 36 adverse reactions in 21,000 patients in another study [71]. Two case reports described a spurious hypocalcemia after Gd administration [72, 73].

When compared to iodinated contrast media, GBCA are considered to be less nephrotoxic. This is likely attributed to their lower viscosity and the need to administer significantly lower volumes. Several studies in healthy patients as well as individuals with mild and moderate renal failure suggested that overall nephrotoxicity is quite low ranging from 0% to 5% [74, 75]. The risk of nephrotoxicity has been reported to be much higher in patients with more advanced renal disease and after intra-arterial injection of GBCA [76–79]. The exact mechanism of nephrotoxicity of GBCA is not well known. However, GBCA and iodinated contrast media share the same pharmacodynamics, their nephrotoxic effects are often clinically similar, and they may cause renal damage through similar mechanisms.

More recently, Gd has been associated with a newly recognized condition called nephrogenic systemic fibrosis (NSF), which is discussed in a later section.

Dialysis in the Removal of Gadolinium

Though GBCA clearance is delayed in renal failure, these compounds are of low molecular weight, not protein bound, and have a small volume of distribution [80–82]. These properties allow for good clearance with HD. Okada et al. reported the removal rate of gadopentetate in 11 patients after a 4 h HD treatment [81]. The average Gd removal was 78.2% of the administered dose after the first, 95.6% after the second, 98.7% after the third, and 99.5% after the fourth treatment. A similar observation was reported after administering gadodiamide to 13 patients. An average of 98.9% of the administered dose was removed after three HD treatments.

Ueda et al. evaluated the clearances of three different GBCA in an in vitro system using low-flux cellulose diacetate and higher-flux cellulose triacetate hemodializers [83]. The clearance of all three GBCA was significantly higher when using the cellulose triacetate dialyzer with larger pore size.

The clearance of GBCA using PD is much slower. Joffee et al. evaluated the removal of gadodiamide in nine CAPD patients. After 22 days only 69% of the administered dose had been removed [84]. Hence, the clearance of GBCA by PD is inefficient and generally considered inadequate.

Nephrogenic Systemic Fibrosis

In 2000, Cowper et al. described a new condition characterized by unusual, debilitating, and frequently fatal skin induration in patients with acute or chronic renal failure [85]. The induration presented as tender plaques or nodules on the limbs and trunk, differentiable from scleromyxedema by absence of facial involvement and negative serological features. Histological characteristics included a markedly thickened dermis yet unremarkable epidermis, increased mucin deposition between widely separated collagen bundles, and absence of necrosis or ulceration. The disease was initially labeled as nephrogenic fibrosing dermopathy [86]. As more patients were recognized [87–93], other systemic manifestations of the disease became clear, leading to a change in the name to NSF. The exact cause of this disease was and still remains unknown. However, in 2005, multiple reports emerged of a strong association with prior Gd administration in patients who developed NSF disease 4–8 weeks later [94, 95]. Subsequently, Gd was detected in the skin lesions of some patients with NSF, increasing the likelihood that the association was causal [96, 97].

In renal failure, free Gd can potentially be liberated into tissue. Several GBCA are marketed (Table 37.2). The potential for free Gd dissociation depends on several factors, including presence or absence of ionic charge (more ionic = less likely to dissociate), chemical structure (linear more likely to dissociate than cyclic ring of chelate around Gd), and kinetic stability (half-life at pH 0.1; shorter stability more likely to dissociate). Consistent with this paradigm, the nonionic, linear chelate with a short half-life (gadodiamide) has been associated with the highest incidence of NSF. Macrocyclic GBCA result in the lowest possible gadolinium deposition in tissues. The dose of GBCA administered may also play a role. GBCA were approved for use in MRI at a dose of

Table 37.2 FDA-approved GBCAs

Commercial name	Generic name	Chemical structure
Dotarem	Gadoterate meglumine	Macrocyclic
Eovist	Gadoxetate disodium	Linear
Gadavist	Gadobutrol	Macrocyclic
Magnevist	Gadopentetate dimeglumine	Linear
MultiHance	Gadobenate dimeglumine	Linear
Omniscan	Gadodiamide	Linear
OptiMARK	Gadoversetamide	Linear
ProHance	Gadoteridol	Macrocyclic

0.1 mmol/kg. However, in order to avoid the nephrotoxicity of iodinated HOCM, many radiologists started using high-dose GBCAS (0.3–0.9 mmol/kg) for magnetic resonance angiography [98]. Doses above 0.3 mmol/kg were never formally tested or approved by any regulatory agency in the USA or Europe [99]. In the USA, the Food and Drug Administration (FDA) expanded the age range for use of gadopentate demegluine to patients less than 2 years of age to parallel current regulatory guidelines in Europe. The range of dosing for GBCAs has continued to decrease with dosing for several agents in pediatrics in the 0.05–0.1 mmol/kg range.

Of the several hundred NSF cases reported, only a few were seen in children [88, 89, 100–102]. So far, 23 children have been reported with NSF, across 3 major data sources [103]. Seventeen had documented exposure to GBCA. No characteristics that were specific to children were noted. The youngest affected child was 6 years of age.

Even though HD can remove gadolinium, cases exist where prompt treatment was administered and yet did not prevent the development of subsequent NSF. Patients on PD have a 7.5-fold higher attack rate of NSF presumably as a result of slower clearance.

Current recommendations for GBCA use vary between the USA and Europe (Table 37.3). Both groups agree that GBCA risk of NSF is high when the GFR is known to be below 30 mL/min/1.73 m^2 but differs on the specifics of the recommendations. The American College of Radiology recommends that a recent GFR assessment be reviewed prior to GBCA administration in high-risk patients, such as those with known prior renal disease and hypertension or following liver transplantation.

With the emergence of NSF, the pendulum may have swung back in favor of iodinated contrast agents for imaging when renal failure is at an advanced stage [104]. Iodinated contrast nephrotoxicity is somewhat more predictable and perhaps reversible, with less threat to life. Nevertheless, any contrast imaging in patients with renal failure is currently not without risk [105].

Table 37.3 Current recommendations on use of GBCA

US Food and Drug Administration	European medicines agency
Considers all GBCA as increasing risk for NSF (class effect)	Separates out the GBCAs as below
No absolute contraindications for GBCA use; advises caution when GFR below 30 mL/min/1.73 m^2	Specifies that three GBCAs (gadodiamide, gadoversetamide, and gadopentetate dimeglumine) are contraindicated in patients with GFR <30 mL/min/1.73 m^2 and should be used with caution when GFR between 30 and 60 mL/min/1.73 m^2
All GBCAs considered risky with liver transplantation	Gadodiamide contraindicated in patients about to undergo or with a liver transplant
Prompt hemodialysis recommended after an at-risk patient has received a GBCA, but prompt is not defined	Hemodialysis post-GBCA administration not specifically discussed

Creation and Maintenance of Venous Access for Hemodialysis

Many pediatric patients will require hemodialysis leading up to transplantation. The prudent use of vascular access devices is paramount in children as there is great potential to permanently injure vessels with imprudent device or technical factors. In general, the principles and standards outlined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) are pertinent to pediatric hemodialysis patients [106]. There are some unique factors related to pediatric patients that warrant special attention however.

The proper vessel for line placement and special attention toward a mindset of vessel preservation become more impactful in pediatric patients who may require long-term, potentially life-long, venous access for hemodialysis. Indwelling venous catheters coupled with repetitive endothelial injury from venipunctures contribute to intimal hyperplasia and ultimately vessel stenosis or occlusion. For these reasons

the smallest possible catheter should be chosen for the intended purpose. KDOQI guidelines on pediatric patients suggest some weight-based guidelines, but there is no abundant evidence, and best practice is to have a multidisciplinary approach to determine what flow rates are needed and what vessels are available for placement. Placing twin tunneled catheters and catheters less than 8 French is generally not undertaken. Contemporary tunneled hemodialysis catheters for pediatrics are available in sizes down to 8 French, but many operators choose to place 10 French devices owing to their more predictable flow rates and more durable polyurethane construction [107].

Vessel preservation strategies are well established in the adult setting and probably even more important in the pediatric setting owing to smaller veins and the potential for life-long vascular access needs. The veins in the neck (internal jugular, external jugular) should be the first choice with preference on the right side. The subclavian vein should be avoided to avoid potential injury or subsequent stenosis that would preclude future catheter placement or fistula creation in the affected upper extremity [106, 108]. Ultrasound guidance is the standard of care for all hemodialysis catheter placements and helps reduce puncture attempts and resultant vessel trauma. If veins in the neck have been exhausted, femoral, translumbar, or transhepatic approaches can be considered on a case-by-case basis.

In pediatric hemodialysis patients over 20 kg, arteriovenous fistula creation is also used to achieve vascular access needs. Maintenance of fistula patency is aggressively undertaken similar to adult fistula patients. There should be a low threshold for detailed evaluation of any suboptimal functioning fistula. Duplex ultrasound is an excellent starting point for noninvasive surveillance. Following that, angiography with potential for more elaborate interventional, image-guided procedures such as pharmacomechanical thrombolysis, angioplasty, or stenting can be undertaken depending on the specific problem uncovered [109–112] .

In some cases where there is extensive venous stenosis or occlusion, the use of advance imaging-guided techniques can be used to recanalize mediastinal access for catheter placement [113, 114]. Various methods have been described utilizing ultrasound, fluoroscopic, and venographic guidance. Figures 37.3 and 37.4 show a successful percutaneous imaging-guided recanalization of an

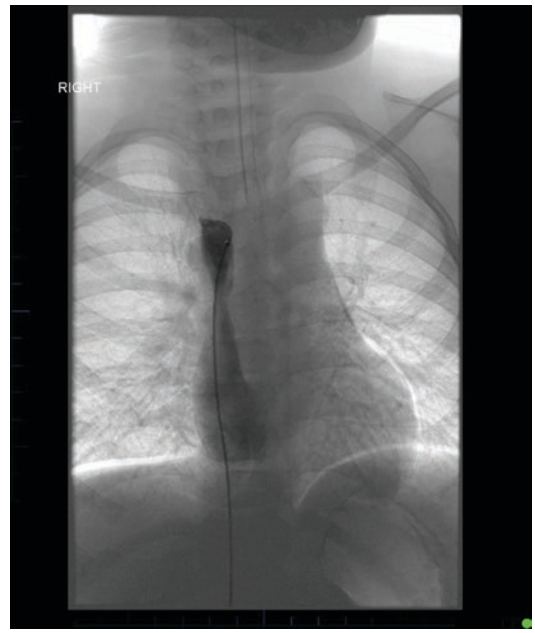

Fig. 37.3 Contrast study in a child showing SVC occlusion from multiple prior infected hemodialysis catheters

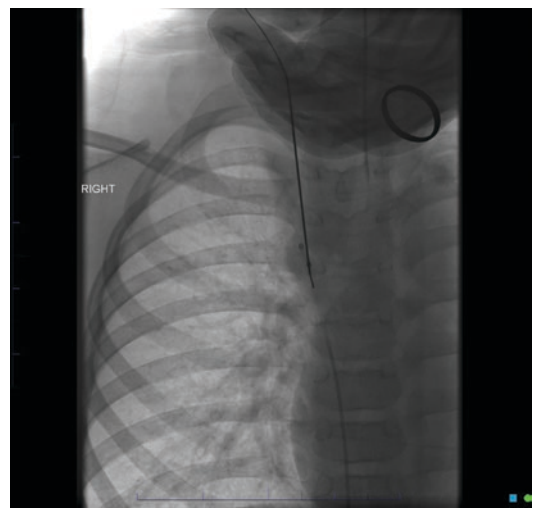

Fig. 37.4 The same child, after successful recanalization of an occluded upper SVC

occluded upper SVC in a child with SVC occlusion from multiple prior infected hemodialysis catheters requiring removal and replacement.

Role of Imaging for Acquired Cystic Kidney Disease

The failed native kidneys can develop acquired renal cysts [115]. The diagnosis of acquired cystic kidney disease (ACKD) requires the presence of four or more renal cysts affecting both of the atrophied or small kidneys. The incidence of ACKD is 7% if the patient is predialysis but rises to 22% if on dialysis and is also higher with longer duration of ESRD. In children, the reported rate is between 21% and 45% [116]. One to three cysts are seen in more than 50% of dialysis patients. A higher risk for ACKD is seen in males [117] and black patients; they also have larger cysts [118]. But cyst development is not related to the cause of ESRD or the modality of dialysis. The presenting features include gross hematuria (if urine is still produced),while anuric patients can present with bilateral flank pain from cyst enlargement and bleeding, though many cysts are asymptomatic. ACKD is not the same as autosomal dominant polycystic kidney disease (ADPKD), which can be differentiated by the positive family history and the large size of the kidneys in ADPKD.

The major worry about ACKD is that ~2% of patients with ACKD can develop renal cell carcinoma (RCC) [119], especially those patients receiving chronic dialysis for more than 10 years or those with numerous or complex cysts. This rate is about sixfold higher than the general population.

The current recommendations for dialysis patients are as follows: (A) to obtain a baseline screening renal ultrasound scan for ACKD around 3 years after the initiation of dialysis. (B) In patients with an initial negative ultrasound, repeat renal ultrasonography is recommended every 3 years or if symptoms arise. (C) In patients found to have one to three simple cysts at any ultrasound, subsequent yearly renal ultrasonography is recommended. (D) Patients meeting the definition of ACKD or with complex cysts should have contrast-enhanced CT scanning to look for neoplastic lesions. Iodinated contrast is not an issue here since the kidneys have already failed. However, GBCA-contrast MRI is contraindicated. The role of noncontrast magnetic resonance imaging in assessing these lesions has not been established. (E) These patients should also be referred to urology. Native kidney nephrectomy may be indicated.

References

1. Zandieh S, Muin D, Bernt R, Krenn-List P, Mirzaei S, Haller J. Radiological diagnosis of dialysis-associated complications. Insights Imaging. 2014;5(5):603–17.
2. Bahrainwala JZ, Leonberg-Yoo AK, Rudnick MR. Use of radiocontrast agents in CKD and ESRD. Semin Dial. 2017;30(4):290–304.
3. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR Am J Roentgenol. 2008;191(2):409–15.
4. Masch WR, Wang CL, Davenport MS. Severe allergic-like contrast reactions: epidemiology and appropriate treatment. Abdom Radiol (NY). 2016;41(8):1632–9.
5. Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, Cho SH. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology. 2012;264(2):414–22.
6. Faucon AL, Bobrie G, Clement O. Nephrotoxicity of iodinated contrast media: from pathophysiology to prevention strategies. Eur J Radiol. 2019;
7. Nouh MR, El-Shazly MA. Radiographic and magnetic resonances contrast agents: essentials and tips for safe practices. World J Radiol. 2017;9(9):339–49.
8. Almen T. Visipaque–a step forward. A historical review. Acta Radiol Suppl. 1995;399:2–18.
9. Katzberg RW. New and old contrast agents: physiology and nephrotoxicity. Urol Radiol. 1988;10(1):6–11.
10. McClennan BL. Ionic versus nonionic contrast media: safety, tolerance, and rationale for use. Urol Radiol. 1989;11(4):200–2.
11. Morris TW. X-ray contrast media: where are we now, and where are we going? Radiology. 1993;188(1):11–6.
12. Media ACoDaC. ACR manual on contrast media. Reston, VA: American College of Radiology; 2018.
13. Dean PB, Kivisaari L, Kormano M. Contrast enhancement pharmacokinetics of six ionic and nonionic contrast media. Investig Radiol. 1983;18(4):368–74.
14. Eloy R, Corot C, Belleville J. Contrast media for angiography: physicochemical properties, pharmacokinetics and biocompatibility. Clin Mater. 1991;7(2):89–197.

15. Rapoport SI, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. Am J Phys. 1972;223(2):323–31.
16. Rapoport SI, Levitan H. Neurotoxicity of X-ray contrast media. Relation to lipid solubility and blood-brain barrier permeability. Am J Roentgenol Radium Therapy, Nucl Med. 1974;122(1):186–93.
17. Blaufox MD, Sanderson DR, Tauxe WN, Wakim KG, Orvis AL, Owen CA Jr. Plasmatic diatrizoate-I-131 disappearance and glomerular filtration in the dog. Am J Phys. 1963;204:536–40.
18. Donaldson IM. Comparison of the renal clearances of inulin and radioactive diatrizoate ("Hypaque") as measures of the glomerular filtration rate in man. Clin Sci. 1968;35(3):513–24.
19. Mudge GH. The maximal urinary concentration of diatrizoate. Investig Radiol. 1980;15(6 Suppl):S67–78.
20. Katzberg RW, Pabico RC, Morris TW, Hayakawa K, McKenna BA, Panner BJ, Ventura JA, Fischer HW. Effects of contrast media on renal function and subcellular morphology in the dog. Investig Radiol. 1986;21(1):64–70.
21. Katzberg RW, Schulman G, Meggs LG, Caldicott WJ, Damiano MM, Hollenberg NK. Mechanism of the renal response to contrast medium in dogs. Decrease in renal function due to hypertonicity. Investig Radiol. 1983;18(1):74–80.
22. Katzberg RW, Donahue LA, Morris TW, Ventura JA, Krutchen AE, Proskin HM, Sovak M, Cos LR. Ioxilan, a third generation low osmolality nonionic contrast medium. Systemic and renal hemodynamic effects. Investig Radiol. 1990;25(1):46–51.
23. Nordby A, Tvedt KE, Halgunset J, Haugen OA. Intracellular penetration and accumulation of radiographic contrast media in the rat kidney. Scanning Microsc. 1990;4(3):651–64. discussion 64-6
24. Lorusso V, Taroni P, Alvino S, Spinazzi A. Pharmacokinetics and safety of iomeprol in healthy volunteers and in patients with renal impairment or end-stage renal disease requiring hemodialysis. Investig Radiol. 2001;36(6):309–16.
25. Katzberg RW. Contrast medium-induced nephrotoxicity: which pathway? Radiology. 2005;235(3):752–5.
26. Persson PB, Tepel M. Contrast medium-induced nephropathy: the pathophysiology. Kidney Int Suppl. 2006;100:S8–10.
27. Liss P, Nygren A, Erikson U, Ulfendahl HR. Injection of low and iso-osmolar contrast medium decreases oxygen tension in the renal medulla. Kidney Int. 1998;53(3):698–702.
28. Ueda J, Nygren A, Hansell P, Erikson U. Influence of contrast media on single nephron glomerular filtration rate in rat kidney. A comparison between diatrizoate, iohexol, ioxaglate, and iotrolan. Acta Radiol. 1992;33(6):596–9.
29. Hardiek K, Katholi RE, Ramkumar V, Deitrick C. Proximal tubule cell response to radiographic contrast media. Am J Physiol Renal Physiol. 2001;280(1):F61–70.
30. Hizoh I, Strater J, Schick CS, Kubler W, Haller C. Radiocontrast-induced DNA fragmentation of renal tubular cells in vitro: role of hypertonicity. Nephrol Dial Transpl. 1998;13(4):911–8.
31. Heinrich MC, Kuhlmann MK, Grgic A, Heckmann M, Kramann B, Uder M. Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells in vitro. Radiology. 2005;235(3):843–9.
32. Heydenreich G, Larsen PO. Iododerma after high dose urography in an oliguric patient. Br J Dermatol. 1977;97(5):567–9.
33. Goodfellow T, Holdstock GE, Brunton FJ, Bamforth J. Fatal acute vasculitis after high-dose urography with iohexol. Br J Radiol. 1986;59(702):620–1.
34. Rivera M, Teruel JL, Castano JC, Garcia Otero G, Ortuno J. Iodine-induced sialadenitis: report of 4 cases and review of the literature. Nephron. 1993;63(4):466–7.
35. Zhang G, Li T, Wang H, Liu J. The pathogenesis of iodide mumps: a case report. Medicine (Baltimore). 2017;96(47):e8881.
36. Younathan CM, Kaude JV, Cook MD, Shaw GS, Peterson JC. Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. AJR Am J Roentgenol. 1994;163(4):969–71.
37. Hamani A, Petitclerc T, Jacobs C, Deray G. Is dialysis indicated immediately after administration of iodinated contrast agents in patients on haemodialysis? Nephrol Dial Transpl. 1998;13(4):1051–2.
38. Harasawa H, Yamazaki C, Masuko K. Side effects and pharmacokinetics of nonionic iodinated contrast medium in hemodialyzed patients. Nihon Igaku Hoshasen Gakkai Zasshi. 1990;50(12):1524–31.
39. Horiuchi K, Yoshida K, Tsuboi N, Akimoto M, Tajima H, Kumazaki T. Elimination of non-ionic contrast medium by hemodialysis in patients with impaired renal function. Nihon Ika Daigaku Zasshi. 1999;66(5):305–7.
40. Kierdorf H, Kindler J, Winterscheid R, Hollmann HJ, Vorwerk D, Speck U. Elimination of the nonionic contrast medium iopromide in end-stage renal failure by hemodialysis. Fortschr Geb Rontgenstrahlen Nuklearmed Erganzungsbd. 1989;128:119–23.
41. Matzkies FK, Reinecke H, Tombach B, Kosch M, Hegger K, Milius M, Hohage H, Kisters K, Kerber S, Schaefer RM. Influence of dialysis procedure, membrane surface and membrane material on iopromide elimination in patients with reduced kidney function. Am J Nephrol. 2000;20(4):300–4.
42. Matzkies FK, Tombach B, Kisters K, Schuhmann G, Hohage H, Schaefer RM. Clearance of iopromide during haemodialysis with high- and low-flux membranes. Acta Radiol. 1999;40(2):220–3.
43. Moon SS, Back SE, Kurkus J, Nilsson-Ehle P. Hemodialysis for elimination of the nonionic contrast medium iohexol after angiography in

patients with impaired renal function. Nephron. 1995;70(4):430–7.
44. Schindler R, Stahl C, Venz S, Ludat K, Krause W, Frei U. Removal of contrast media by different extracorporeal treatments. Nephrol Dial Transpl. 2001;16(7):1471–4.
45. Sterner G, Frennby B, Mansson S, Ohlsson A, Prutz KG, Almen T. Assessing residual renal function and efficiency of hemodialysis–an application for urographic contrast media. Nephron. 2000;85(4):324–33.
46. Teraoka T, Sugai T, Nakamura S, Hirasawa H, Oda S, Shiga H, Suga M, Yamane S, Ishii H, Yamagata S, Satoh N, Ueda S. Prediction of iopromide reduction rates during haemodialysis using an in vitro dialysis system. Nephrol Dial Transpl. 2005;20(4):754–9.
47. Ueda J, Furukawa T, Higashino K, Takahashi S, Araki Y, Sakaguchi K. Elimination of iomeprol by hemodialysis. Eur J Radiol. 1996;23(3):197–200.
48. Ueda J, Furukawa T, Takahashi S, Sakaguchi K. Elimination of ioversol by hemodialysis. Acta Radiol. 1996;37(5):826–9.
49. Waaler A, Svaland M, Fauchald P, Jakobsen JA, Kolmannskog F, Berg KJ. Elimination of iohexol, a low osmolar nonionic contrast medium, by hemodialysis in patients with chronic renal failure. Nephron. 1990;56(1):81–5.
50. Johnsson E, Attman PO, Samuelsson O, Haraldsson B. Improved clearance of iohexol with longer haemodialysis despite similar Kt/V for urea. Nephrol Dial Transpl. 1999;14(10):2407–12.
51. Donnelly PK, Burwell N, McBurney A, Ward JW, Walls J, Watkin EM. Clearance of iopamidol, a non-ionic contrast medium, by CAPD in patients with end-stage renal failure. Br J Radiol. 1992;65(780):1108–13.
52. Iwamoto M, Hiroshige K, Suda T, Ohta T, Ohtani A, Nakashima Y. Elimination of iomeprol in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int. 1999;19(4):380–5.
53. Lehnert T, Keller E, Gondolf K, Schaffner T, Pavenstadt H, Schollmeyer P. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transpl. 1998;13(2):358–62.
54. Vogt B, Ferrari P, Schonholzer C, Marti HP, Mohaupt M, Wiederkehr M, Cereghetti C, Serra A, Huynh-Do U, Uehlinger D, Frey FJ. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am J Med. 2001;111(9):692–8.
55. Frank H, Werner D, Lorusso V, Klinghammer L, Daniel WG, Kunzendorf U, Ludwig J. Simultaneous hemodialysis during coronary angiography fails to prevent radiocontrast-induced nephropathy in chronic renal failure. Clin Nephrol. 2003;60(3):176–82.
56. Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, Trabattoni D, Fabbiocchi F, Montorsi P, Bartorelli AL. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med. 2003;349(14):1333–40.
57. Marenzi G, Lauri G, Campodonico J, Marana I, Assanelli E, De Metrio M, Grazi M, Veglia F, Fabbiocchi F, Montorsi P, Bartorelli AL. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. Am J Med. 2006;119(2):155–62.
58. Hawkins IF Jr, Mladinich CR, Storm B, Croker BP, Wilcox CS, Akins EW, Drake W. Short-term effects of selective renal arterial carbon dioxide administration on the dog kidney. J Vasc Interv Radiol. 1994;5(1):149–54.
59. Palm F, Bergqvist D, Carlsson PO, Hellberg O, Nyman R, Hansell P, Liss P. The effects of carbon dioxide versus ioxaglate in the rat kidney. J Vasc Interv Radiol. 2005;16(2 Pt 1):269–74.
60. Shifrin EG, Plich MB, Verstandig AG, Gomori M. Cerebral angiography with gaseous carbon dioxide CO2. J Cardiovasc Surg. 1990;31(5):603–6.
61. Dimakakos PB, Stefanopoulos T, Doufas AG, Papasava M, Gouliamos A, Mourikis D, Deligiorgi H. The cerebral effects of carbon dioxide during digital subtraction angiography in the aortic arch and its branches in rabbits. AJNR Am J Neuroradiol. 1998;19(2):261–6.
62. Hawkins IF, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. Radiol Clin N Am. 2009;47(5):813–25. v-vi
63. McCullough BJ, Kolokythas O, Maki JH, Green DE. Ferumoxytol in clinical practice: implications for MRI. J Magn Reson Imaging. 2013;37(6):1476–9.
64. Kramer JH, Grist TM. Peripheral MR angiography. Magn Reson Imaging Clin N Am. 2012;20(4):761–76.
65. Pouliquen D, Le Jeune JJ, Perdrisot R, Ermias A, Jallet P. Iron oxide nanoparticles for use as an MRI contrast agent: pharmacokinetics and metabolism. Magn Reson Imaging. 1991;9(3):275–83.
66. Ruangwattanapaisarn N, Hsiao A, Vasanawala SS. Ferumoxytol as an off-label contrast agent in body 3T MR angiography: a pilot study in children. Pediatr Radiol. 2015;45(6):831–9.
67. Kim HK, Lee GH, Chang Y. Gadolinium as an MRI contrast agent. Future Med Chem. 2018;10(6):639–61.
68. Lorusso V, Pascolo L, Fernetti C, Anelli PL, Uggeri F, Tiribelli C. Magnetic resonance contrast agents: from the bench to the patient. Curr Pharm Des. 2005;11(31):4079–98.
69. Swan SK, Lambrecht LJ, Townsend R, Davies BE, McCloud S, Parker JR, Bensel K, LaFrance ND. Safety and pharmacokinetic profile of gadobenate dimeglumine in subjects with renal impairment. Investig Radiol. 1999;34(7):443–8.
70. Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. AJR Am J Roentgenol. 2009;193(4):1124–7.
71. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR Am J Roentgenol. 1996;167(4):847–9.

72. Prince MR, Erel HE, Lent RW, Blumenfeld J, Kent KC, Bush HL, Wang Y. Gadodiamide administration causes spurious hypocalcemia. Radiology. 2003;227(3):639–46.
73. Emerson J, Kost G. Spurious hypocalcemia after Omniscan- or OptiMARK-enhanced magnetic resonance imaging: an algorithm for minimizing a false-positive laboratory value. Arch Pathol Lab Med. 2004;128(10):1151–6.
74. Niendorf HP, Alhassan A, Geens VR, Clauss W. Safety review of gadopentetate dimeglumine. Extended clinical experience after more than five million applications. Invest Radiol. 1994;29 Suppl 2:S179–82.
75. Arsenault TM, King BF, Marsh JW Jr, Goodman JA, Weaver AL, Wood CP, Ehman RL. Systemic gadolinium toxicity in patients with renal insufficiency and renal failure: retrospective analysis of an initial experience. Mayo Clin Proc. 1996;71(12):1150–4.
76. Erley CM, Bader BD, Berger ED, Tuncel N, Winkler S, Tepe G, Risler T, Duda S. Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotaemic patients. Nephrol Dial Transpl. 2004;19(10):2526–31.
77. Ergun I, Keven K, Uruc I, Ekmekci Y, Canbakan B, Erden I, Karatan O. The safety of gadolinium in patients with stage 3 and 4 renal failure. Nephrol Dial Transpl. 2006;21(3):697–700.
78. Sam AD 2nd, Morasch MD, Collins J, Song G, Chen R, Pereles FS. Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. J Vasc Surg. 2003;38(2):313–8.
79. Kane GC, Stanson AW, Kalnicka D, Rosenthal DW, Lee CU, Textor SC, Garovic VD. Comparison between gadolinium and iodine contrast for percutaneous intervention in atherosclerotic renal artery stenosis: clinical outcomes. Nephrol Dial Transpl. 2008;23(4):1233–40.
80. Rodby RA. Dialytic therapies to prevent NSF following gadolinium exposure in high-risk patients. Semin Dial. 2008;21(2):145–9.
81. Okada S, Katagiri K, Kumazaki T, Yokoyama H. Safety of gadolinium contrast agent in hemodialysis patients. Acta Radiol. 2001;42(3):339–41.
82. Saitoh T, Hayasaka K, Tanaka Y, Kuno T, Nagura Y. Dialyzability of gadodiamide in hemodialysis patients. Radiat Med. 2006;24(6):445–51.
83. Ueda J, Furukawa T, Higashino K, Yamamoto T, Ujita H, Sakaguchi K, Araki Y. Permeability of iodinated and MR contrast media through two types of hemodialysis membrane. Eur J Radiol. 1999;31(1):76–80.
84. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol. 1998;5(7):491–502.
85. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet. 2000;356(9234):1000–1.
86. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. Am J Dermatopathol. 2001;23(5):383–93.
87. Baron PW, Cantos K, Hillebrand DJ, Hu KQ, Ojogho ON, Nehlsen-Cannarella S, Concepcion W. Nephrogenic fibrosing dermopathy after liver transplantation successfully treated with plasmapheresis. Am J Dermatopathol. 2003;25(3):204–9.
88. Dharnidharka VR, Wesson SK, Fennell RS. Gadolinium and nephrogenic fibrosing dermopathy in pediatric patients. Pediatr Nephrol. 2007;22(9):1395.
89. Jain SM, Wesson S, Hassanein A, Canova E, Hoy M, Fennell RS, Dharnidharka VR. Nephrogenic fibrosing dermopathy in pediatric patients. Pediatr Nephrol. 2004;19(4):467–70.
90. Mackay-Wiggan JM, Cohen DJ, Hardy MA, Knobler EH, Grossman ME. Nephrogenic fibrosing dermopathy (scleromyxedema-like illness of renal disease). J Am Acad Dermatol. 2003;48(1):55–60.
91. Perazella MA, Ishibe S, Reilly RF. Nephrogenic fibrosing dermopathy: an unusual skin condition associated with kidney disease. Semin Dial. 2003;16(3):276–80.
92. Streams BN, Liu V, Liegeois N, Moschella SM. Clinical and pathologic features of nephrogenic fibrosing dermopathy: a report of two cases. J Am Acad Dermatol. 2003;48(1):42–7.
93. Swartz RD, Crofford LJ, Phan SH, Ike RW, Su LD. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. Am J Med. 2003;114(7):563–72.
94. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transpl. 2006;21(4):1104–8.
95. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol. 2006;17(9):2359–62.
96. High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2007;56(1):21–6.
97. Thakral C, Abraham JL. Gadolinium-induced nephrogenic systemic fibrosis is associated with insoluble Gd deposits in tissues: in vivo transmetallation confirmed by microanalysis. J Cutan Pathol. 2009;36(12):1244–54.
98. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? Semin Dial. 2008;21(2):129–34.
99. Penfield JG. Nephrogenic systemic fibrosis and the use of gadolinium-based contrast agents. Pediatr Nephrol. 2008;23(12):2121–9.
100. Auron A, Shao L, Warady BA. Nephrogenic fibrosing dermopathy in children. Pediatr Nephrol. 2006;21(9):1307–11.
101. DiCarlo JB, Gupta EA, Solomon AR. A pediatric case of nephrogenic fibrosing dermopathy:

improvement after combination therapy. J Am Acad Dermatol. 2006;54(5):914–6.
102. Jan F, Segal JM, Dyer J, LeBoit P, Siegfried E, Frieden IJ. Nephrogenic fibrosing dermopathy: two pediatric cases. J Pediatr. 2003;143(5):678–81.
103. Nardone B, Saddleton E, Laumann AE, Edwards BJ, Raisch DW, McKoy JM, Belknap SM, Bull C, Haryani A, Cowper SE, Abu-Alfa AK, Miller FH, Godinez-Puig V, Dharnidharka VR, West DP. Pediatric nephrogenic systemic fibrosis is rarely reported: a RADAR report. Pediatr Radiol. 2014;44(2):173–80.
104. Karcaaltincaba M, Oguz B, Haliloglu M. Current status of contrast-induced nephropathy and nephrogenic systemic fibrosis in children. Pediatr Radiol. 2009;39(Suppl 3):382–4.
105. Steen H, Schwenger V. Good MRI images: to gad or not to gad? Pediatr Nephrol. 2007;22(9):1239–42.
106. Vascular Access Work G. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006;48 Suppl 1:S248–73.
107. Chick JF, Reddy SN, Yam BL, Kobrin S, Trerotola SO. Institution of a hospital-based central venous access policy for peripheral vein preservation in patients with chronic kidney disease: a 12-year experience. J Vasc Interv Radiol. 2017;28(3):392–7.
108. Araujo C, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, Dias T, Fougo JL. A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. Eur J Surg Oncol. 2008;34(2):222–6.
109. Itoga NK, Ullery BW, Tran K, Lee GK, Aalami OO, Bech FR, Zhou W. Use of a proactive duplex ultrasound protocol for hemodialysis access. J Vasc Surg. 2016;64(4):1042–9 e1.
110. Neuen BL, Gunnarsson R, Webster AC, Baer RA, Golledge J, Mantha ML. Predictors of patency after balloon angioplasty in hemodialysis fistulas: a systematic review. J Vasc Interv Radiol. 2014;25(6):917–24.
111. Bautista AB, Suhocki PV, Pabon-Ramos WM, Miller MJ Jr, Smith TP, Kim CY. Postintervention patency rates and predictors of patency after percutaneous interventions on intragraft stenoses within failing prosthetic arteriovenous grafts. J Vasc Interv Radiol. 2015;26(11):1673–9.
112. Gogalniceanu P, Stuart S, Karunanithy N, Kessaris N, Roebuck D, Calder F. Endovascular intervention in the maintenance and rescue of paediatric arteriovenous fistulae for hemodialysis. Pediatr Nephrol. 2019;34(4):723–7.
113. Hadziomerovic A, Hirji Z, Coffey N. Modified inside-out technique for continued use of chronically occluded upper central veins. J Vasc Interv Radiol. 2017;28(5):757–61.
114. Keller EJ, Gupta SA, Bondarev S, Sato KT, Vogelzang RL, Resnick SA. Single-center retrospective review of radiofrequency wire recanalization of refractory central venous occlusions. J Vasc Interv Radiol. 2018;29(11):1571–7.
115. Levine E, Slusher SL, Grantham JJ, Wetzel LH. Natural history of acquired renal cystic disease in dialysis patients: a prospective longitudinal CT study. AJR Am J Roentgenol. 1991;156(3):501–6.
116. Chan EYH, Warady BA. Acquired cystic kidney disease: an under-recognized condition in children with end-stage renal disease. Pediatr Nephrol. 2018;33(1):41–51.
117. Narasimhan N, Golper TA, Wolfson M, Rahatzad M, Bennett WM. Clinical characteristics and diagnostic considerations in acquired renal cystic disease. Kidney Int. 1986;30(5):748–52.
118. Matson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. Medicine (Baltimore). 1990;69(4):217–26.
119. Farivar-Mohseni H, Perlmutter AE, Wilson S, Shingleton WB, Bigler SA, Fowler JE Jr. Renal cell carcinoma and end stage renal disease. J Urol. 2006;175(6):2018–20; discussion 21.

38 Extracorporeal Therapy for Drug Overdose and Poisoning

Vimal Chadha

Introduction

Poisoning continues to be a significant cause of morbidity and mortality. The 2018 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS): 36th Annual Report published information on 2,099,751 human exposure cases of poisoning of which more than half (59%) were children and adolescents <20 years old, with majority (75%) occurring in children ≤5 years [1]. A male predominance was found among cases involving children ≤12 years, but this gender distribution was reversed in teenagers and adults, with females comprising the majority of reported exposures [1]. Prescription drugs, over-the-counter medications, illicit drugs, and common household substances can all be responsible for poisoning. The top five most frequently involved substances in all human exposures were analgesics (10.9%), household cleaning substances (7.3%), cosmetics/personal care products (6.5%), sedatives/hypnotics/antipsychotics (5.5%), and antidepressants (5.2%). In children ≤5 years, analgesics (9%) were surpassed by cosmetics/personal care products (12.1%) and household cleaning substances (10.7%) [1].

Of note, there has been a steady decline (15.7% since 2008) in the number of poisoning cases, but this has been accompanied by an increase (4.45% per year since 2000) in the number of cases with serious outcomes. The most rapidly increasing substance categories resulting in more serious outcomes for the past 10 years have been antidepressants, stimulants/street drugs, antihistamines, and anticonvulsants [1]. While most (76.7%) poison exposures are still unintentional, suicide attempts by adolescents are becoming an important emerging trend; suicidal intent was suspected in 19.1% (almost double since 2008) of cases. It is noteworthy that in 13% of exposures (273,581 cases), poisoning resulted due to therapeutic errors such as inadvertent double dosing, incorrect dosing, wrong medication taken or given, and inadvertent exposure to someone else's medication.

The management of poisoning continues to be a significant burden on the healthcare system. In 2018, approximately one-third (31%) of all cases received treatment in a healthcare facility. While half of them were treated and released without hospital admission, 97,963 (15%) had to be admitted for critical care management, and 78,401 (12%) were admitted to a non-critical

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care unit. Despite being the most common age group with poisonings, only 12.5% of children ≤5 years and 18.4% of children between 6 and 12 years were managed in a healthcare facility compared to 66% of teenagers (13–19 years) and 50% of adults. Similarly, children younger than 6 years also experienced the least (<2%) of the exposure-related fatalities [1].

Poison Characteristics

In the discipline of clinic toxicology, poison generally refers to any agent (drug or toxin) that can kill, injure, or impair normal physiologic function. A poison is often referred to as a xenobiotic, a chemical substance found within an organism that is not naturally produced or expected to be present within the organism. The term also includes any naturally existing substances in an organism that are present in abnormally higher concentrations.

For practical purposes, the poisons can be divided into two broad categories: those that cause tissue damage and those that do not. Tissue damage is defined as irreversible or slowly reversible structural or functional changes in one or more organ systems that occur as a direct result of the poison (or its toxic metabolite) in the body. Poisons such as salicylates, acetaminophen, and methanol fall in this category, and they can cause direct tissue damage despite provision of intensive supportive care [2–5]. Thus, in patients poisoned with this group of chemicals, use of a specific antidote (if available) and/or active removal of the poison by extracorporeal therapies (ECTs) is necessary to prevent irreversible tissue damage. The second group of poisons such as barbiturates and other common sedative/hypnotic drugs does not have any direct tissue-damaging effect but causes indirect harm due to respiratory compromise or hypotension. These patients can be treated with specific antidotes (if available) and supportive care, provided they will metabolize and/or excrete the poison in a reasonable time.

Management of the Poisoned Patient

The general approach to the management of an acute poisoning includes:

1. Patient stabilization (maintenance of the airway, ventilation, and hemodynamic status).
2. Establishing accurate diagnosis by clinical evaluation which in many cases is aided by identification and determination of blood concentration of the toxic substance. Recognition of toxidromes (constellation of symptoms and signs associated with certain class of poisons) can be valuable in expediting diagnosis.
3. Decontamination (removal of poison from site of absorption such as GI tract or skin).
4. Administration of antidotes, if available.
5. Supportive care (treatment of hypotension, arrhythmias, respiratory failure, electrolyte imbalance, and seizures).
6. Enhancing elimination of poison by manipulation of urinary pH.
7. Removal of poison by ECTs.

Fortunately, the vast majority of patients with poisoning recover with appropriate supportive care and/or timely usage of specific antidote therapy. As a result, a very limited number of patients require ECTs, but they are also the most critically sick patients where a judicious usage of ECT can determine their outcome. According to the NPDS 36th Annual Report, ECTs were utilized in 2817 (2.9%) of 97,963 patients admitted for critical care management [1].

Since poisons achieve their toxic effects on target organs via the bloodstream, it seems logical that their elimination from the blood should result in amelioration of the patient's condition. Accordingly, changes in the serum poison levels are the most frequently used parameters of response to extracorporeal therapy in intoxication; however, this pretext can be misleading and provides false assurance of dialysis efficacy (vide infra). To better understand these perplexities, the nephrologist ought to be well versed

with the basic concepts of pharmacokinetics and principles of detoxification when dealing with the management of an acutely poisoned patient. These concepts also help in determining the usefulness of extracorporeal therapy as well as selection of the optimum modality for drug removal.

Extracorporeal therapies are typically reserved for a small subset of patients that can be divided into the following five subgroups:

(a) Patients intoxicated with poisons that cause direct tissue damage and are life-threatening (e.g., salicylate overdose)
(b) Patients intoxicated with poisons that can cause permanent disability (e.g., blindness with methanol overdose)
(c) Patients intoxicated with poisons that do not cause direct tissue damage, but the patient's ability to metabolize or excrete the toxic substance is compromised (e.g., metformin overdose with renal impairment)
(d) Patients intoxicated with poisons in which active poison removal is considered to avoid prolonged supportive care and its associated complications (e.g., barbiturate overdose with coma requiring mechanical ventilation)
(e) Patients intoxicated with poisons who develop signs of toxicity despite provision of standard supportive measures

Pharmacokinetic Concepts

The extracorporeal removal (dialyzability) of a substance is determined by various physicochemical and pharmacokinetic properties. These properties predict the extent to which ECT enhances the total body clearance, thereby lowering the total body poison load faster than without treatment. By far, the primary determinants of poison removal by ECT are the molecular weight (MW), volume of distribution (V_d), and protein binding; additional factors such as hydro- and lipophilicity, ionization, and rate of intercompartmental transfer also play a significant role.

Molecular Weight

The lower the MW, the more likely that a poison is dialyzable. While older cuprophane dialyzers were able to clear substances with MW up to 500 Da, contemporary high-efficiency high-flux dialyzers with diffusive modalities are capable of clearing poisons in the middle MW range (≤15,000 Da). In contrast, convective modalities such as hemofiltration and hemodiafiltration can permit clearance of solutes approaching 25,000 Da.

Volume of Distribution

Volume of distribution (V_d) is an imaginary space that represents the volume of fluid in which a known amount of drug would have to be diluted to yield the measured serum concentration. Theoretically, if the body is presumed to be a single compartment and a substance is homogenously distributed in body water without binding to protein or accumulating in tissues, it would have an apparent V_d equal to the total body water.

$$V_d\left(\text{Liters}\right) = 0.6\,\text{L/kg} \times \text{body weight}\left(\text{kg}\right) \quad (38.1)$$

For some substances such as methanol that distribute in body water without significant binding to tissue or plasma protein and without significant accumulation in adipose tissue, the apparent V_d corresponds to a physiologic space: in this case equivalent to total body water. However, most substances are not homogeneously distributed but rather vary in their concentration throughout the body as a result of lipid solubility, protein binding, active cellular transport, and pH gradients, and as a result V_d can vary over a wide range of values (0.2 L/kg for valproic acid to 20 L/kg for imipramine). A V_d significantly larger than actual body water reflects a high degree of tissue concentration, while a small V_d suggests concentration within the intravascular space.

Volume of distribution is clinically important in two ways. First, knowing the V_d and plasma concentration of a particular drug allows calculation of the total amount of the drug in the body, as:

$$X(\text{mg}) = V_d(\text{L}) \times C_p(\text{mg/L}) \quad (38.2)$$

where X is the total amount of the drug in milligrams (mg) and C_p is the plasma concentration in mg/L. Second, V_d is one of the factors that determine accessibility of a drug to removal by extracorporeal therapy. A large V_d implies that the amount of drug present in blood represents only a small fraction of the total body load; therefore, as the V_d increases, the usefulness of any ECT decreases substantially. Thus, even if a hemodialysis session extracts most of the drug present in blood passing through the circuit, the amount of drug removed represents a small percentage of the total body drug burden. Although there is no precise cut-off, a V_d > 1–2 L/kg usually limits usefulness of ECT [6]. On the contrary, poisons with a smaller V_d (< 1 L/kg) are more amenable to removal by ECT. Volume of distribution of some of the common substances involved in poisoning is listed in Table 38.1. It is important to note that these values for V_d are derived from the general population under normal dosing conditions and may not apply in the situation of a substantial drug overdose. In addition, the presence of renal and/or hepatic dysfunction in a poisoned patient can further alter the value of V_d (see section on toxicokinetics, vide infra).

Protein Binding

Many substances bind with varying affinity to plasma proteins, such as albumin, or to intracellular proteins in the tissues. Thus, in addition to dissolving in fat, substances can accumulate in tissues according to their degree of protein binding. A poison-protein complex may exceed 65,000 Da and is too large to be filtered. Highly protein-bound (>80%) substances are therefore not amenable to therapy with extracorporeal modalities. However, at toxic levels the protein binding sites are usually saturated, thus increasing the proportion of free fraction which potentially increases poisoning severity because the

Table 38.1 Pharmacokinetic properties of some of the drugs frequently involved in poisoning

Drug	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Preferred extracorporeal modality
Acetaminophen	151	0.8–1.0	25	IHD
Carbamazepine	236	0.8–1.4	75	IHD
Digoxin	765	5–8	20–30	—
Ethanol	46	0.7	0	IHD
Ethylene glycol	62	0.5–0.8	0	IHD
Isopropanol	60	0.7	0	IHD
Lithium	7	0.7–0.9	10	IHD
Metformin	129	1–5	0	IHD
Methanol	32	0.6–0.8	0	IHD
Phenobarbital	232	0.25–1.2	20–60	IHD
Phenytoin	252	0.6–0.8	90	IHD[a]
Salicylate	180	0.2	90[b]	IHD
Thallium	204	3–10	0	IHD
Theophylline	180	0.5	50	IHD
Tricyclic antidepressant	263–314	5–78	73–98	—
Valproate	144	0.1–0.5	94[c]	IHD
Vancomycin	1449	<0.4 -1	<60	IHD[d]

IHD intermittent hemodialysis
[a]Relatively limited effect, used in select patients with severe toxicity
[b]Protein binding decreases to 30% with toxic levels
[c]Protein binding decreases to 15% with toxic levels
[d]Use high-efficiency high-flux dialyzer

free fraction exerts toxicity, but this also facilitates removal by the ECT. This explains the high removal rate of protein-bound drugs such as valproate and salicylates, both of which exhibit saturable binding at toxic levels [7, 8]. Of note, when the protein binding is <80%, there is little difference between the removal of a substance that is, for example, 20% protein-bound and one that is 70% protein-bound because of the logarithmic nature of extracorporeal solute removal (Fig. 38.1) [9]. It is also important to note that most drug-protein bonds are weak and easily reversible, and protein binding can be altered by a number of variables such as pH and drug competition for the binding sites.

Hydro- and Lipophilicity

Hydrophilic poisons distribute primarily in total body water, have a smaller V_d, and are more readily removed by ECT. Lipid solubility affects the accumulation of drug in lipid-rich tissues such as adipose tissue and the brain. The degree of lipid solubility of a substance is expressed by its partition coefficient, which is an in vitro measurement of the ratio of lipid (non-polar) phase to aqueous (polar) phase concentration of its non-ionized form. Lipid-soluble drugs can accumulate extensively in the adipose tissue and act as a reservoir with poor accessibility due to decreased vascular perfusion.

Ionization

Non-ionized substances are more lipid soluble and, therefore, more easily transported across cellular membranes in the body than their ionized form. The pK of the substance is the pH at which it is half ionized and half non-ionized. An acid is increasingly ionized as the pH rises above its pK, and a base is increasingly ionized as pH falls below its pK. Therefore, pH gradients across the cell membranes can affect the extent of diffusion by trapping the ionized form on one side. In the stomach and kidney, where large pH gradients exist (or can be induced) with respect to plasma, this phenomenon can have therapeutic implications to prevent absorption and enhance clearance.

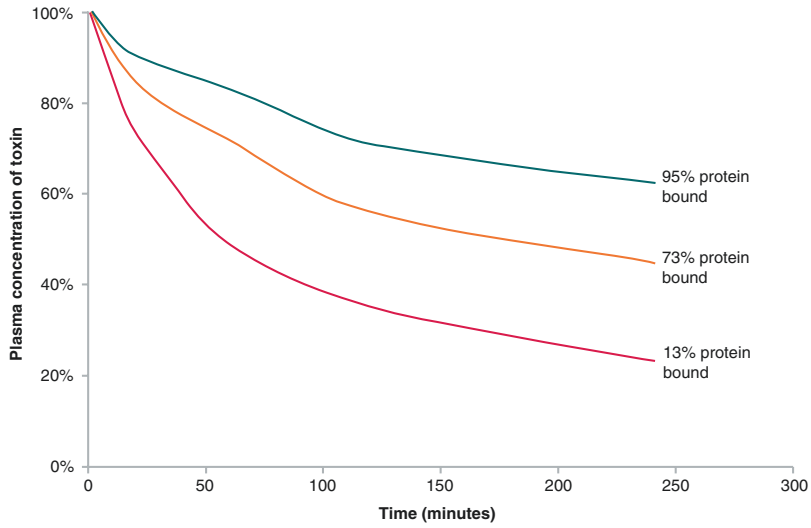


Fig. 38.1 Removal of toxins via HD decreases with greater degrees of protein binding. Comparison of removal of three uremic toxins (p-cresyl glucuronide, 13% protein bound; indole-3-acetic acid, 73% protein bound; and p-cresyl sulfate, 95% protein bound) during a single HD session averaged over 10 patients. Blood flow rates were 300 mL/min, dialysate flow rates were 700 mL/min, and dialyzer urea clearances varied. (Modified from King et al. [9])

Intercompartmental Transfer

In a single-compartment model, a change in plasma level would reflect a similar change in levels throughout the body. Unfortunately, most substances in the body are distributed in multiple compartments, and movement across these compartments is variable and dependent on several factors as listed above. Knowledge of these parameters is crucial in understanding the relationship between blood level and drug removal during extracorporeal therapies [10].

Rebound

The increase in plasma poison concentration following a session of intermittent ECT is commonly seen with poisons that have a large V_d. This phenomenon of rebound happens when the rate of poison redistribution within the body is slower than the rate of removal by an ECT. Except in situations where the rebound is caused by ongoing absorption of the poison from the gastrointestinal tract, when supplementary treatments may be required, it is uncertain if rebound by itself is concerning. For example, in lithium poisoning, the rebound after a session of dialysis actually moves the lithium away from the site of toxicity (CNS) to a relatively more benign compartment (the vascular space) [11].

Endogenous Clearance

To be worthwhile, the rate of poison removal by an extracorporeal method should be a significant addition to the endogenous (systemic) clearance (sum of renal and non-renal clearance). If endogenous clearance is high, then an ECT is unlikely to significantly increase total clearance enough to justify its use [12, 13]. For example, endogenous metformin clearance in the presence of normal kidney function is 600 mL/min and far exceeds the clearance achieved by HD (240 mL/min). In this situation, ECT will usually not be recommended for metformin overdose unless the endogenous clearance is impaired due to concomitant decreased kidney function, and ECT is the only means of providing useful clearance. It is commonly suggested that ECT can be considered worthwhile if the endogenous clearance of the poison is below 4 mL/kg/min [6]. It has also been recommended that extracorporeal clearance must represent at least 30% of total clearance to be a significant contributor to drug removal in vivo [14], but the utility of this parameter is questionable under certain situations [15].

Toxicokinetics

The reported pharmacokinetic characteristics of the drugs are normally evaluated in the context of therapeutic levels. One should be cognizant of the fact that many of these properties for the same drug can change with toxic levels (toxicokinetics). Some of the highly protein-bound drugs such as valproate and salicylates can have significant free fraction at toxic levels as the protein binding sites become saturated. For example, the protein binding of salicylate falls from 90% at therapeutic concentrations to 50% when it reaches 800 mg/dL; valproic acid's protein binding decreases markedly from 94% at therapeutic levels to 15% at drug levels >1000 mg/L. In contrast, carbamazepine (protein binding 75%) and phenytoin (protein binding 90%) show little to no saturable binding in overdose conditions. The V_d for several drugs (e.g., salicylates) can also change with higher doses, especially in the presence of renal and/or hepatic impairment. Furthermore, the drug elimination kinetics for certain drugs can change from first order to zero order, thus extending the elimination half-life.

Specific Issues in Neonates and Young Infants

The implications and management of poisoning in newborns and young infants require understanding of their unique physiology. Primarily, the organs that play an important role in susceptibility to and moderation of toxic reactions such as the liver and kidney are immature in their

function. Their gastric emptying is slower, and gastric pH is higher which can enhance absorption of certain drugs, thus increasing their susceptibility to toxicity. Once absorbed, the drug distribution varies considerably during the neonatal period and infancy largely due to age-related variations in protein binding, body fat, and total body water [16]. Overall, protein binding of drugs is reduced, and body fat and total body water are increased in the neonate. This may result in an increase in the apparent V_d and consequent increase in the elimination half-life of the drug. Furthermore, the reduction in protein binding may result in an increased concentration of free (unbound) drug with a potentially augmented pharmacological response for a given drug concentration in the plasma. As mentioned before, due to the immaturity of their liver function, this group of patients has a decreased capacity to metabolize drugs in the liver due to significantly lower activity of cytochrome P450-dependent mixed-function oxidases. In addition, the renal clearance of drugs is reduced, and various tubular functions are suboptimal.

Finally, successful usage of extracorporeal techniques in infants and young children is technically complex and can be carried out only in few specialized centers. Obtaining a suitable vascular access can also become very challenging. In these situations, exchange transfusion that can be easily performed in neonates may be used successfully for eliminating certain toxins that have a low V_d.

Extracorporeal Clearance

The efficacy of any extracorporeal therapy is assessed by the accurate determination of the amount of drug removed from the body. Several parameters such as dialysance or clearance, efficiency ratio, extraction ratio, and mass removal are commonly utilized to scientifically assess drug removal from the body in an attempt to determine the success or failure of the intervention.

Dialysance (D) is a measure of solute removal by dialysate and in most modern systems is technically same as clearance (C), as concentration of the toxic substance in the dialysate is minimal in single-pass dialysis with high dialysate flow rates. Clearance (C) for hemodialysis is expressed as:

$$C = Q_b \times (A - V) / A \tag{38.3}$$

where Q_b is the blood flow rate, A is the arterial or inlet concentration, and V is the venous or outlet blood concentration of the toxic substance. Note that (A – V)/A is termed the extraction ratio (E_x) that represents the solute removed as a fraction of the maximum it is theoretically possible to remove. For continuous renal replacement therapy, clearance (C) is expressed as:

$$C = E / P \times Qe \tag{38.4}$$

where E is the effluent concentration, P is the plasma concentration of the toxic substance, and Q_e is the effluent flow rate which can be Q_{uf} (ultrafiltrate), or Q_d (dialysate), or $Q_{uf} + Q_d$. The term E/P is also known as sieving coefficient that is equivalent to extraction ratio (E_x). As is apparent, these clearance calculations are based on plasma concentration of the substance, and the results can be misleading in terms of effectiveness of dialysis therapy unless drug distribution and inter-compartmental kinetics (vide supra) are also taken into account. To understand this better, consider a drug "x" with a large volume of distribution of 20 L/kg. One gram of this drug when given to a 30 kg child will yield a plasma concentration of 0.0016 mg/mL (eq. 2). With maximal extraction at a blood flow rate of 200 mL/min, clearance could theoretically be 200 mL/min, which is equivalent to drug removal of 0.32 mg/min or 76.8 mg in 4 hours, which is less than 10% of the total given dose. As illustrated by this example, the dialysis is highly efficient, but it is not very effective as the reduction in drug burden is minimal. However, it is conceivable but unproven that early pre-emptive initiation of ECT during the absorption and distribution phase may promote the removal of a significant amount of poison with a large V_d.

For clinical efficacy, one can compare the drug half-lives or their clearance rates from the

body with and without treatment; this is also known as efficacy ratio. Half-life is calculated as:

$$\text{Half-life}\left(t½\right) = 0.693/K_e$$
$$K_e = \left[\log\left(C_{peak}\right) - \log\left(C_{trough}\right)\right] / t_{interval} \quad (38.5)$$

where K_e is the elimination rate constant and C_{peak} and C_{trough} are two plasma levels separated by time interval "t" (these levels need not be "true" peak and trough as long as they are separated in time and realizing that the longer the interval, the better the estimate). Drug clearance is calculated as:

$$C = 0.693 \times V_d / t‰ \quad (38.6)$$

where V_d is the volume of distribution of drug in question. Efficacy ratio can then be calculated as t'½/t½ or C′/C, where t'½ and C′ are half-life and clearance with treatment and t½ and C are half-life and clearance without treatment, respectively.

Half-life calculation based on serial plasma concentrations obtained during ECT can help in estimating the duration of ECT to achieve a safe target concentration for the poison being removed.

Extracorporeal Modalities

Intermittent hemodialysis (IHD) that is one of the most common ECT was in fact utilized over more than 100 years ago (much before it became a well-recognized therapy for patients with end-stage kidney disease) for salicylate removal from poisoned animals [17]. By the 1970s, most poisonings were considered amenable to treatment by dialysis based on two intuitive assumptions: (1) ECTs can remove poison, and (2) removal of poison enhances survival [18]. This dichotomy is, however, well exemplified by paraquat toxicity; while paraquat has all the physical characteristics associated with high ECT clearance (i.e., low molecular weight, low protein binding, and low V_d), dialysis will generally not alter the dreadful clinical course unless it is initiated early after ingestion [19]. Conversely, dialysis seems to improve outcome of metformin poisoning, although metformin does not seem to be very dialyzable because of high V_d [20]. With these kinds of clinical situations, in addition to a better understanding of pharmacokinetic/toxicokinetic principles (vide supra), improvement in supportive care, availability of effective antidotes, and lack of any well-designed trials to test the efficacy of ECTs, the overall usefulness of ECTs became controversial and marred with uncertainty [21]. Nonetheless, the introduction of better (high-efficiency, high-flux) dialysis membranes that can remove poisons once considered undialyzable has permitted newer opportunities for their application. In summary, ECTs can play a crucial, if not essential, role in a subset of intoxications as discussed before.

Intermittent Hemodialysis (IHD)

Intermittent hemodialysis is the most widely available, least expensive, and the quickest to implement ECT modality [22]. For these reasons, IHD remains the preferred modality for the majority of poisonings. According to the NPDS 36th Annual Report, IHD was the most common (90%) of 2817 ECTs used for the management of poisoning [1]. During IHD, the poison diffuses down the concentration gradient from the plasma through a semipermeable membrane to dialysate flowing in a countercurrent direction. In contrast to other ECTs, HD removes the poison rapidly due to the high blood and dialysate flow rates. Because poisoned patients are at low risk of dialysis disequilibrium, IHD can be initiated with higher clearance, and the dialysis duration can be prolonged depending on the clinical context. As the metabolic derangements seen in patients with poisoning can be very different from patients with ESKD, dialysate composition should be tailored for the patient; in addition, high clearance and longer duration of IHD can cause hypokalemia and hypophosphatemia requiring replacement of both electrolytes.

While hemodialysis has a long track record for safety, it is associated with many potential complications that are outlined elsewhere in the text (see Chapters 24 and 25). In particular, one must be aware that the dialysis process may remove other drugs, such as antibiotics and

vasopressor agents. Thus, these drugs must be delivered distal to the dialyzer and will perhaps require higher doses to be effective. Nonetheless, currently IHD has supplanted all other ECT modalities and is the preferred ECT modality for removal of the majority of poisons.

Continuous Renal Replacement Therapy (CRRT)

Continuous renal replacement therapies provide clearance through both convection and diffusion mechanisms, either alone or in combination. For larger molecules, convection can provide better clearance than that achieved by diffusion. However, the total clearance with CRRT per unit time is 50% to 80% less than that obtained with IHD because of the lower effluent flow rates. This can be disadvantageous in a patient with acute poisoning and manifestations of cellular toxicity who requires rapid and immediately effective therapy. Nonetheless, CRRT has been historically favored for the removal of drugs that distribute in multiple compartments with slow equilibration. In these situations, CRRT has been considered beneficial as continuous removal of the drug from the vascular compartment maintains a favorable gradient and facilitates its release from the inaccessible compartments into the vascular compartment. As a result, the typical rebound phenomenon resulting in high serum levels due to redistribution seen after HD is not seen with CRRT modalities. The advantages of avoiding this rebound phenomenon are debatable [23]. Currently, CRRT usage is reserved only for patients who cannot tolerate HD due to hemodynamic instability. It should also be noted that, while receiving CRRT, the patients must remain immobile for prolonged times to ensure proper machine function.

Sustained Low-Efficiency Dialysis (SLED)

SLED is a hybrid technique usually provided as a prolonged treatment using both reduced dialysate and blood flow rates (Q_D and Q_B, respectively). Often times, SLED is reserved for hemodynamically unstable patients who would alternatively be candidates for CRRT [24]. SLED differs from CRRT in the following three key areas:

1. SLED is still an intermittent therapy with usual runs of 6 to 12 hours.
2. The dialysate flow rate (Q_D) is higher than that used during CRRT.
3. SLED can be administered using the standard HD equipment.

Even though SLED uses a higher Q_D than CRRT, small solute clearance between these two modalities is reportedly similar [25]. On the other hand, the modeled clearance of middle and large solutes during CRRT is greater than during SLED, likely due to the extended duration and additional convective clearance provided by CRRT [25].

Although SLED and CRRT may limit hemodynamic instability in patients requiring fluid removal, it is questionable if this would be the case in poisoned patients when no net ultrafiltration is required. When poison removal is urgent, SLED and CRRT are not the treatments of choice unless no other method is available or ultrafiltration is needed in an unstable patient [23, 26].

Therapeutic Plasma Exchange (TPE)

TPE is the extracorporeal blood purification technique used for removal of large molecular weight substances from plasma such as pathogenic autoantibodies, immune complexes, and endotoxins (see also Chap. 48). In general, a single exchange of 1 plasma volume (3 L for a 70 kg patient) removes approximately 63% of all solutes in the plasma, and an exchange of 1.5 plasma volume removes about 78% [27], which under normal conditions corresponds to removal of 40–60 ml of plasma/kg over 2–3 hours [28]. TPE's role in the treatment of acute poisoning is only considered for tightly and/or highly (>95%) protein-bound poisons with very low V_D (0.2 L/kg) and poisons with MW over 50,000 Da such as monoclonal antibodies [29, 30]. As most commonly encountered poisons are small or middle sized, there are no well-established clinical

indications for the use of TPE in the treatment of the poisoned patient. Nonetheless, there are reports that support its usage in patients with mushroom (Amanita Phalloides) [31], vincristine [32], and cisplatin [33] poisoning.

Exchange Transfusion

Exchange transfusion is rarely used for management of poisonings. It has been successfully used in management of toxicity with drugs that are highly bound to erythrocytes, like cyclosporine [34, 35] or tacrolimus [36]. Exchange transfusion has the advantage of being simpler to use in infants and has been tried in that population for poisonings with salicylates [37], theophylline [38], and barbiturates [39].

Hemoperfusion

During hemoperfusion, blood is percolated through a cartridge coated with activated charcoal (resin-coated cartridges are no longer used in many countries); poisons are adsorbed irrespective of their MW and protein binding, making this modality a better choice for highly protein-bound poisons [15]. These cartridges can also absorb lipid-soluble substances. Substances with molecular weight up to 40,000 Da are effectively removed by this technique. A standard hemodialysis machine can generally be used for hemoperfusion with a cartridge inserted in place of the dialyzer.

There are certain well-documented complications with hemoperfusion such as platelet depletion, drop in white blood cells, and clotting in the cartridge. It can also cause hypoglycemia and hypocalcemia and, as with any extracorporeal therapy, results in undesirable removal of other therapeutic drugs from the patient. The cartridges usually get saturated and must be changed every 4–6 hr. Finally, hemoperfusion does not correct acid-base or electrolyte abnormalities, nor volume overload. Thus, it may be necessary to perform hemodialysis in addition to hemoperfusion.

Despite the theoretical appeal of hemoperfusion for the treatment of intoxications, its use remains quite limited and decreasing over time. According to the NPDS 36th Annual Report, hemoperfusion was used for only 43 poisoning cases [1]. The cartridges are not freely available in all hospitals, and modern high-efficiency high-flux dialyzers may give clearance rates for certain poisons that approach those achieved with hemoperfusion.

Molecular Adsorbent Recirculating System (MARS)

The molecular adsorbent recirculating system (MARS) (see also Chap. 46) employs dialysis across a membrane impregnated with albumin and a 20% albumin dialysate, thus attracting highly protein-bound substances. In addition, charcoal and anion exchange resin cartridges are employed to filter the dialysate, regenerating it for continued use [40]. MARS may be of interest in the setting of poisons that have a predilection for liver toxicity, as the system is reportedly capable of removing certain hepatotoxins, restoring hemodynamics, diminishing hepatic encephalopathy, and improving renal function [40]. MARS is not available in many medical centers, and its role as ECT for poison removal is very limited.

Single-Pass Albumin Dialysis (SPAD)

In the absence of MARS availability, SPAD has been used with similar efficacy. Albumin can be added to the dialysate bag during CVVHD where it acts as a "sink" to bind any free toxin that crosses the dialyzer membrane with a concentration gradient from the blood to the dialysate side [41, 42]. 400 mL of 25% albumin (100 gm) is added to a 5 L bag of dialysate resulting in final albumin concentration of 1.85% [43]. Most of the clearance during CVVHD is then provided as diffusive clearance, but with very high dialysate flows, the running cost increases as albumin is not being regenerated for further use. This technique has been used with success in enhancing the clearance of valproic acid and carbamazepine [43, 44].

Peritoneal Dialysis

In peritoneal dialysis, the clearance kinetics is dependent on intrinsic characteristics of the membrane and the mesenteric circulation, and not amenable to significant external adjustments (see also Chap. 13). In cases with intoxication, peritoneal dialysis is only 10–25% as effective as hemodialysis. Thus, the role of peritoneal dialysis in detoxification is limited to situations where other modalities are not available, contraindicated, or not possible due to lack of vascular access.

The efficacy (in terms of time) of various ECTs in achieving a safe concentration in a patient poisoned with methanol is graphically illustrated in Fig. 38.2 [45]. The superiority of the IHD over other ECTs is clearly apparent.

Therapeutic Decisions

When confronted with a case of poisoning, the physician must consider many parameters in choosing the appropriate therapeutic modality. A simplified decision-making approach is provided in the algorithm (Fig. 38.3). The list of toxic substances that have been subjected to extracorporeal therapies is quite long, and information is available on more than 200 substances. However, the ability to remove a toxic substance by extracorporeal therapy is not equivalent to an indication for these procedures. One must take into account the patient's underlying health (including any comorbidities), the toxicity of the absorbed substance, the presence of or likelihood of advancing to severe illness, the availability of extracorporeal therapies, and the availability of acceptable alternatives (good supportive care, antidotes). While the availability of antidotes such as N-acetylcysteine, flumazenil, fomepizole, and Fab have significantly changed some clinical management plans, it is often impossible to identify the small group of patients who will fail to respond to intensive supportive care alone. Thus, the decision to institute extracorporeal therapy is based on clinical judgment. Some of the broad criteria as suggested by Winchester et al. [46] and Rosenbaum et al. [47] for initiating extracorporeal therapy are provided in Table 38.2.

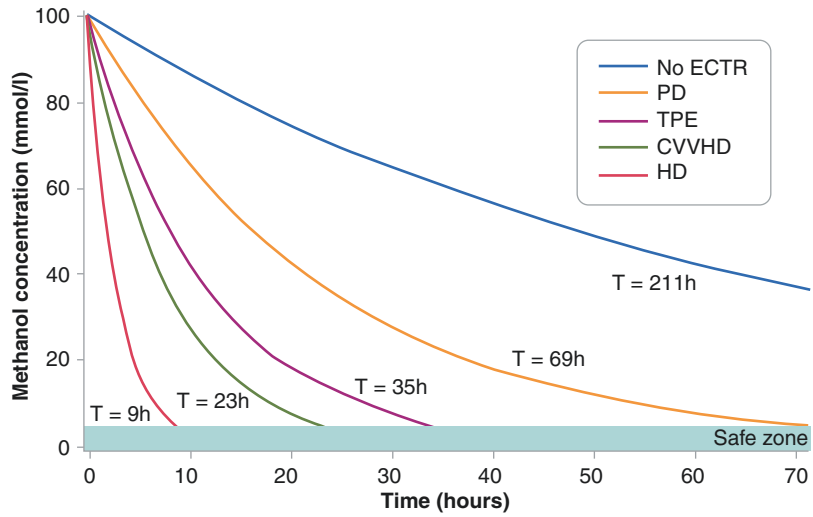
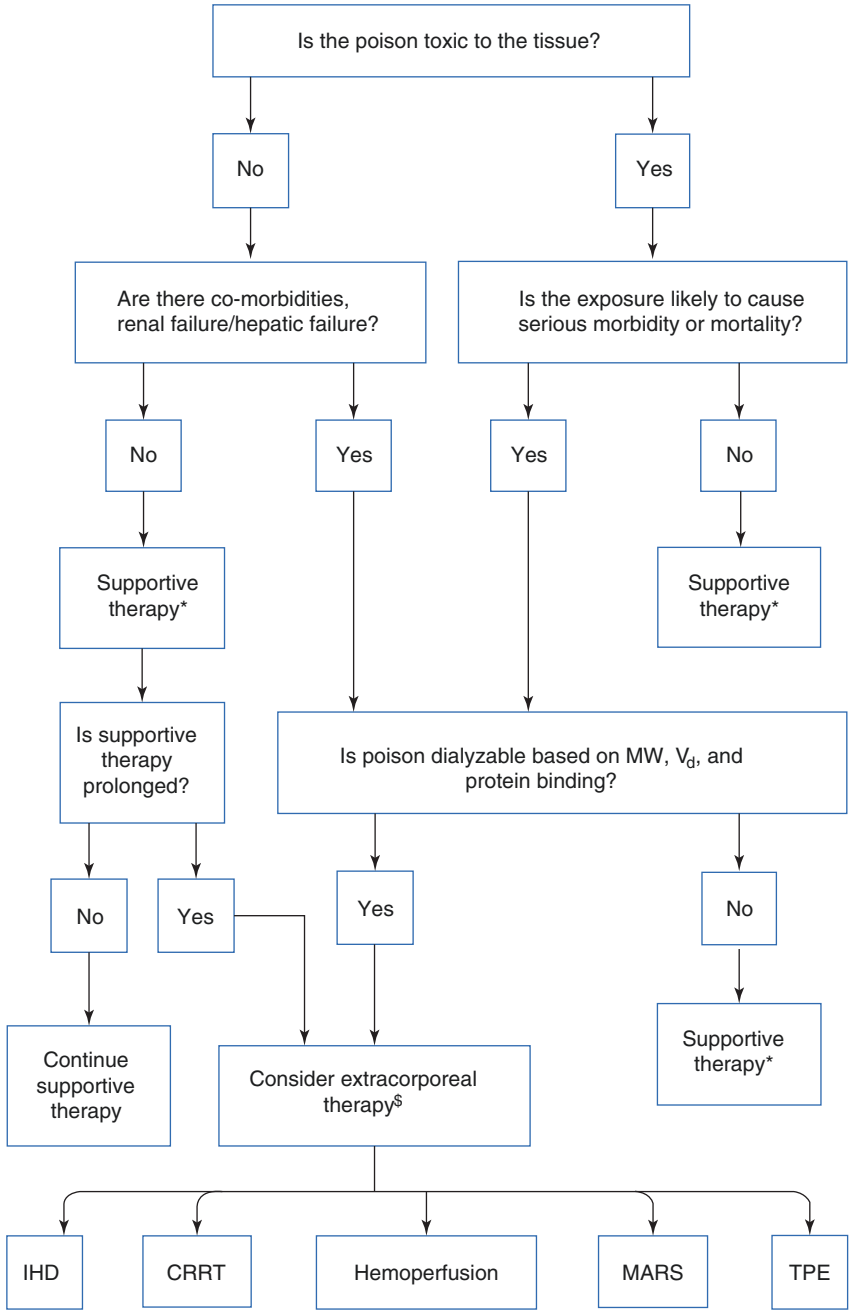


Fig. 38.2 Simulation of the effect of different extracorporeal treatments for methanol poisoning. Theoretical model of a methanol-poisoned patient with an initial concentration of 100 mmol/L (320 mg/dL) treated with fomepizole and either nothing, hemodialysis (HD), continuous venovenous hemodialysis (CVVHD), therapeutic plasma exchange (TPE), or peritoneal dialysis (PD). The time (T) to achieve a safe plasma concentration is shown. Assumptions are V_d = 0.6 L/kg, weight = 70 kg, endogenous body clearance of methanol with fomepizole = 10 ml/min, HD methanol clearance = 240 mL/min, CVVHD methanol clearance = 80 mL/min, TPE methanol clearance = 50 ml/min, and PD methanol clearance = 20 mL/min. (Modified from Ghannoum et al. [45])



*Specific antidote to be used when available; $ Choice of particular extracoporeal therapy is based on the type of poison and patient's hemodynamic staus. IHD: Intermittent hemodialysis; CRRT: Continuous renal replacement therapies; MARS: Molecular adsorbents recirculating system; TPE: Therapeutic plasma exchange.

Fig. 38.3 Simplified approach to a patient with poisoning

Table 38.2 Criteria for extracorporeal therapy (Modified from Refs. [46, 47])

Potentially lethal plasma concentration of intoxicant known to be cleared effectively from blood by extracorporeal therapy
Significant quantity of circulating toxin that is metabolized to a more noxious substance (e.g., methanol, ethylene glycol)
Ingestion and probable absorption of a potentially lethal dose
Severe clinical intoxication with abnormal vital signs
Impairment of normal route of excretion
Progressive clinical deterioration despite carful medical management
Prolonged coma with its potential hazards (e.g., aspiration pneumonia, septicemia)
Need for prolonged assisted ventilation
Persistent hypotension or need for vasoactive therapy
Poisoning by agents with delayed toxicity (e.g., paraquat).

Finally, although several studies have shown enhanced drug elimination using several techniques, the data regarding how these methods affect morbidity and mortality are often lacking.

In 2011, a multidisciplinary and multinational collaborative known as EXTRIP (Extracorporeal Treatment In Poisoning) was established to clarify the role of ECTs in clinical practice through the development of evidence- and expert opinion-based recommendations [13]. Since inception, the group has published treatment recommendations for 13 poisons that include acetaminophen, barbiturates, carbamazepine, digoxin, lithium, metformin, methanol, phenytoin, salicylates, thallium, theophylline, tricyclic antidepressants, and valproic acid [48–60]. The executive summaries of all EXTRIP recommendations are available at http://www.extrip-workgroup.org/recommendations.

More recently, the Pediatric Continuous Renal Replacement Therapy (PCRRT) workgroup have also published their recommendations on renal replacement therapy in the management of intoxications in children [61].

As detailed management of individual poisonings with ECTs and antidotes is beyond the scope of this chapter, the reader is referred to recently published recommendations from the EXTRIP and PCRRT workgroups. Summaries of some of the common poisonings and their management are included below, with most of the information derived from the EXTRIP recommendations [48–60].

Acetaminophen

Worldwide, acetaminophen is the most common analgesic used and, therefore, one of the most commonly overdosed medications; it is also the leading cause of drug-induced liver failure in many countries. The MW is 151 Da with V_d of 0.8 to 1 L/kg; the protein binding is low at 10–30% and does not change much with toxic levels. A single acute ingestion of >150 mg/kg in adults and >200 mg/kg in children is considered toxic with a lethal dose of >500 mg/kg. Although acetaminophen is readily dialyzable, ECT is not warranted in most cases, because of the effectiveness of N-acetylcysteine (NAC) especially with early and less severe presentations. The EXTRIP workgroup suggests ECT for severe acetaminophen poisoning when patients manifest signs of mitochondrial dysfunction (altered mental status and severe metabolic acidosis) prior to the onset of hepatic failure. Many patients with severe acetaminophen poisoning also develop AKI with or without associated hepatotoxicity which might be another indication for utilizing an ECT. Acetaminophen concentrations are typically obtained when absorption is thought to be complete at 4 hr. post ingestion or as soon as possible thereafter. Subsequent treatment decisions are guided by plotting the acetaminophen concentration on the Rumack-Matthew nomogram [48]. ECT is suggested if acetaminophen levels are more than 1000 mg/L (>700 mg/L with signs of mitochondrial dysfunction) and NAC has not been administered. ECT is suggested even after NAC has been administered when the levels are >900 mg/L and patient has signs of mitochondrial dysfunction. NAC should be continued during ECT, and the dose increased based on ECT (25% with CRRT and 50% with IHD) as NAC is dialyzable. IHD is the preferred modality for acetaminophen poisoning, but CRRT can be used as support for AKI or hepatic failure. Exchange transfusion can be used in neonates.

Continuation of ECT is recommended until sustained clinical improvement is apparent [48].

Salicylates

Salicylate (MW 180 Da) has low V_d of 0.2 L/kg (up to 0.5 L/kg in overdose); it is highly protein bound (90%), but the binding decreases to 30% with toxic levels. Salicylate toxicity primarily results from uncoupling of mitochondrial oxidative phosphorylation. The clinical manifestations range from tinnitus, vomiting, metabolic acidosis, primary respiratory alkalosis, agitated delirium, and/or somnolence; severe toxicity is associated with acute respiratory distress syndrome, AKI, hyperthermia, seizures, and shock. Most fatalities are due to cerebral edema. Events that lower blood pH can lead to rapid shifts of salicylate across the blood-brain barrier with worsening toxicity manifestations. Early consideration of ECT is critical in severe salicylate poisoning regardless of the salicylate blood concentration. Most sources acknowledge that clinical status is a more important factor than the salicylate concentration in the decision to initiate ECT. Nonetheless, high salicylate concentrations (>100 mg/dL and 90 mg/dL in the presence of impaired kidney function) are indications of ECT regardless of signs and symptoms. ECT is also suggested for severe acidosis (pH <7.2) even in the absence of other indications. IHD is the preferred ECT modality, and CRRT is an alternative as is exchange transfusion in neonates [56].

Barbiturates

Phenobarbital (the long-acting barbiturate) is the most frequently associated barbiturate in cases of self-poisoning. Hepatic metabolism is the main route of endogenous clearance of all barbiturates. Phenobarbital is a weak acid, and ~25% is excreted unchanged in the urine; it is amenable to enhanced removal using urinary alkalization. However, urinary alkalization is no longer recommended as first-line treatment because it does not increase the renal clearance significantly and multiple-dose activated charcoal (MDAC) is considered superior. Optimal supportive care is of paramount importance. Indications for ECT in a case of barbiturate poisoning are prolonged coma, respiratory depression necessitating mechanical ventilation, shock, persistent toxicity, or increasing or persistently elevated serum barbiturate concentrations despite treatment with MDAC. Serum concentrations >50 mg/L can induce coma, and concentrations >80 mg/L can be fatal. IHD is the preferred ECT; MDAC should be continued during ECT. Cessation of ECT is indicated when clinical improvement is apparent [49].

Carbamazepine

Carbamazepine has a narrow therapeutic index. Its structure is similar to tricyclic antidepressants. The MW is 236 Da with V_d of 0.8–1.4 L/kg; it is highly protein bound (70–80%), and the binding does not change with overdose. It is therefore only moderately dialyzable. MDAC is useful, but ECT is recommended in cases of multiple seizures that are refractory to treatment, life-threatening dysrhythmias, and prolonged coma or respiratory depression requiring mechanical ventilation. IHD is the preferred ECT modality and should be continued until clinical improvement is apparent [50]. Albumin-enhanced CVVHD has also been successfully used in a pediatric patient with severe carbamazepine overdose [44].

Valproic Acid (VPA)

VPA (MW 144 Da) has a low V_d (0.1–0.5 L/Kg) and exhibits saturable plasma protein binding with 94% bound at therapeutic concentrations (50–100 mg/L) and 15% when concentration exceeds 1000 mg/L. The increase in the free fraction (active drug) at higher total VPA concentrations likely leads to greater clinical toxicity. The drug is primarily metabolized in the liver and <3% is excreted unchanged in the urine. Severe VPA poisoning is associated with coma and respiratory depression requiring mechanical ventila-

tion, cerebral edema, hemodynamic instability, and shock that may lead to a fatal outcome. Most patients have a benign clinical course and require only supportive treatment. The use of MDAC in the treatment of VPA poisoning is currently not recommended. L-carnitine is proposed as an antidote for VPA poisoning. ECT is recommended for serum VPA concentration >1300 mg/L or patients with features of cerebral edema or shock. ECT is suggested for serum VPA concentration >900 mg/L, or patients with coma or respiratory depression requiring mechanical ventilation, or acute hyperammonemia or severe acidosis (pH <7.10). VPA is moderately dialyzable. IHD is the preferred ECT modality that should be continued until clinical improvement is apparent or the serum VPA concentration is between 50 and 100 mg/L [60]. Albumin-enhanced CVVHD has been used successfully in a pediatric patient with VPA overdose [43].

Phenytoin

Phenytoin is a small molecule (MW 252 Da) with a small V_d, but because of its extensive protein binding (90%), it is not readily dialyzable. Overdose is characterized by cerebellar and vestibular effects such as multidirectional nystagmus, dizziness, nausea, vomiting, and ataxia. Severe overdose may result in coma and marked respiratory depression. Death or irreversible injury following phenytoin poisoning is infrequent. Management of patients with phenytoin toxicity is largely supportive, although ECT could be reasonable in select cases of severe poisoning. IHD is the preferred ECT modality with intermittent hemoperfusion as an alternative [55].

Lithium

Lithium is a small molecule (MW 7 Da) and has low V_d (0.7–0.9 L/Kg) and no protein binding; therefore, it is readily dialyzable. While it may cause mild gastrointestinal and cardiac toxicity, the main toxic effects are seen in the central nervous system that include ataxia, myoclonus, and tremors. Severe manifestations include seizures, delirium, and coma. It is noteworthy that clinical presentation does not correlate well with lithium levels. ECT is recommended if lithium level is >4 mEq/L in the presence of renal impairment or in the presence of altered consciousness, seizures, or life-threatening dysrhythmias irrespective of the lithium level. ECT should be continued for a minimum of 6 hours if the lithium cannot be readily measured.

Unlike most toxins, lithium travels from cells to plasma via sodium channels and thus equilibrates more slowly than nearly all other dialyzable toxins. As a result, repeat HD sessions are commonly needed as rebound of plasma levels is seen several hours after HD. IHD is the preferred initial ECT modality for rapid resolution of life-threatening symptoms. This can be followed by repeated IHD sessions or a prolonged (~6 hr) HD session. CRRT remains a good alternative modality. Cessation of ECT is recommended when the lithium level is <1.0 mEq/L or clinical improvement is apparent or after a minimum of 6 hrs of ECT if ability to measure lithium level is not readily available [52].

Methanol

Methanol (MW 32 Da) is not bound to proteins and has a V_d of 0.6–0.8 L/Kg making it a readily dialyzable molecule. Methanol is metabolized by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase into formaldehyde and formic acid, respectively. Both of these metabolites cause direct mitochondrial toxicity affecting mainly the central nervous system resulting in blindness, coma, and paresis. As these consequences are secondary to neural tissue death, these are often poorly reversible. While ADH inhibitor fomepizole is commonly used to treat methanol poisoning, it does not remove the accumulated toxic metabolites (formaldehyde and formic acid), both of which are also readily dialyzable. As the endogenous clearance of methanol is very slow (t½ of ~50 hours), aggressive removal with ECT is often ideal especially in view of the high cost of fomepizole. The EXTRIP

workgroup recommends ECT for severe methanol poisoning with acidosis, seizures, or vision deficits or for serum concentration >70 mg/dL after fomepizole therapy; in the absence of fomepizole therapy, ECT is indicated for levels >50 mg/dL. IHD is the ECT modality of choice; CRRT is an alternative. Fomepizole (if available) should be continued during ECT. ECT can be discontinued when the methanol concentration is <20 mg/dL and a clinical improvement is observed [54].

Ethylene Glycol

Ethylene glycol is also a small alcohol molecule (MW 62 Da) with no protein binding and V_d of 0.5–0.8 L/kg and is, therefore, readily dialyzable. It is metabolized by ADH, followed by lactate dehydrogenase ultimately resulting in production of oxalate which is the metabolite primarily responsible for end-organ toxicity. The intermediate metabolite, glycolic acid, is mostly responsible for metabolic acidosis. Ethylene glycol toxicity results in sedation, coma, AKI, and occasionally CNS and myocardial damage. As access to real-time serum levels is uncommon, diagnosis of ethylene glycol poisoning commonly relies upon measuring the osmolality gap (the difference between the calculated and measured serum osmolality). Most patients with ethylene glycol poisoning can be treated with fomepizole alone in the presence of normal kidney function. ECT is recommended in the presence of severe acidosis, AKI, or unavailability of fomepizole. IHD is the ECT modality of choice with CRRT being an alternative [9].

Metformin

Metformin is a small molecule (MW 165 Da) with negligible protein binding and large V_d of 1–5 L/kg. Metformin undergoes limited metabolism and is eliminated largely unchanged by the kidneys. Endogenous clearance is usually >500 mL/min but decreases proportionately with decreasing renal function. Metformin-associated lactic acidosis (MALA) is uncommon but associated with a high mortality of 30%. Although MALA usually occurs in the presence of impaired kidney function, rarely a large acute overdose can also produce severe toxicity characterized by lactic acidosis, shock, and multi-organ failure. Metformin is moderately dialyzable, with an average t½ of 4 hours with HD and 16 hours with CRRT. The EXTRIP workgroup recommends HD for severe acidemia and lactate levels >20 mmol/L and suggests consideration of HD at lower levels with concomitant organ failure [53].

Conclusion

The field of toxicology continues to expand with the introduction of newer drugs and chemicals. Basic understanding of pharmacokinetic and toxicokinetic principles helps guide the management of patients with overdose and poisoning. While improvement in supportive care and the availability of antidotes have improved the outcome of several poisonings, ECTs continue to play an important but limited role. The background information provided in this chapter should help guide the nephrologist in making the right choices.

References

1. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, Hashem HA, Ryan ML. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. Clin Toxicol. 2019;57:1220–413.
2. Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose. Ed: Shannon MW, Borron SW, Burns M. 4th edition, Philadelphia, W. B. Saunders.
3. Gonda A, Gault H, Churchill D, Hollomby D. Hemodialysis for methanol intoxication. Am J Med. 1978;64(5):749–58.
4. Hill JB. Salicylate intoxication. N Engl J Med. 1973;288:1110–3.
5. Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. Arch Intern Med. 1981;141:380–5.
6. Fertel BS, Nelson LS, Goldfarb DS. Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. J Intensive Care Med. 2010;25:139–48.

7. Higgins RM, Connolly JO, Hendry BM. Alkalization and hemodialysis in severe salicylate poisoning: comparison of elimination techniques in the same patient. Clin Nephrol. 1998;50:178–83.
8. Franssen EJ, van essen GG, portman AT, de Jong J, Go G, Stegeman CA, Uges DR. Valproic acid toxicokinetics: serial hemodialysis and hemoperfusion. Ther Drug Monit. 1999;21:289–92.
9. King JD, Kern MH, Jaar BG. Extracorporeal removal of poisons and toxins. Clin J Am Soc Nephrol. 2019;14:1408–15.
10. Gibson T, Atkinson A, Loo J, Rowland M. Effect of changes in intercompartment rate constants on drug removal during hemoperfusion. J Pharm Sci. 1978;67:1178–9.
11. Amdisen A. Serum level monitoring and clinical pharmacokinetics of lithium. Clin Pharmacokinet. 1977;2:73–92.
12. Roberts DM, Buckley NA. Pharmacokinetic considerations in clinical toxicology: clinical applications. Clin Pharmacokinet. 2007;46:897–939.
13. Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (extracorporeal treatments in poisoning) workgroup: guideline methodology. Clin Toxicol. 2012;50:403–13.
14. Maher JF, Schreiner GE. The dialysis of poisons and drugs. Trans Am Soc Artif Intern Organs. 1968;14:440–53.
15. Ghannoum M, Roberts DM, Hoffman RS, Ouellet G, Roy L, Decker BS, Bouchard J. A stepwise approach for the management of poisoning with extracorporeal treatments. Semin Dial. 2014;27:362–70.
16. Routledge PA. Pharmacokinetics in children. J Antimicrob Chemother. 1994;34:19–24.
17. Abel JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the circulating blood by dialysis. Trans Assoc Am Phys. 1913;58:51–4.
18. Knepshield JH, Schreiner GE, Lowenthal DT, Gelfand MC. Dialysis of poisons and drugs-annual review. Trans Am Soc Artif Intern Organs. 1973;19:590–633.
19. Hampson EC, Pond SM. Failure of hemoperfusion and hemodialysis to prevent death in paraquat poisoning. A retrospective review of 42 patients. Med Toxicol Adverse Drug Exp. 1988;3:64–71.
20. Guo PY, Storsley LJ, Finkle SN. Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdoses of metformin. Semin Dial. 2006;19:80–3.
21. Ghannoum M, Nolin TD, Lavergne V, Hoffman RS, for the EXTRIP workgroup. Blood purification in toxicology: nephrology's ugly duckling. Adv Chronic Kid Dis. 2011;18:160–6.
22. Bouchard J, Lavergne V, Roberts DM, Cormier M, Morissette G, Ghannoum M. Availability and cost of extracorporeal treatments for poisonings and other emergency indications: a worldwide survey. Nephrol Dial Transplant. 2017;32:699–706.
23. Kim Z, Goldfarb DS. Continuous renal replacement therapy does not have a clear role in the treatment of poisoning. Nephron Clin Pract. 2010;115:c1–6.
24. Fiaccadori E, Maggiore U, Parenti E, Greco P, Cabassi A. Sustained low-efficiency dialysis (SLED) for acute lithium intoxication. Nephrol Dial Transplant. 2008;24:329–32.
25. Liao Z, Zhang W, Hardy PA, Poh CK, Huang Z, Kraus MA, Clark WR, Gao D. Kinetic comparison of different acute dialysis therapies. Artif Organs. 2003;27:802–7.
26. Goodman JW, Goldfarb DS. The role of continuous renal replacement therapy in the treatment of poisoning. Semin Dial. 2006;19:402–7.
27. Kale-Pradhan PB, Woo MH. A review of the effects of plasmapheresis on drug clearance. Pharmacotherapy. 1997;17(4):684–95.
28. El-Ghariani K, Unsworth DJ. Therapeutic apheresis-plasmapheresis. Clin Med. 2006;6(4):343–7.
29. Sketris IS, Parker WA, Jones JV. Plasmapheresis: its effect on toxic agents and drugs. Plasma Ther Transfus Technol. 1984;5:305–17.
30. Hastings D, Patel B, Torloni AS, et al. Plasmapheresis therapy for rare but potentially fatal reaction to rituximab. J Clin Apher. 2009;24:28–31.
31. Jander S, Bischoff J, Woodstock BG. Plasmapheresis in the treatment of Amanita phalloides poisoning: II. A review and recommendations. Ther Apher. 2000;4:308–12.
32. Pierga JY, Beuzeboc P, Dorval T, Palangie T, Pouillart P. Favourable outcome after plasmapheresis for vincristine overdose. Lancet. 1992;340:185.
33. Chu G, Mantin R, Shen YM, Baskett G, Sussman H. Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management. Cancer. 1993;72:3707–14.
34. Kwon SU, Lim SH, Rhee I, kim SW, Kim JK, Kim DW, Jeon ES. Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. J Heart Lung Transplant. 2006;25:483–5.
35. Moorman MT, Epstein RB, Smith JW, O'Neal C, Holter JL. Management of cyclosporine overdose in a hematopoietic stem cell transplant patient with sequential plasma exchange and red blood cell exchange. J Clin Apher. 2011;26:156–8.
36. McCarthy H, Inward C, Marriage S, Astley P, Tizard EJ. Red cell exchange transfusion as a rescue therapy for tacrolimus toxicity in a pediatric renal transplant. Pediatr Nephrol. 2011;26:2245–8.
37. Manikian A, Stone S, Hamilton R, Foltin G, Howland MA, Hoffman RS. Exchange transfusion in severe infant salicylism. Vet Hum Toxicol. 2002;44:224–7.
38. Osborn HH, Henry G, Wax P, Hoffman R, Howland MA. Theophylline toxicity in a premature neonate – elimination kinetics of exchange transfusion. J Toxicol Clin Toxicol. 1993;31:639–44.

39. Sancak R, Kucukoduk S, Tasdemir HA, Belet N. Exchange transfusion treatment in a newborn with phenobarbital intoxication. Pediatr Emerg Care. 1999;15:268–70.
40. Sen S, Jalan R. The role of the Molecular Adsorbents Recirculating System (MARS) in the management of liver failure. Perfusion. 2004;19:43–8.
41. Patzer J. Principles of bound solute dialysis. Ther Apher Dial. 2006;10:118–24.
42. Ouellet G, Bouchard J, Ghannoum M, Decker BS. Available extracorporeal treatments for poisoning: overview and limitations. Semin Dial. 2014;27:342–9.
43. Chadha V, Pattaragarn A, Lowry J, Garg U, Blowey DL. Enhancement of valproic acid removal during CVVHD by the addition of albumin to dialysate. (Abst). Pediatr Nephrol. 2002;17:C149.
44. Askenazi DJ, Goldstein SL, Chang IF, Elenberg E, Feig DI. Management of a severe carbamazepine overdose using albumin enhanced continuous venovenous hemodialysis. Pediatrics. 2004;113(2):406–9.
45. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Use of extracorporeal treatments in the management of poisonings. Kidney Int. 2018;94:682–8.
46. Winchester JF. Dialysis and hemoperfusion in poisoning. Adv Ren Replace Ther. 2002;9:26–30.
47. Rosenbaum JL, Kramer MS, Raja RM, et al. Current status of hemoperfusion in toxicology. Clin Toxicol. 1980;17:493–500.
48. Gosselin S, Juurlink DN, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, Hoffman RS, on behalf of the EXTRIP group. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. Clin Toxicol. 2014;52:856–67.
49. MactierR LM, Mardini J, Ghannoum M, Lavergne V, Gosselin S, Hoffman RS, Nolin ND, on behalf of the EXTRIP workgroup. Extracorporeal treatment for barbiturate poisoning: recommendations from the EXTRIP workgroup. Am J Kid Dis. 2014;64:347–58.
50. Ghannoum M, Yates C, Galvao TF, Sowinski KM, THV V, Coogan A, Gosselin S, Lavergne V, Nolin TD, Hoffman RS, on behalf of EXTRIP workgroup. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2014;52:993–1004.
51. Mowry JB, Burdmann EA, Aneeuw K, Ayoub P, Ghannoum M, HoffmanRS LV, Nolin TD, Gosselin S, on behalf of EXTRIP workgroup. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2016;54:103–14.
52. Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, Lavergne V, Nolin TD, Ghannoum M, on behalf of EXTRIP workgroup. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin J Am Soc Nephrol. 2015;10:875–87.
53. Calello DP, Liu KD, Wiegand T, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M, on behalf of EXTRIP workgroup. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the extracorporeal treatments in poisoning workgroup. Crit Care Med. 2015;43:1716–30.
54. Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, Nolin TD, Lavergne V, Hoffman RS, Ghannoum M, on behalf of the Extracorporeal Treatments in Poisoning Workgroup. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43:461–72.
55. Anseeuw K, Mowry JB, Burdmann EA, Ghannoum M, Hoffman RS, Gosselin S, Lavergne V, Nolin TD, on behalf of the EXTRIP workgroup. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP (extracorporeal treatments in poisoning) workgroup. Am J Kid Dis. 2016;67:187–97.
56. Juurlink DN, Gosselin S, Kielstein JT, Ghannoum LV, Nolin TD, Hoffman RS, on behalf of the EXTRIP workgroup. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP workgroup. Ann Emerg Med. 2015;66:165–81.
57. Ghannoum M, Nolin TD, Goldfrab DS, Roberts DM, Mactier R, Mowry JB, Dargan PI, MacLaren R, Hoegberg LC, Laliberte M, Calello D, Kielstein JT, Anseeuw K, et al. Extracorporeal treatment for thallium poisoning: recommendations from the EXTRIP workgroup. Clin J Am Soc Nephrol. 2012;7:1682–90.
58. Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS, on behalf of the EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Theophylline. Clin Toxicol. 2015;53:215–29.
59. Yates C, Galvao T, Sowinski KM, Mardini K, Botnaru T, Gosselin S, Hoffman RS, Nolin TD, Lavergne V, Ghannoum M, on behalf of the EXTRIP workgroup. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP workgroup. Semin Dial. 2014;27:381–9.
60. Ghannoum M, Laliberte M, Nolin TD, MacTier R, Lavergne V, Hoffman RS, Gosselin S, on behalf of the EXTRIP workgroup. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol. 2015;53:454–65.
61. Raina R, Grewal MK, Blackford M, Symons JM, Somers MJG, et al. Renal replacement therapy in the management of intoxications in children: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRT) workgroup. Pedaitr Nephrol. 2019;34:2427–48.

Part VII

Outcome of Chronic Dialysis

39 Long-Term Outcome of Chronic Dialysis in Children

Masataka Honda, Chikako Terano, Tomohiro Inoguchi, Kaori Kikunaga, Ryoko Harada, and Jaap W. Groothoff

Introduction

In developed countries, chronic dialysis and kidney transplantation in children have become standard approaches to end-stage kidney disease (ESKD) care since the early 1970s. Contrary to the situation in adults, few patients with childhood-onset ESKD have experienced a long course of dialysis. Kidney transplantation, preferably preemptive without prior dialysis, is widely accepted as the optimal mode of chronic renal replacement therapy (RRT) for children who have ESKD. Yet, in practice, most children with ESKD have initiated RRT management with dialysis while awaiting the availability of a kidney to be transplanted. In some cases, dialysis is required for a longer time, either before initial transplantation or following the loss of an initial transplant when retransplantation is much more difficult to accomplish. As a result, patients with childhood-onset ESKD have most often experienced one or more courses of short-term dialysis and a long period with a functioning graft. Data on the long-term effects of dialysis during childhood are therefore scarce; however, variable access to kidney transplantation, even within developed countries, has provided important insights into the consequences of long-term dialysis in children.

In this chapter, we review existing data on the long-term outcome of RRT in children, focusing on the role of dialysis and its associated potential long-term hazards. We pay special attention to one of the most life-threatening late technical complications of peritoneal dialysis (PD), encapsulating peritoneal sclerosis (EPS). Most of the data included in the chapter come from registry studies, all of which have the important limitation of incomplete and unverified data. Another limitation is that almost all of the data come from developed countries, with only a few reports from other countries that account for a large part of the world.

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Epidemiology

Worldwide and Nationwide Registries

While there is little information on long-term outcomes in children receiving dialysis, some worldwide, nationwide, and regional registries provide valuable data. Prominent national and international registries consulted here include the following: the United States Renal Data System (USRDS), which is a compulsory registration system that includes children under 21 years of age in the USA; the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which contains voluntary data reporting derived from children under 21 years of age in North America; the United Network for Organ Sharing (UNOS), which collects data on all patients who are registered for kidney transplantation in the USA; the European Society for Paediatric Nephrology, the European Renal Association, and the European Dialysis and Transplant Association (ESPN/ERA-EDTA), which is a voluntary organization that coordinates an international European RRT registry for all patients; and the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry, which is a comprehensive, compulsory database which includes information from children and adolescents with chronic kidney disease (CKD) who initiate RRT at up to 20 years of age in Australia and New Zealand. Additional national registries which include limited long-term data pertaining to dialysis in children include the following: United Kingdom Renal Registry, National Dutch Registry (RENINE/LERIC study), Italian Registry (Italian Registry of Pediatric Chronic Peritoneal Dialysis), Polish Registry, Canadian Organ Replacement Register (CORR), Registry of Taiwan, and the Japanese Registry (Japanese Study Group of Pediatric Peritoneal Dialysis [JSPPD]) [1–18].

Age, Modality, and Primary Kidney Disease at the Start of Dialysis

When preemptive transplantation is not feasible for the pediatric patient who develops ESKD, PD and hemodialysis (HD) are the only available options. The initial dialysis modality chosen for pediatric patients might be a factor that influences long-term outcomes. HD is most often used as the initial treatment modality for ESKD in adults [10], while HD and PD are chosen with near-equal frequency in children. However, the dialysis modality at RRT initiation varies greatly by country. The initial treatment modality by country based on registry data is shown in Table 39.1.

Overall, dialysis is chosen for approximately 75–80% of pediatric patients as the first treatment modality for management of ESKD. Whereas in the ESPN/ERA-EDTA, ERA-EDTA, and USRDS registries HD was recorded as the initial treatment prescribed for 40–55% of patients [8–12], HD was the initial modality for only 15–35% of patients in the ANZDATA, Polish, Canadian, UK, and Japanese Registries [13–18] (Table 39.1).

When the initial dialysis modality was examined by era using data from the ERA-EDTA and the ANZDATA registries, there was no difference in the choice of the first treatment regimen [12, 16]. However, when the relationship between age at the start of dialysis and modality was analyzed, the proportion of patients prescribed PD was higher for younger children with ESKD, and the proportion of patients initially prescribed HD gradually increased with age, as shown in Fig. 39.1 [10]. In the 2018 USRDS report, PD was the most common initial ESKD treatment modality for children aged 9 years and younger, and HD was the most common initial modality for patients aged 10 years and older. Based on data from other registries as well, HD was used more often in older children, while PD was the preferred therapy in children less than 5 years of age (Table 39.2). In

the Italian Registry, the median age at the start of dialysis in 295 PD patients was 7.7 ± 4.8 years, whereas the median age of the 1163 HD patients was 11.4 ± 3.1 years; 102 PD patients (34%) and only three HD patients were less than 5 years of age at the initiation of dialysis [19].

The primary kidney disease in patients with ESKD also varies by age and country (Table 39.3). Congenital anomalies of the kidney and urinary tract (CAKUT) are the main causes of ESKD across all age groups worldwide. Hereditary nephropathies are common in the youngest group of patients, while focal segmental glomerulosclerosis (FSGS) and glomerulonephritis have been found to be less common in the youngest age groups, especially those less than 5 years of age. Thus, the primary potential confounding factors in any analysis of initial dialysis modality in children are patient age at initiation and the country in which the child was being treated.

Long-Term Dialysis in Pediatric Patients

Even among children for whom dialysis was chosen as the first RRT modality, most have received a kidney transplant within a few years. The time to transplant has become shorter over time, and thus the dialysis duration has also become shorter. As a result, unlike in adults, there is little information on children who undergo long-term dialysis awaiting kidney transplantation.

The Polish Registry has reported a median duration of dialysis in children of 1.83 years (range, 0.2–16.3 years), while the CORR Registry revealed a median duration of dialysis of 559.5 days in 2004 and 388 days in 2012 [17, 20]. Over 50% of patients in the ANZDATA Registry who received RRT between 1963 and 2002 received their first kidney transplant within 1 year of starting dialysis, and over 90% received a kidney transplant within 3 years [16]. Since 2005, the median time from dialysis initiation to initial transplant in the USA has continued to decrease, and it was at its lowest in 2015, at 12.9 months in the USRDS Registry. In 2015, the median time to transplant was shorter for HD patients (12.1 months) compared with PD patients (13.6 months; Fig. 39.2) [10]. The Dutch late outcome cohort study, Late Effects of Renal Insufficiency in Children (LERIC), of 249 children with an onset of RRT at age 0–15y between 1972 and 1992 reported a mean dialysis time of survivors of 4.7 years (HD 2.3 years; PD 2.4 years) and 19.7 transplant years after a mean follow-up of 25.5 RRT years [5]. In 2010, five and 33 out of 249 patients had received PD and HD for more than 10 years, respectively [21].

In the ESPN/ERA-EDTA Registry, Kaplan-Meier survival curve analysis showed that among the 500 and 2591 patients who started HD before and after 5 years of age, respectively, there were 14.7% and 18.4% patients who continued HD 3 years later. These figures were 12.0% and 22.1%, respectively, for the 1498 and 1884

Table 39.1 Initial treatment modality for ESKD

Registry	Age (years)	PD (%)	HD (%)	RTX (%)	Reference
ERA-EDTA	0–19	25	53	23	[8, 12]
ESPN/ERA-EDTA	0–14	38	41.4	20.3	[11]
USRDS	0–21	25.7	51.2	20.0	[9, 10]
ANZDATA	0–18	48.3	33.9	17.7	[16]
Poland	0–18	61.5	32.3	6.2	[13]
Japan	0–19	60.6	15.7	21.9	[14]
Canada	0–19	50.2	27.1	22.7	[17]
UK	0–15	45	35	22	[15]

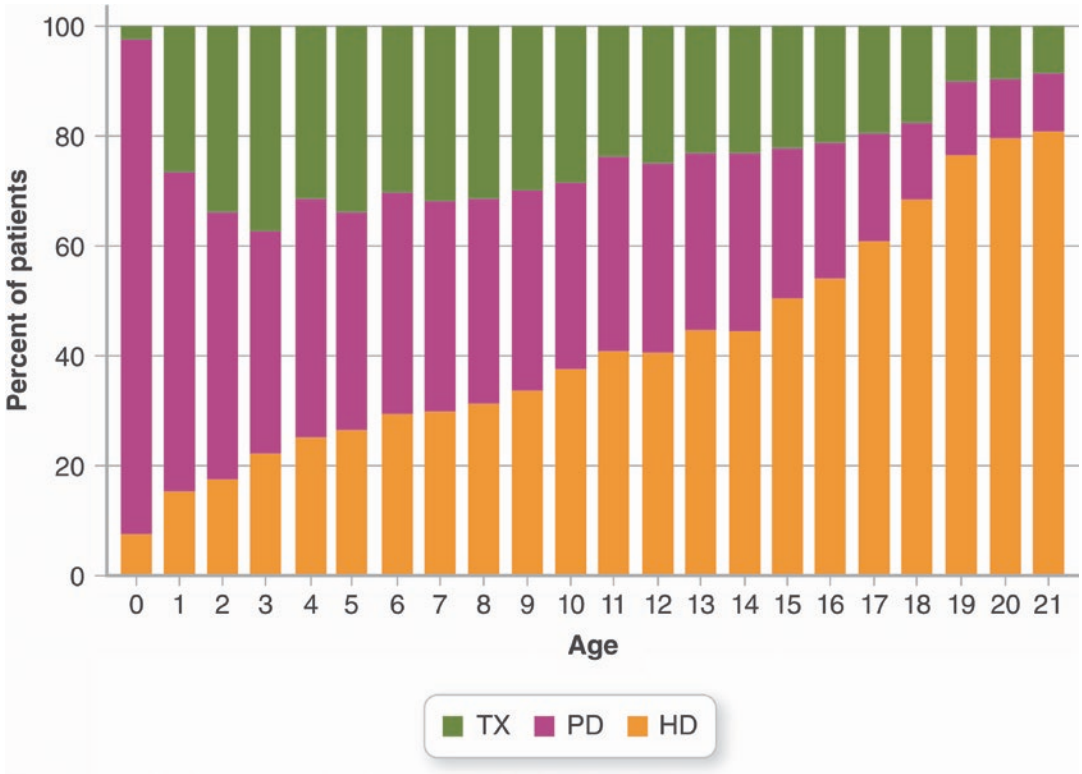
PD peritoneal dialysis, *HD* hemodialysis, *RTX* renal transplantation

patients who initiated PD before and after 5 years of age [22]. In the USRDS Registry, among the 845 and 5103 patients who started dialysis before and after 5 years of age, there were 8.2% and 22.1% patients, respectively, who continued dialysis 5 years later [23].

Based on these data, most children with ESKD who have received dialysis as their initial RRT modality received a kidney transplant within a few years, and the times to transplant and dialysis duration have decreased over time. However, there seems to be a subset of patients in whom dialysis has been continued for more than 5 to 10 years, especially in children over 5 years of age who are undergoing PD. Since there is a widely dispersed experience with patients undergoing long-term dialysis (e.g., for 5 or 10 years), these data have only rarely been analyzed or reported.

Patient Survival

The patient survival following dialysis initiation in those who received PD or HD is shown in Table 39.4. The survival rate at 5 years on PD



TX transplantation, *PD* peritonela dialysis, *HD* hemodialysis

Fig. 39.1 Renal replacement therapy modality at initiation by patient age from USRDS. (Modified from Ref. [10])

Table 39.2 Initial treatment modality for ESKD by age

	Japan [14] (2006–2011)				ANZDATA [16] (2012–2017)		ERA-EDTA [12] (2011–2016)			
Age	0–4 y	5–9 y	10–14 y	15–19 y	0–9 y	10–17 y	0–4 y	5–9 y	10–14 y	15–19 y
PD	87.3%	55.0%	54.9%	37.3%	58.0%	42.0%	58.8%	23.2%	16.9%	13.4%
HD	8.2%	11.0%	14.6%	31.4%	28.0%	38.0%	29.4%	42.7%	50.2%	64.8%
RTX	2.5%	32.0%	28.7%	29.7%	15.0%	20.0%	11.8%	34.1%	32.9%	21.8%

PD peritoneal dialysis, *HD* hemodialysis, *RTX* renal transplantation

Table 39.3 Primary kidney disease in patients with ESKD

	ERA-EDTA [12]				Japan [14]				ANZDATA [16]				ESPN/ERA-EDTA [22]		NAPRTCS [25]
Age	0–4 y	5–9 y	10–14 y	15–19 y	0–4 y	5–9 y	10–14 y	15–19 y	0–4 y	5–9 y	10–14 y	15–19 y	0–5 y	6–18 y	0–20 y
CAKUT	35.7	35.6	33.9	23.4	43.0	45.0	40.2	30.5	42.0	26.0	36.0	13.0	34.9	30.6	30.3
hypo-/dysplastic kidney									27.0	15.0	22.0	6.0			14.2
reflux nephropathy									0.0	5.0	7.0	2.0			3.5
PUV									15.0	6.0	7.0	5.0			12.6
Glomerulonephritis	15.2	16.3	14.6	22.2	0.0	6.0	6.1	13.6	4.0	20.0	20.0	34.0	13.3	20.6	11.9
FSGS					3.8	16.0	15.2	16.1	2.0	12.0	7.0	9.0			14.4
Cystic kidney disease	9.5	15.9	12.5	5.8	10.8	10.0	11.6	5.1	6.0	5.0	2.0	5.0	8.7	9.5	2.9
Hereditary nephropathy	14.5	6.1	6.5	6.6	19.0	7.0	10.4	13.6	4.0	0.0	2.0	1.0	10.2	6.0	1.8
HUS	3.3	2.7	1.7	3.2	1.0	1.2	1.7	1.7	0.0	0.0	3.0	1.0	6.1	3.3	3.1
Metabolic disorder	1.8	2.7	3.1	1.4					0.0	0.0	0.0	1.0	2.7	2.5	0.6
Missing, unknown	9.3	13.9	16.3	19.6	5.1	4.0	8.0	12.6	37.0	23.0	17.0	26.0	9.6	7.9	7.5

CAKUT congenital anomalies of the kidney and urinary tract, *PUV* posterior urethral valves, *FSGS* focal segmental glomerulosclerosis, *HUS* hemolytic uremic syndrome

was 86.0–92.0% and on HD was 84.0–87.3% in the registry of the USRDS, Italian Registry, Registry of Taiwan, and the JSPPD; likewise, the combined 5-year survival on HD and PD was 89.5% in the ESPN-ERA/EDTA registry [10, 12, 19, 22, 24, 25].

Figure 39.3a, b show the estimated patient survival rates for children aged <5 years and ≥5 years, respectively, at the beginning of ESKD treatment with dialysis, based on data derived from the USRDS Registry [23]. The survival rate in those who initiated dialysis at <5 years of age was worse than in those aged ≥5 years; however, the rate has improved significantly in recent years. The same trend was observed with the NAPRTCS data: the age at dialysis initiation has had an impact on patient survival, and the survival rate has improved in recent years [25]. The Taiwan Registry has provided similar data – a significant risk of decreased survival was associated with a younger age at the start of dialysis compared with older patients (Fig. 39.4) [24].

Mortality Rate

Mortality rate by dialysis modality and patient age at initiation is shown in Table 39.5. Data on mortality risk are significantly influenced by the follow-up time: the longer the follow-up time, the lower the adjusted hazard. For instance, the Polish registry with a follow-up time between 7 and 14 years showed a mortality rate that was 74 times higher for children with ESKD when compared to children without ESKD. In contrast, the mortality rates were "only" 30 times greater than normal in both the ANZDATA and the Dutch LERIC study, both long-term outcome studies with a follow-up of more than 20 years [4, 5]. In the LERIC study, having received HD longer than PD was associated with a 2.1 times increased mortality risk (CI 95% 1.0–4.4); having been on dialysis longer than the time with a transplant was associated with a 7.2 (CI 95% 2.7–11.8) times increased risk for premature death [5].

Recent reports from the ESPN/ERA-EDTA and USRDS are in line with these observations. The mortality rate was highest during the first year of dialysis in both reports and decreased progressively with time on dialysis [10, 22, 23]. The overall mortality rate in the ESPN/ERA-EDTA Registry was reported as 28 deaths per 1000 patient-years for the period 2000–2013; the rate was 39 deaths per 1000 patient-years for 2011–2015 in the USRDS Registry [9, 22]. According to the latter database, this implies an expected remaining lifetime of 20.6–22.8 years for dialysis patients aged 0–19 years of age as compared to 63.7–77 years for children in the general population and 52.1–57.7 years for transplanted patients aged 0–19 years [10].

Cause of Death

Cardiopulmonary events and infection have been cited as the most common causes of death in all registries, accounting for as many as 50% of deaths in all age groups (Table 39.6). The historical long-term outcome data derived from ANZDATA, German, and Dutch studies have shown that cardiovascular disease (CVD) has the greatest impact (41–50%) on mortality, whereas the more recent registry reports mention mortality rates secondary to CVD of around 20% [4, 5, 20, 22–26].

The ANZDATA Registry reported that the cause of death varied with the type of RRT: cardiovascular causes accounted for 57% of deaths among children receiving HD and 43% of deaths among those receiving PD [4]. This is in line with other studies of CVD in young patients with CKD and on dialysis, which report a 10- to 20-times higher risk of cardiovascular death compared with the healthy age-adjusted population [27, 28]. Although infection was also a major cause of death in the ANZDATA Registry, there is evidence that the proportion of deaths attributed to infection decreased over time, from 39% (12 of 31 deaths) between 1963 and 1972 to 16% (26 of 163) between 1993 and 2002 [4]. The NAPRTCS

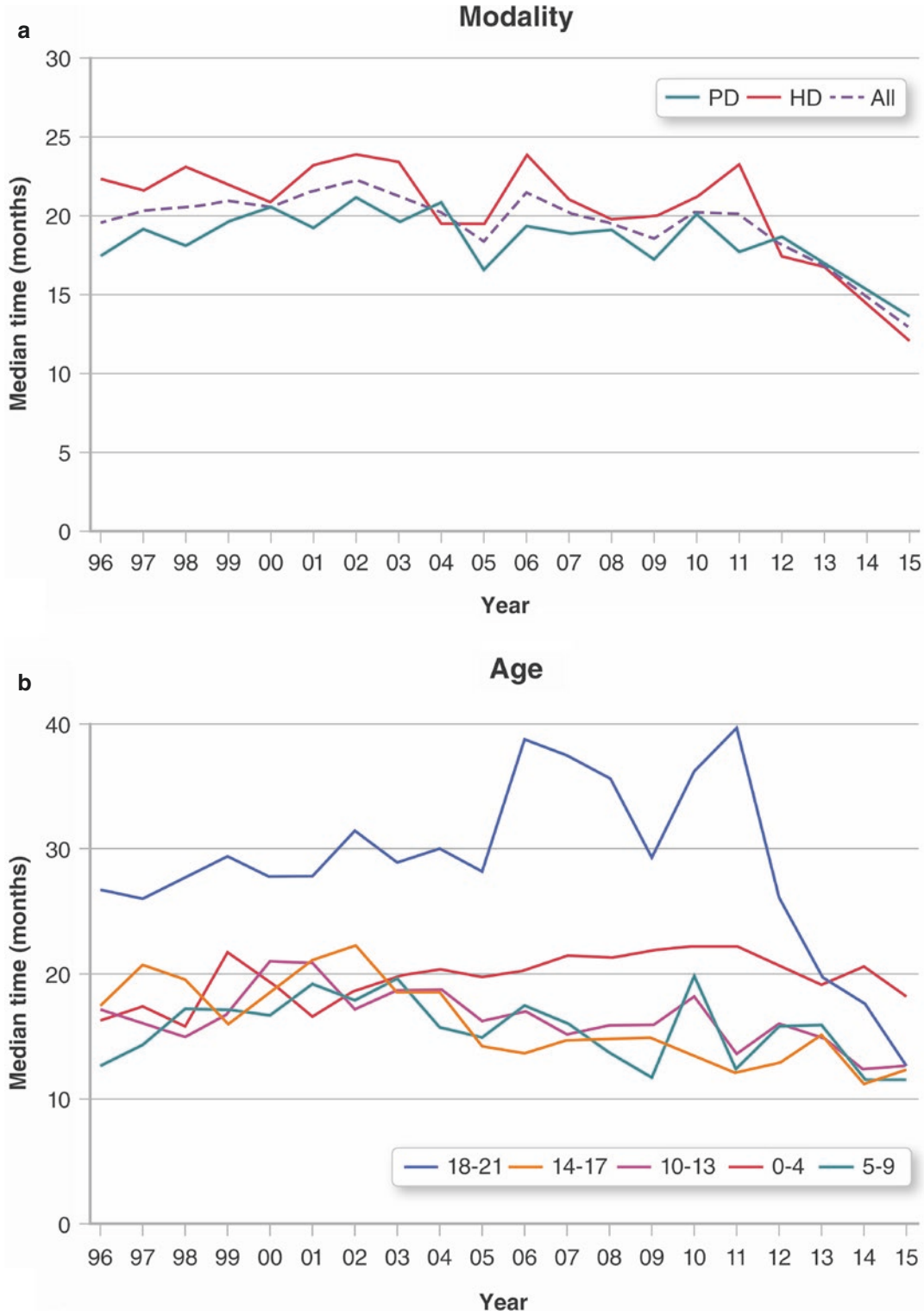


Fig. 39.2 Median time from incident dialysis to first transplant by modality and age, from USRDS. (Modified from Ref. [10])

Table 39.4 Survival rate of pediatric dialysis patients

	USRDS [10] (0–21 years)			Italy [19] (0–14 years)		Taiwan [24] (0–18 years)		Japan [30] (0–15 years)		ESPN/ERA-EDTA [22] (0–19 years)	ERA-EDTA [12] (0–19 years)
Modality	HD	PD	RTX	PD	HD	PD	HD	PD < 1992	PD ≥ 1992	PD + HD	PD + HD
1 year	96.0	97.0	99.0	96.5	98.3	98.1	96.9	96.0	97.0	96.6	96.1
2 years	96.0	94.0	98.0	95.2	96.9					94.5	93.7
3 years	90.0	92.0	98.0	91.6	96.9	91.9	89.9	88.0	95.0		
4 years	87.0	89.0	97.0	91.6	96.9						
5 years	84.0	86.0	86.0	87.5	96.9	88.0	87.3	82.0	92.0	89.5	87.4
7 years						77.7	84.3	77.0	84.0		
10 years						68.4	78.5	71.0	71.0		

PD peritoneal dialysis, *HD* hemodialysis, *RTX* renal transplantation

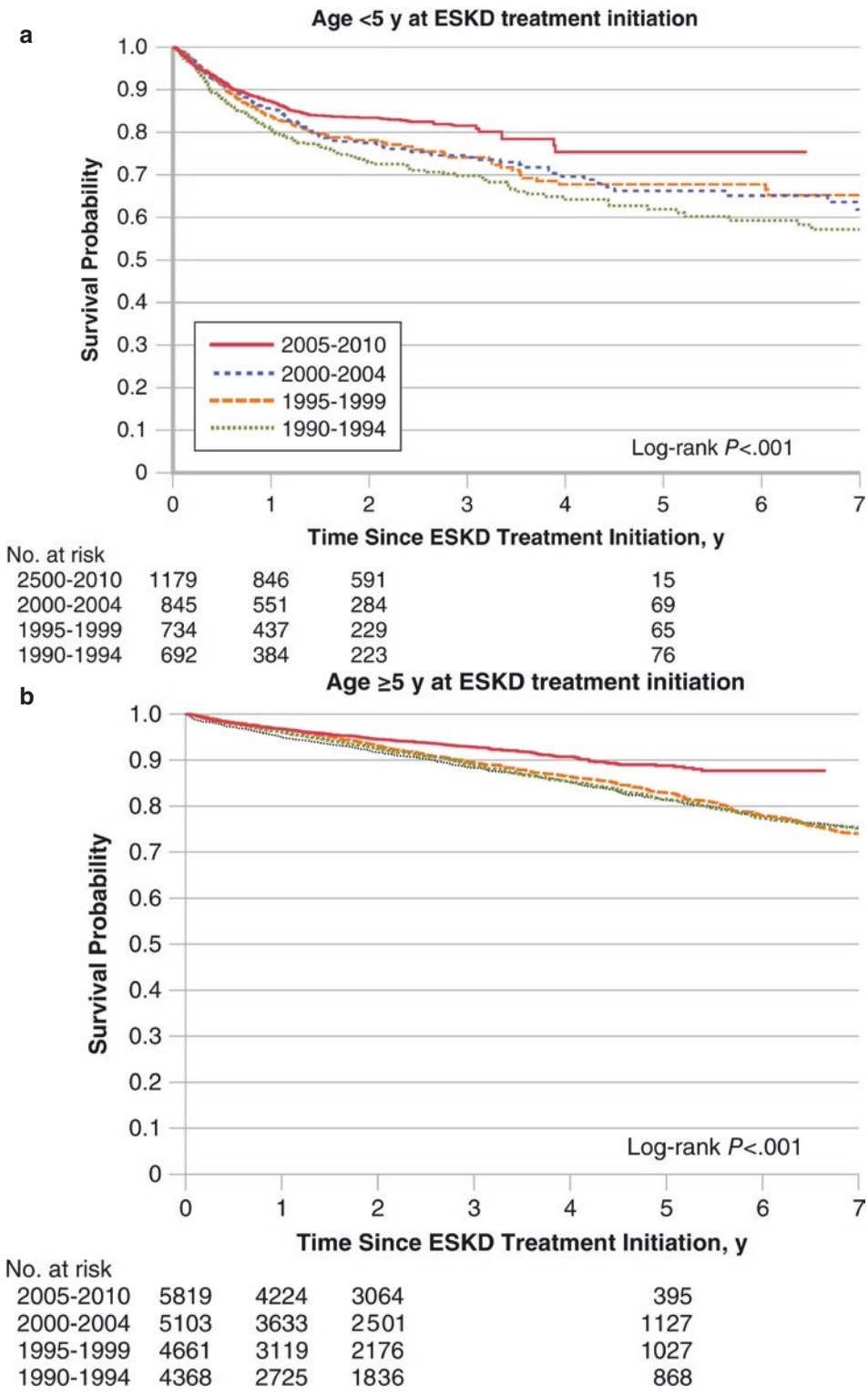


Fig. 39.3 (**a**) Kaplan-Meier estimate of survival for children initiating ESKD treatment at age < 5 years with dialysis (USRDS Registry, 1990–2010). (Modified from Ref. [23]). (**b**) Kaplan-Meier estimate of survival for children initiating ESKD treatment at age ≥ 5 years with dialysis (USRDS Registry, 1990–2010) [23]

Registry has also reported infection to be a common cause of death in the youngest patients on dialysis [29]. In the LERIC study, however, in which patients were followed from RRT initiation in 1972–1992 up to 2010, the infection-related mortality rate over time was U-shaped with a decrease in the mortality rate ratio from 502 in 1972–1992 to 101.8 in 1990–1999, followed by an increase to 352.6 in 2000–2010, the latter likely reflecting the increased impact of transplant years vs. dialysis years over time [21].

The cause of death in association with a very prolonged course of dialysis has only been reported by the Japanese Registry. Honda et al. reported the causes of death in Japanese patients who initiated PD ($n = 843$) and who had received PD for more than 5 years. Major causes of death for patients who continued PD for less than 5 years were heart failure (18%), pneumonia (12%), pulmonary edema (12%), and shock/sudden death (12%). However, in those who continued PD for more than 5 years, the major causes of death were peritonitis (13%), heart failure (13%), cerebrovascular disorder (13%), EPS (7%), sepsis (7%), and pneumonia (7%). Death resulting from peritonitis and encapsulating peritoneal sclerosis (EPS) was only seen in long-term PD patients [30].

Mortality Risk

Young age, era of onset of dialysis, and social factors are the most important determinants of dialysis-related mortality.

Age: Very young age at the initiation of dialysis is an important mortality risk factor according to all outcome studies. In patients initiating dialysis at less than 5 years of age, the crude mortality rate was 57 per 1000 patient-years for patients starting HD and 47.3 per 1000 patient-years for those starting PD, according to the ESPN/ERA-EDTA Registry; this is in contrast to mortality rates of 20.6 and 11.1 per 1000

Table 39.5 The 5-year crude mortality rate with PD and HD reported by ESPN/ERA-EDTA [22]

	HD (deaths/1000 py)	PD (deaths/1000 py)	Total (deaths/1000 py)
0–5 y	57.0	47.3	49.4
6–18 y	20.6	11.1	16.5
Total	26.9	29.0	28.0

PD peritoneal dialysis, *HD* hemodialysis, *py* patient-years

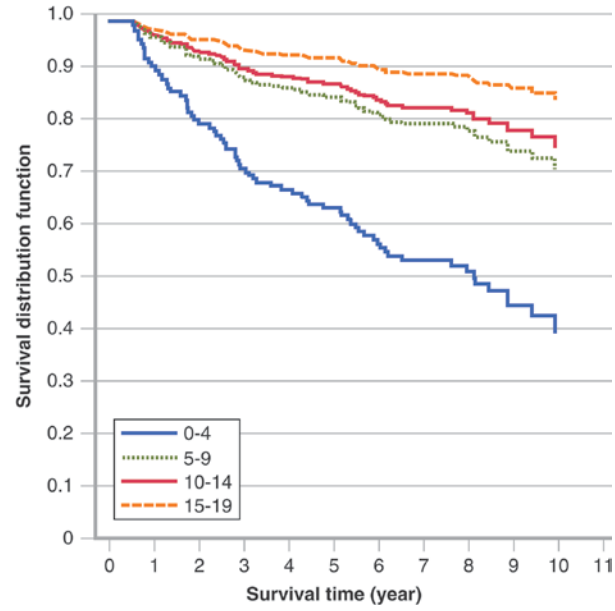


Fig. 39.4 Survival rates between 1995 and 2004 in Taiwan based on age at dialysis initiation. (Modified from Ref. [24])

Table 39.6 Cause of death

	Polish registry [13]			NAPRTCS [25]					NAPRTCS [36]		ESPN/ERA-EDTA [11]	ANZDATA [4]		Japan [14]
	PD	HD	RTX	Total	0–1 y	2–5 y	6–12 y	≥13 y	1992–2001	2002–2011		PD	HD	PD
Infection	34	27	50	21	23.4	16.9	16.4	22.9	21.2	17.1	20.3	43	57	39.3
CVD	23	23	12.5								8.9			17.9
Cardiopulmonary				21.3	22.8	18.3	19.1	22.1	21.4	20.2				
Sudden death	19	15	0								10.3			
Cerebrovascular accident	8	8	0								6.6			0
Hyperkalemia	0	8	0											
Malignancy	8	11	0	6.8	2.9	12.7	8.5	5.7	6.8	6.1	3.1	2	1	0
Hemorrhage				4.3	2.3	1.4	6.4	5	4.3	2				
Dialysis-related complications				3.1	1.8	4.2	4.3	4.3	3.2	6.1				
Other	8	4	3	27.5	25.1	32.4	29.1	26.4	27.8	23.2	17.1			21.4
Unknown	0	4	0	15	20.5	12.7	14.9	12.1	13.9	24.2	30			14.2

PD peritoneal dialysis, *HD* hemodialysis, *RTX* renal transplantation, *CVD* cardiovascular disease

patient-years, for those older than 5 years and on HD and PD, respectively [22] (Table 39.5). In a USRDS study that included information on 23,401 children who started RRT between 1990 and 2010, the mortality rate was 98.8 per 1000 patient-years in children aged <5 years at the onset of therapy and 38.6 per 1000 patient-years for children aged >5 years [23]. In the Canadian long-term outcome study, age at onset of RRT of <1 year was associated with a 7.8 (CI: 4–15) times increased risk of death as compared to those patients age 10–18 years [17].

Era: Since the introduction of chronic dialysis in children, survival of these children has improved over time. The 2018 USRDS report has demonstrated a gradual decline of the 1-year all-cause mortality rate from 49 in 2006–2010 to 39 per 1000 patient-years in 2011–2015. The greatest reduction was found in infants with a 39% reduction in mortality between 2006–2010 and 2011–2015, as compared to a 13.3% reduction in children aged 2–5 years [10] (Fig. 39.3a, b). In the USRDS study of children starting RRT between 1990 and 2010, the mortality rate for patients aged <5 years at RRT treatment initiation dropped from 112.2 per 1000 patient-years in 1990–1994 to 83.4 per 1000 patient-years in 2005–2010; for children with RRT onset at age >5 years, these figures were 44.6 and 25.9 per 1000 patient-years in the two eras [23]. The ESPN/ERA-EDTA Registry reported that 306 deaths occurred in 10,910 patient-years, which is equivalent to a mortality rate of 28.0 per 1000 patient-years during the first 5 years of dialysis treatment [22]). The Taiwan Registry also showed a significant risk of decreased survival associated with a younger age at the start of dialysis compared with older patients (Fig. 39.4) [24]. In the NAPRTCS database, the 3-year survival increased from 90.8% in 1992–1994 to 93.4% in 2004–2006 [25].

HD vs. PD Most registries report a trend toward a higher mortality rate in HD patients as compared to PD patients, with recognition that selection bias and unmeasured case-mix differences might have had pivotal influence on the outcomes. In the ESPN/ERA-EDTA Registry, patients with HD as their initial RRT modality had an adjusted mortality hazard of 1.39 (95% CI 1.06–1.82, adjusted for age, gender, country) compared to those on PD; the adjusted mortality hazard increased to 1.7 during the first year of dialysis, but the difference disappeared after 1–2 years [22]. The 2018 USRDS report revealed the 1-year all-cause mortality rates for HD and PD patients, respectively, to be 5.2 and 2.2 times higher than for transplanted patients [10].

Socioeconomic Status and Race The scarce data on children with ESKD in poorly resourced countries show evidence of worse outcomes as compared to children in developed countries. Of the 90 children with ESKD who were treated with chronic dialysis between 2001 and 2012 in Egypt, for instance, 17 patients died during 11 years of follow-up and only three patients were transplanted [31]. However, a recent study of the ESPN/ERA-EDTA demonstrated that even within Europe, a significant, socioeconomically determined variation in mortality among children on RRT exists between countries. The public health expenditure explained 67% of the variation in RRT-related death among children between countries [32]. The wealthiest countries showed no difference in the 5-year mortality risk between those children treated with HD and PD, whereas in countries with a GDP of less than $ 35,000, patients on HD had an increased mortality risk of 1.66 (1.19–2.3) over those on PD [32]. European and American studies have also demonstrated racial disparities that may impact outcome in the treatment of children with ESKD. A Belgian-Dutch cohort study showed that patients of non-Western origin had a significantly longer time to transplantation (median 30 vs. 15 months) than Western patients [33]. The ESPN/ERA-EDTA Registry also showed that within the European countries, black children and children of Asian origin were less likely to be transplanted over time than Caucasian children (HR 0.49 CI 95% 0.34–0.71 and 0.54 CI 95% 0.41–0.71, respectively) [34]. In the USA, according to USRDS data from 1990 to 2010, black race vs.

white race (HR 1.32 CI 95% 1.21–1.44), public instead of private insurance (HR 1.37 (CI 95% 1.17–1.60), and low socioeconomic status (HR highest economic status vs. lowest 0.82 (CI 95% 0.73–0.092) were all independently associated with a higher mortality risk in children with an onset of RRT at age ≥5 years [7].

Technique Failure Rate

Approximately 8–25% of patients require a change in dialysis modality during their course of dialysis. The Italian Registry report of 295 patients revealed that 14.9% of children on PD and 7.4% of children receiving HD experienced modality failure. The time to technical failure was 29.1 (range, 1.4–102.2) months and 3.6 (range, 1.2–11.5) months for the PD and HD patients, respectively [19]. A similar result was seen in the NAPRTCS Registry data which showed that 17.4% of children on dialysis changed their dialysis modality. Most HD patients who changed their modality did so within the first 6 months, while PD patients appear to have had a slow and steady increase in the rate of modality change over time (Fig. 39.5) [25].

Based on data from the ESPN/ERA-EDTA Registry, including 1063 infants aged 12 months or younger who initiated dialysis therapy, the overall cumulative incidences for dialysis modality switching at 1, 2, and 5 years were 14.5% (range, 12.4–16.7%), 19.7% (range, 17.3–22.2%), and 25.5% (range, 22.7–28.3%), respectively. Patients on HD had a 1.64-fold higher risk of changing dialysis treatment compared to patients on PD. This effect remained even after adjustment for confounders and was stronger during the first year of dialysis therapy (Fig. 39.6) [35]. The causes of dialysis failure are shown in Tables 39.7 and 39.8 [19, 35, 36].

Infection, especially peritonitis/exit site infection, was the major reason for modality change for patients receiving PD, while patient/family choice and vascular access failure were the major reasons for changing from HD. In the long-term data, peritonitis and ultrafiltration (UF) failure were the main reasons for changing dialysis modality in PD patients. The NAPRTCS Registry in particular found that the primary reason for a change in dialysis modality in their earlier cohort (1992–2001) was frequent infection, compared with patient/family choice in their later cohort (2002–2011). PD patients were also most likely to change modality because of infection, whereas HD patients were more likely to change modality because of patient choice [36]. Similar data have been published by the Italian Registry: the cause

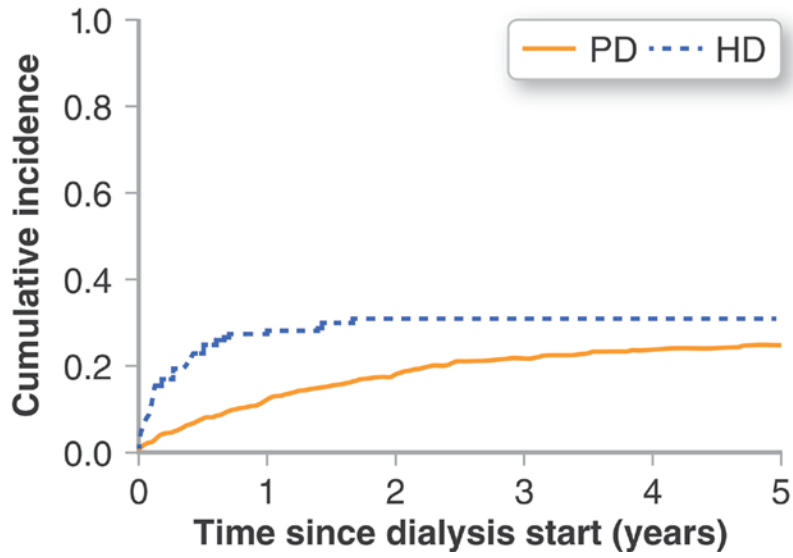


Fig. 39.5 Time to dialysis termination by dialysis modality (NAPRTCS Registry). (Modified from Ref. [25])

and time to technique failure are reported in Table 39.8. Peritonitis/exit site infection was the main reason for changing modality among patients on PD. In five of six patients with a loss of peritoneal function, it occurred in the third year of PD or later. For HD patients, dialysis access failure and patient/family choice were the most frequent causes of technique failure [19]. Data from the ESPN/ERA-EDTA Registry revealed that HD therapy was most often withdrawn because of patient/family decision and poor central catheter function in infants [35]. The reason for the high incidence of HD termination in the first months of a patient's course on HD as a result of a family decision might be that HD is most often performed in the hospital and patients need to receive long and frequent HD, which commonly forces them to live restricted and difficult lives.

The best long-term PD data are available from the Japanese Registry. Honda et al. have reported the causes of PD termination and the outcome of Japanese children under 16 years of age who received PD (n = 843). The technique survival rate on PD significantly improved over time: at 5 years, the technique survival rate was 78% for patients starting PD during or after 1992 compared to a technique survival rate of only 64% for patients who initiated PD before 1992. However, it is of interest that no difference in technique survival of patients on PD was seen before or after 1992 in the cohort of patients who had received

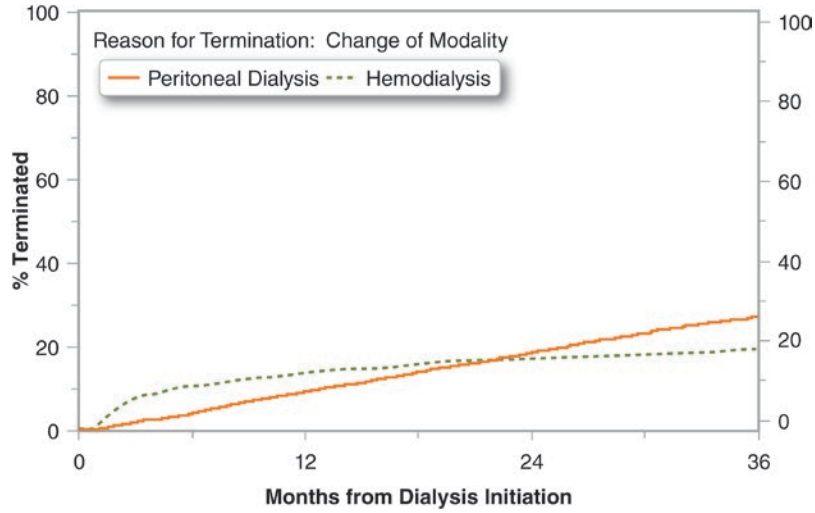


Fig. 39.6 Cumulative incidence curve for modality switching (ESPN/ERA-EDTA Registry). (Modified from Ref. [8])

Table 39.7 Cause of dialysis failure

	NAPRTCS [36]		ESPN/ERA-EDTA [35]	
	1992–2001 (n = 682)	2002–2011 (n = 211)	PD (n = 198)	HD (n = 44)
Frequent infection	32.6	22.7	76	
Patient/family choice	18.6	26.5	6.5	56
Access failure	10.3	9.5	2.2	20
Membrane failure	74	6.6	4.4	–
Excessive hospitalization	1.9	3.8		
Other	17.6	18.5	10.8	20
Unknown	11.4	12.3		

NAPRTCS data are for pediatric patients and ESPN/ERA-EDTA data are for infants aged 12 months or younger who were started on dialysis therapy
PD peritoneal dialysis, *HD* hemodialysis

Table 39.8 Cause and time of technique failure in PD and HD patients reported by the Italian Registry (1989–2000) [19]

	PD (n = 44)		HD (n = 12)	
	(%)	Months (range)	(%)	Months (range)
Peritonitis/exit site infection	65.9	28.6 (1.4–77.1)	–	–
Patient/family choice	2.3	86	50	3.8 (1.5–8.1)
Access failure	2.3	2	50	3.4 (1.2–11.5)
Technical complication	15.9	12.7 (1.5–32.6)	–	–
Membrane failure	13.6	46.3 (7.3–102.2)	–	–
Total	44	29.1 (1.4–102.2)	12	3.6 (1.2–11.5)

Months mean duration of dialysis treatment at technique failure, *PD* peritoneal dialysis, *HD* hemodialysis

PD for more than 8 years. In the patients who received PD for more than 5 years, PD was terminated in 44 children (29%) because the patients underwent transplantation. Transfer to HD occurred in 14 children (35%) because of peritonitis, in 13 children (33%) because of UF failure, in 5 children (13%) because of insufficient dialysis, and in 8 children (20%) for other causes. A higher percentage of transfer to HD because of UF failure and/or under dialysis (46% of total transitions) was associated with a longer period of PD care (Table 39.9) [37].

Most important was the finding that long-term PD (e.g., >8 years) was associated with the potential development of EPS. Membrane failure resulting from causes other than bacterial peritonitis was observed in patients who had been on PD for more than 5 years. In these patients, peritoneal biopsy commonly showed peritoneal sclerosis with membrane thickening. Therefore, membrane failure and EPS may be the main problems for long-term PD

Table 39.9 Outcome and cause of PD termination in children after 1991 [30]

		<5 years	≧5 years
		n (%)	n (%)
Total		527	151
Continuance of PD		148(28)	43(29)
Transplantation		244(46)	44(29)
Recovery		14(3)	1(1)
Unknown, lost		37(10)	8(6)
Transfer to HD		50(10)	40(27)
Cause of transfer HD	Peritonitis	28(56)	14(35)
	UF failure	7(14)	13(33)
	Insufficient dialysis	6(12)	5(13)
	Catheter trouble	3(6)	0(0)
	Other, unknown	6(12)	8[a](20)
Death		34(7)	15(10)
Cause of death	Peritonitis	0(0)	2(13)
	Sepsis	1(3)	1(7)
	Pneumonia	4(12)	1(7)
	Cerebrovascular disorder	2(6)	2(13)
	Heart failure	6(18)	2(13)
	Pulmonary edema	4(12)	0(0)
	Shock, sudden death	4(12)	0(0)
	Others, unknown	13(36)	7[b](53)

PD peritoneal dialysis, *HD* hemodialysis, *UF* ultrafiltration

[a]Long-term PD (three patients), after surgery (two), patient's request (two), psychological problem (one)

[b]Convulsion (one patient), EPS (one), unknown (two), original disease (two), gastric perforation (on

patients, even in the absence of bacterial peritonitis [37].

Complications of Long-Term Dialysis

Cardiovascular Disease

CKD, ESKD, and dialysis treatment are well-known risk factors for CVD in adult patients, especially those adults who receive long-term dialysis. Cardiovascular events in dialysis patients include cardiac failure, ischemic heart disease, arrhythmia, cardiomyopathy, valvular heart disease, and peripheral vascular disease.

The morbidity and mortality rates for patients with CVD are higher in adult dialysis patients compared with the normal population. The incidence of sudden cardiac death and fatal arrhythmia in adult dialysis patients has been found to be 5–7%, which is 25- to 70-fold higher compared with the general population [38–40]. Adult cardiovascular mortality rates are approximately ten- to 20-fold higher in dialysis patients compared with the general population [40], and it accounts for approximately 50% of deaths in chronic dialysis patients [41]. Therefore, guidelines for the management of CVD in adult dialysis patients have been published, including the European Best Practice Guidelines issued by the ERA-EDTA and the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines that were issued by the National Kidney Foundation [42, 43]. Although these guidelines describe various cardiovascular risk factors in dialysis patients, long-term dialysis itself was not included as a risk factor for CVD.

CVD is also an important complication in pediatric dialysis patients and impacts their long-term outcome. The most common CVD event in pediatric dialysis patients is arrhythmia, followed by vascular heart disease and cardiomyopathy [43]. CVD is also one of the most important causes of death in pediatric dialysis patients, as noted previously. Many registry studies have shown the association between pediatric dialysis patients and CVD mortality (Table 39.10).

CVD has been shown to be responsible for approximately 21% of deaths in pediatric dialysis patients in the NAPRTCS Registry [36], and CVD-related mortality accounted for 18.3% of deaths in pediatric dialysis patients based on registry data from 36 European countries [22]. Likewise, the Australia and New Zealand Dialysis and Transplant Registry long-term outcome study reported that 57% of HD patients and 43% of PD patients died as a result of CVD, indicating that premature CVD is without question a life-threatening complication of prolonged dialysis, although some of these deaths may have occurred during adulthood as part of long-term follow-up [4]. Finally, a Japanese registry of pediatric PD patients, including a substantial proportion of long-term dialysis patients because of the decreased frequency of kidney transplantation in Japan, reported that CVD-related mortality was the leading cause of death in patients who were on PD for fewer than and more than 5 years, accounting for 18% and 13% of death in these patients, respectively [37].

Table 39.10 Cardiovascular mortality in pediatric RRT patients

Author	Year published	Year date collected	No. of subjects	Total deaths	%CVD deaths
Weaver [36]	2017	1992–2011	6482 Dialysis patients	539	21.1%
Chesnaye [22]	2016	2000–2013	6473 Dialysis patients	306	18.3%
McDonald [4]	2004	1963–2002	1634 RRT patients	PD 97 HD 197	HD 57% PD 43%
Honda [30]	2010	1991–2003	<5 years 527 ≧5 years 151 PD patients	<5 years 34 ≧5 years 15	<5 years 18% ≧5 years 13%

RRT renal replacement therapy, *PD* peritoneal dialysis, *HD* hemodialysis

In pediatric dialysis patients in contrast to adult patients, however, CVD is usually asymptomatic because these patients have a different disease composition compared with adults, and the CVD does not often result in serious outcomes such as ischemic heart disease or death. Thus, surrogate markers, including left ventricular hypertrophy (LVH), left ventricular mass index (LVMI), and carotid artery intima-media thickness (CIMT), are most often used in clinical studies on CVD in pediatric dialysis patients. There are also no guidelines specifically for the management of CVD in pediatric dialysis patients, other than those related to blood pressure management. It is important to recognize that uncontrolled hypertension is the only proven modifiable factor that is associated with mortality secondary to CVD, and registry data from the USRDS and the ESPN/ERA-EDTA provide evidence that blood pressure management remains suboptimal [22, 23].

Long-Term Dialysis and CVD in Adults

It is well known that CVD-related mortality is high during the first year of dialysis in adult dialysis patients. However, an increased risk of CVD in association with long-term dialysis has also been reported [44].

Risk factors for CVD in dialysis patients are classified into traditional risk factors, including age, hypertension, diabetes, and smoking, and kidney disease-related risk factors, such as extracellular fluid volume overload, vascular calcification, hyperphosphatemia, oxidative stress, vascular endothelial dysfunction, chronic inflammation, and anemia. These risk factors worsen the cardiac function in dialysis patients in a complex manner (Fig. 39.7) [44, 45].

Long-term dialysis patients have an increased risk of CVD as a result of the long-term exposure to many of these risk factors. Typically, long-term extracellular fluid volume excess and erythropoietin therapy, as well as a reduction in vascular compliance because of progressive arteriosclerosis, result in refractory hypertension in many patients, which is associated with a significant increased risk for left ventricular hypertrophy and subsequent cardiac failure. As noted above, there have also been many reports of a high incidence of arrhythmia and vascular and valvular calcification in adult long-term dialysis patients [46–48].

Long-Term Dialysis and CVD in Children

While there are fewer pediatric long-term dialysis patients compared with the adult dialysis population, there have been a few reports pertaining to children using the CVD surrogate markers of LVH and CIMT, which have addressed their relationship to the duration of dialysis.

Litwin et al. measured the CIMT, the wall cross-sectional area (WCSA), and the lumen cross-sectional area (LCSA) using ultrasonography in 24 patients with CKD stages 3–5 (CKD group) and in 32 patients with ESKD (19 post-HD renal transplant recipients [D-Rtx] and 13 HD patients [D-D]) who were less than 18 years old, and these parameters were normalized to standard deviation scores (SDS). The CIMT-SDS and WCSA-SDS were significantly higher in the patients with a history of dialysis compared to those with CKD (D-D 2.2 ± 1.4 years, D-Rtx 2.3 ± 1 year vs. CKD 1.0 ± 1.5 years, $P < 0.001$). Additionally, the total duration of dialysis was correlated with the CIMT-SDS 1-year post-renal transplantation ($r = 0.46$, $P < 0.01$) [49].

Oh et al. assessed the CIMT in 39 patients with ESKD with childhood-onset CKD (HD patients, PD patients, and transplant recipients with a history of dialysis who were 19–39 years of age) using high-resolution ultrasound. The cumulative time on dialysis was 6.9 ± 6.3 years in HD patients, 2.3 ± 3.5 years in transplant recipients with a history of HD, 2.5 ± 3.1 years in PD patients, and 1.5 ± 2 years in transplant recipients with a history of PD. In addition to serum calcium, the total duration of dialysis predicted CIMT independently (partial $R^2 = 0.10$, $P = 0.03$) [26]. The Dutch LERIC study showed increased vascular stiffness in a cohort of 130 patients aged 20–40 years with onset of dialysis at age <15 years, as expressed by an increased incremental elasticity on carotid ultrasound; the duration of uncontrolled hypertension and age were the most important determinants [50].

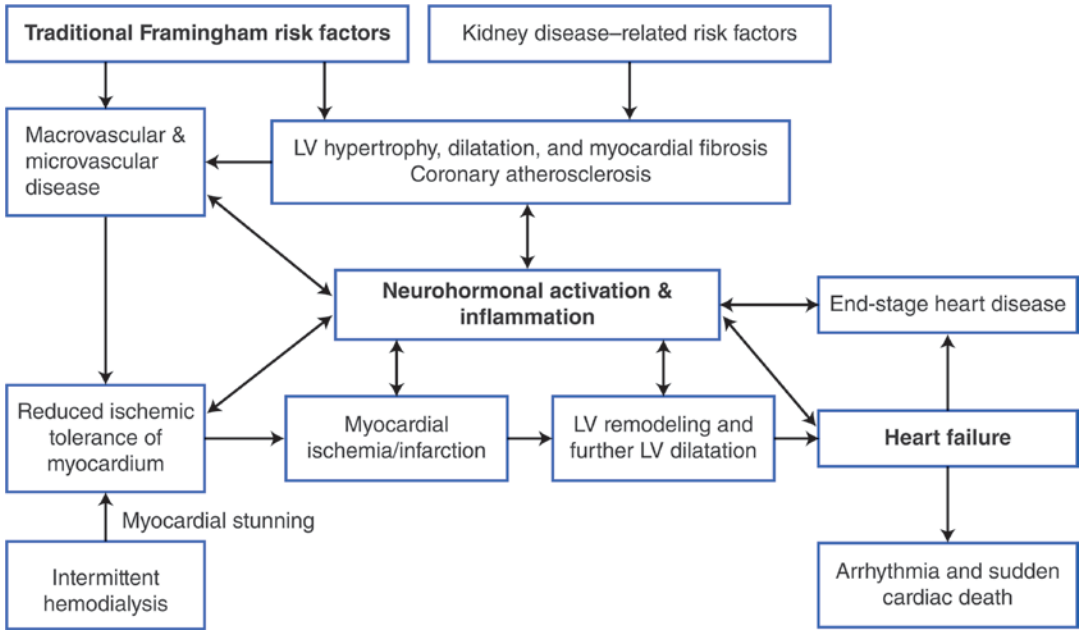


Fig. 39.7 Pathogenesis of heart failure in long-term dialysis patients. (Modified from Ref. [44])

Vascular calcification is a known risk factor for progressive CVD. Coronary artery calcification (CAC), in particular, is reported to be a predictor of cardiovascular events and cardiovascular mortality in adult dialysis patients [51]. While adult long-term dialysis patients are well known to have a high incidence of vascular calcification, the association between long-term dialysis and vascular calcification has also been noted in pediatric patients (Table 39.11) [52].

Al-Biltagi et al. assessed CAC in 50 pediatric HD patients using electron beam computed tomography (EBCT) and reported that CAC was observed in 20% of patients and that patients with CAC had a longer total duration of dialysis (74.5 ± 9.5 months vs. 52.7 ± 8.3 months, $P = 0.0006$) compared to those without CAC [53]. Goodman et al. assessed CAC in 39 young ESKD patients who had a history of undergoing dialysis (7–30 years old, PD patients, HD patients, and post-dialysis transplant recipients). CAC was observed in none of the 23 patients who were younger than 20 years of age, but it was present in 14 of 16 patients who were 20 to 30 years old. Compared to those patients without CAC, those with CAC had a longer duration of dialysis (4 ± 4 years vs. 14 ± 5 years, $P < 0.001$) [54]. Similarly, Srivaths et al. assessed for CAC in 16 young HD patients (9.1–21.2 years) using computed tomography (CT) and reported that five of 16 patients had CAC and that those patients with CAC had a longer duration of dialysis (49.4 ± 15.3 months vs. 17.2 ± 10.5 months, $P = 0.0002$) (Table 39.11) [55].

All studies identified a long duration of dialysis, in addition to chronic kidney disease-mineral bone disorder (CKD-MBD)-related factors such as hyperphosphatemia, as risk factors for CAC. Long-term dialysis patients may, of course, have an increased risk of vascular calcification because of the longer exposure to abnormal mineral metabolism.

In conclusion, long-term dialysis may increase the risk of CVD in pediatric dialysis patients, in a manner that is similar to what occurs in adult patients. To address this issue, various treatment guidelines recommend appropriate management

of blood pressure, CKD-MBD, anemia, and dyslipidemia after the start of dialysis to reduce CVD events. Echocardiography should be performed for cardiac function assessment at least once every 6–12 months. Some registries have also shown lower mortality rates among children who have received a kidney transplant compared with those who remain on dialysis [4]. If possible, fairly prompt access to transplantation should, in turn, be encouraged if at all possible, to reduce the duration of dialysis.

Chronic Kidney Disease-Mineral and Bone Disorder

CKD-MBD is also an extremely important pathological condition for pediatric patients with ESKD. Complications that are specific to children are deformed extremities and failure to thrive. Abnormal bone metabolism also causes calcification of the arteries as noted above, and as with adults, this may increase the risks of cardiovascular lesions and death.

In adults, studies have been conducted using life prognosis as an outcome, while in children, it is difficult to evaluate the impact of CKD-MBD on long-term patient survival. As alternative endpoints, bone lesions, cardiovascular calcification, and failure to thrive have been studied. However, data are limited even for these endpoints in children on long-term dialysis.

Bone Disease

In 2007, the International Pediatric Peritoneal Dialysis Network (IPPN) established a prospective clinical registry designed to collect detailed clinical and biochemical data on children receiving PD [56]. To date, 3771 patients treated with PD from 43 countries worldwide have been registered (http://www.pedpd.org/index.php?id=14).

Based on the IPPN database, clinical symptoms and/or radiological signs of bone diseases were observed in 139 of 890 PD patients (15%) when they were registered [56]. These included radiological signs of osteodystrophy/rickets (9.4%), radiological osteopenia (4.5%), deformed extremities (5%), and bone pain (1.4%). Tissue calcification was reported in 14 patients (1.5%). Among 271 patients who were followed up for 12 months, signs and symptoms of CKD-MBD continued in 20 patients (7.4%), improved in 32 patients (11.8%), and newly developed in 17 patients (6.3%) [56].

In terms of the relationship between dialysis duration and bone lesions, clinical bone disease has been associated with a longer duration of dialysis. In a cohort of 247 Dutch patients who developed ESKD at the age of 0–14 years and started renal replacement therapy (including renal transplantation) between 1972 and 1992 (dialysis duration, 4.1 [range, 0–25.6] years), bone symptoms were observed in 36.8% of the patients, bone deformities in 25.5%, and fractures in 13.4% [57].

Table 39.11 Studies of vascular calcification in pediatric RRT patients

Author	Year published	Number age (years)	Methods of RRT	Cumulative time on dialysis	Risk factors of CAC
Al-Biltagi [53]	2017	53 patients 17.3 ± 3.6	HD, PD, TX	6.7 ± 1.9	Dialysis vintage PTH
Goodman [54]	2000	39 patients 19 ± 7	HD, PD, TX	14 ± 5	Longer dialysis vintage Higher BMI Serum P and ca × P
Srivaths [55]	2010	16 patients 19.1 ± 2.1	HD	4.1 ± 1	Longer dialysis vintage Higher P Lower Chol

Adapted from Querfeld et al. [45]

RRT renal replacement therapy, *CAC* coronary artery calcification, *PD* peritoneal dialysis, *HD* hemodialysis, *Tx* transplantation, *PTH* parathyroid hormone, *BMI* body mass index

Vascular and Valvular Calcification

As noted earlier in this chapter, CAC is frequently observed in adult dialysis patients, and it is associated with the prognosis for long-term outcome [58]. It has also been reported in young adults with pediatric onset of dialysis by Groothoff et al. and Goodman et al., respectively [50, 54]. In the Dutch study, carotid arterial wall thickness was increased in young adults with ESKD, and hypertension was a primary determinant of this complication [50]. In the study by Goodman et al., 92% of patients had CAC, patients with CAC had a longer dialysis duration (14 ± 5 years vs. 4 ± 4 years) compared to those without calcification, and calcification was frequently seen in patients with high serum phosphorus levels, elevated calcium-phosphorus product, and a high calcium intake [54]. In this study, the calcification score, which is used as an indicator of calcification, and dialysis duration were associated.

Thus, vascular calcification in ESKD may start during childhood age, and long-term dialysis appears to be an important risk factor for CAC.

Longitudinal Growth

In dialysis patients, malnutrition, endocrine dysfunction, anemia, inappropriate dialysis, and acidosis all contribute to the risk for a patient's course to be complicated by failure to thrive. Therefore, it is difficult to isolate the influence of CKD-MBD on growth. There are, at the same time, many reports on an association between failure to thrive and dialysis duration.

In the long-term outcome Dutch LERIC study, more than 61% of subjects were severely growth retarded with a height SDS lower than -2SD; the dialysis vintage in years for these patients was twice as much as in the non-severely growth retarded group, with very few of the latter group having received recombinant growth hormone therapy [57]. However, a recent ESPN/ERA-EDTA Registry study showed that even today, many children with RRT and on dialysis do not reach a normal target height and that recombinant growth hormone therapy is often not prescribed, even in countries with secured financial compensation [59, 60].

In the IPPN registry, the mean standardized height of the enrolled PD patients was low (−2.43 SD), and the height was below the third percentile in 39% of patients. The annual prospective change in standardized height tended to be inversely correlated with parathyroid hormone (PTH). Patients with a mean PTH >500 pg/mL had a significantly lower height SDS compared to children with lower PTH levels (Fig. 39.8) [56].

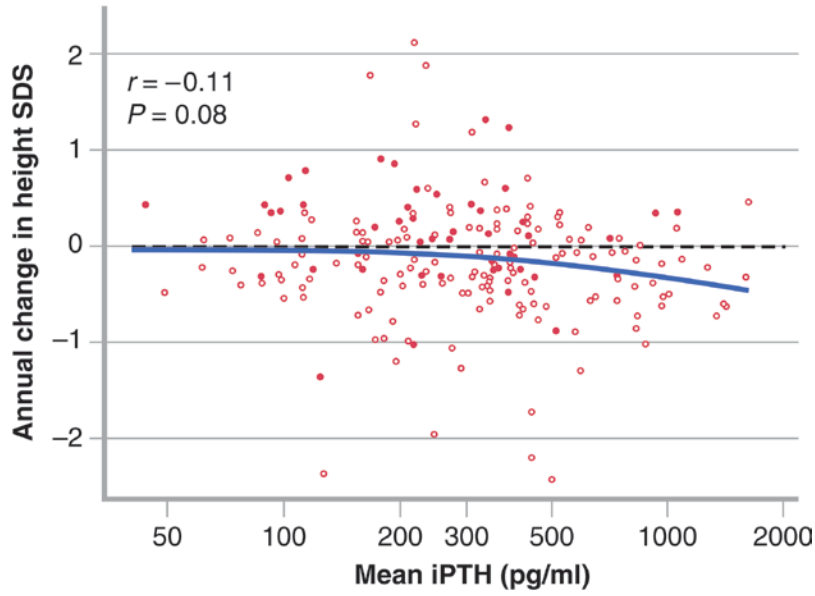


Fig. 39.8 CKD-MBD and longitudinal growth. Time-averaged mean plasma intact parathyroid hormone concentrations and change in standardized height in 214 pre- and early pubertal children followed prospectively for at least 12 months. Full circles indicate patients receiving recombinant growth hormone. (Modified from Ref. [56]). SDS, standard deviation score

Thus, to help optimize growth in ESKD patients, as well as to decrease fracture risk, biochemical correction of CKD-MBD parameters (normalization of Ca, P) and control of PTH (2−3X normal value) are considered to be essential.

Peritoneal Dysfunction and Encapsulating Peritoneal Sclerosis (EPS)

Peritoneal dysfunction and EPS associated with long-term PD are the most significant and severe complications of long-term PD in children, and they are directly linked to the long-term prognosis of dialysis patients. Peritoneal dysfunction, which is characterized by inadequate ultrafiltration (UF) and inadequate solute clearance, is the second leading cause of PD termination next to infection [36]. A report from Japan indicated that about one-half (49%) of patients who were on PD for 5 years or more were switched to HD because of UF failure and insufficient dialysis [30].

Because PD has many advantages for pediatric dialysis patients, particularly in constitutionally small patients, it is essential to thoroughly understand these complications so as to optimize the use of PD.

Peritoneal Dysfunction

Peritoneal dysfunction is characterized by increased peritoneal permeability and subsequent UF failure. The increased peritoneal permeability is characterized by an increase in the dialysate-to-plasma creatinine ratio (D/P Cr), which is calculated using the peritoneal equilibration test (PET). The associated peritoneal morphology has been evaluated through laparoscopy [61], peritoneal biopsy [62, 63], mesothelial cell cytology [64], and other methods.

There have been many reports on factors that may affect peritoneal permeability, including catheterization [65], PD-related peritonitis [66–69], and a prolonged period on dialysis [70]. As part of the investigation of the relationship between dialysis duration and peritoneal permeability, it has been reported in adults that peritoneal permeability was actually enhanced by early exposure to higher intraperitoneal glucose concentrations [70]. In children, it has been reported that there was no change in PET category for approximately 2 years after the initiation of PD [71, 72], but that an increased D/P Cr and a decreased D/D_0 Glu were observed thereafter [73]. Kaku et al. performed 202 standardized PETs in 129 children and reported that the duration of PD was positively correlated with D/P Cr and negatively correlated with D/D_0 Glu, showing that long-term peritoneal dialysis worsens peritoneal function, possibly more than episodes of peritonitis (Fig. 39.9) [74].

Peritoneal morphological changes, such as peritoneal thickening and vascular damage, have been found to progress in association with the prolongation of PD (Fig. 39.10). Moreover, severe peritoneal thickening is associated with a decreased UF capacity [75]. This suggests a close association between peritoneal dysfunction and peritoneal structural changes.

The results described above were obtained from patients using a peritoneal dialysis solution with a low pH. Subsequent studies were conducted to evaluate differences in PET results associated with the use of neutral pH dialysate and a low pH dialysate [76, 77]. No differences in small molecule transport rates were noted, and PD with neutral pH dialysate had little effect on peritoneal permeability or morphology for more than 3 years [78]. At the same time, there have been some reports which have shown that the use of neutral pH dialysate was associated with a decreased UF [79, 80], so the effects of neutral pH dialysate are not consistent in all studies.

Factors in the peritoneal effluent, such as matrix metalloproteinase-2 (MMP-2), interleukin-6 (IL-6), hyaluronan, vascular endothelial growth factors (VEGFs), cancer antigen 125 (CA125), and coagulation-fibrinolysis factors, have all been reported as markers for peritoneal injury. Increasing serum β2-microglobulin levels have also been reported to be useful markers of peritoneal injury and morphological changes [81–90]. In particular, the level of CA125 in the PD effluent often tends to decrease as the dialysis

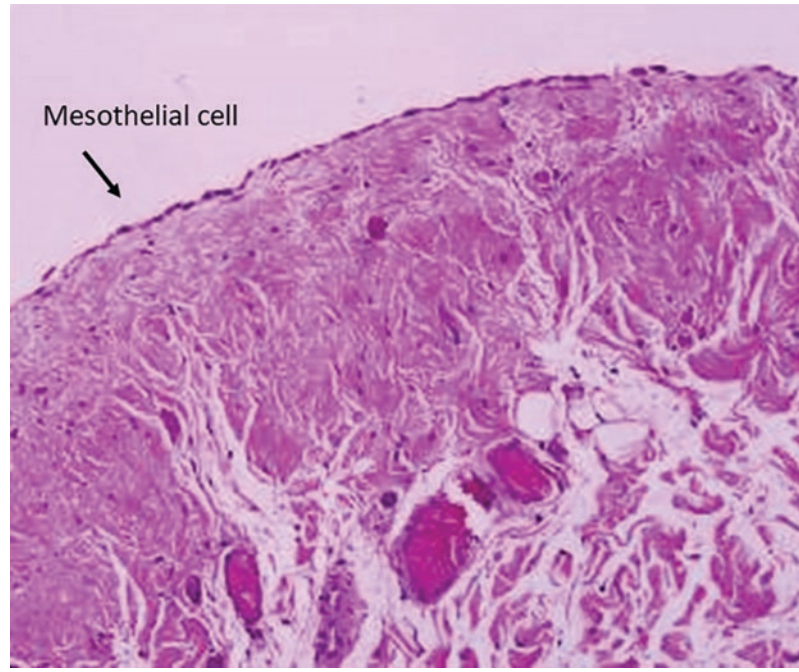


Fig. 39.10 Mild thickening of peritoneal membrane with increase of collagen fiber

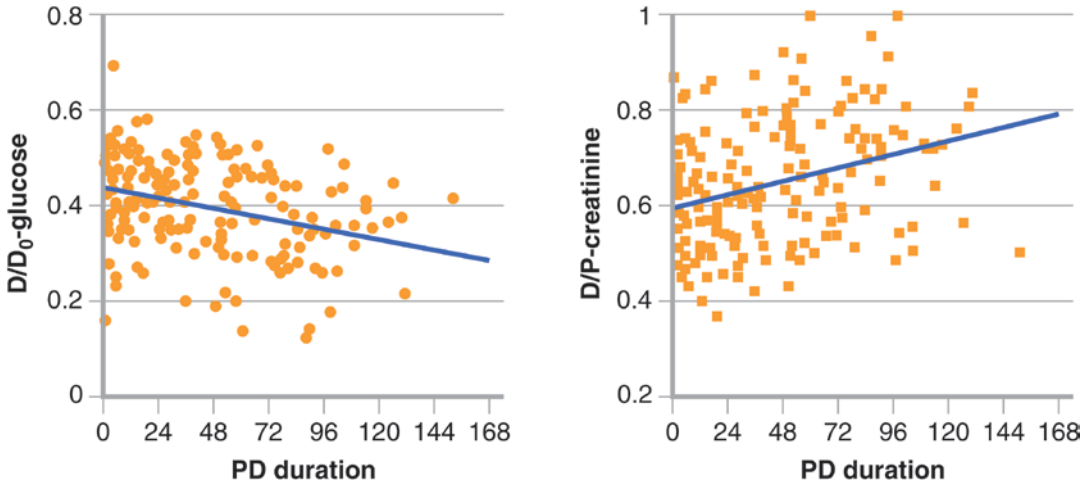


Fig. 39.9 Correlation between peritoneal membrane permeability and peritoneal dialysis duration. [Modified from Ref. [74])

period is prolonged, and it has been reported to be consistent with actual morphological findings [91].

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is the most serious complication of PD. EPS is defined as a clinical syndrome with persistent, intermittent, or recurrent obstructive ileus, which is accompanied by extensive adhesions of the diffusely thickened peritoneum [92]. EPS has a poor prognosis, with a mortality rate of 25–56% in adults and 13–27% in children [93–97].

Pathophysiology

While the pathophysiology of EPS is unclear, EPS is very likely to be of multifactorial etiology. The peritoneum normally consists of a single layer of mesothelial cells, submesothelial connective tissue, and arterioles [98]. Mesothelial cells act as a barrier against all peritoneal injuries and play important roles in the transport of water and solutes, inflammation, and tissue repair. Conventional peritoneal dialysis solutions are characterized by acid pH, high lactate concentration, high osmotic pressure, high glucose concentration, and glucose degradation products (GDPs) which are formed during high-temperature sterilization. GDPs stimulate mesothelial cells to produce transforming growth factor-beta (TGF-β) and VEGFs [99]. The profibrotic factor TGF-β induces epithelial-to-mesenchymal transition of mesothelial cells, which further progresses to EPS through mediation by factors such as VEGF and plasminogen activator inhibitor 1 [100–102] (Fig. 39.11).

A "two-hit" theory has been proposed to explain the pathogenesis of EPS (Fig. 39.12). Prolonged exposure to bioincompatible dialysis solutions causes peritoneal mesothelial cells to detach and disappear, leading to peritoneal fibrosis and peritoneal hypertrophy. In addition, hyalinizing vasculopathy occurs, and the thickened peritoneal capillary wall and the lumen narrowing change peritoneal permeability (first hit). Under those conditions, inflammatory stimuli such as bacterial peritonitis (second hit) result in the proliferation of peritoneal capillaries and an increase in peritoneal permeability. This increases the penetration of large molecular substances such as fibrin and results in fibrin deposition on the peritoneal surfaces [75].

Further degeneration and sclerosis of the fibrinous membrane subsequently results in compression of the intestine, leading to clinical manifestations. The fibrinous membrane extends from the parietal peritoneum to the visceral peritoneum, sometimes with accumulation of ascitic fluid inside, which is readily detected by abdominal CT. Even mild inflammation may trigger capsular formation in patients with severe peritoneal dysfunction and morphological changes. Conversely, severe inflammation may induce EPS in patients with even mild peritoneal dysfunction and morphological changes. Thus, even short-term PD patients may develop EPS if inflammation is severe. Additionally, diffuse calcinosis between the capsule and the degenerated peritoneum may occur in patients with severe fibrosis or secondary hyperparathyroidism.

Incidence of EPS

Based on various single-center and multicenter studies and national registry observational cohort studies involving adults, the prevalence of EPS is estimated to be between 0.4% and 8.9% (Table 39.12). On the other hand, there are only two reports of children, consisting of the Japanese multicenter study and the Italian registry of pediatric chronic dialysis. These cohorts reported that the incidence of EPS after 5 years on PD in children was 6.6% and 21.1%, respectively [95, 103].

EPS Development Can Be Predicted

Previous studies involving many patients have suggested that the development of EPS may be associated with abnormalities of D/P Cr [104–106], mesothelial cell area [106], MMP-2 [90, 107], IL-6 [108], and CA125 in the PD effluent [91].

Because the PET is an established method for assessing peritoneal permeability, it is recommended that the PET be performed on a regular basis, at least once per year, in patients on PD. Assessment of peritoneal function through the PET is noninvasive and highly objective, easy to perform, and economical. Whereas the D/P Cr is not sufficiently conclusive to be able to predict the development of EPS based on a single assessment, it can be monitored for any change over time [104, 105]. A continuously increasing D/P Cr, with results demonstrating at least 12 consecutive months of high D/P Cr, indicates progressive severe peritoneal deterioration, and discontinuation of PD should be considered in this situation. Although mesothelial cell cytology has been demonstrated to correlate with the risk of EPS [106], it is not a very sensitive or specific predictor of EPS. The same is true for the afore-

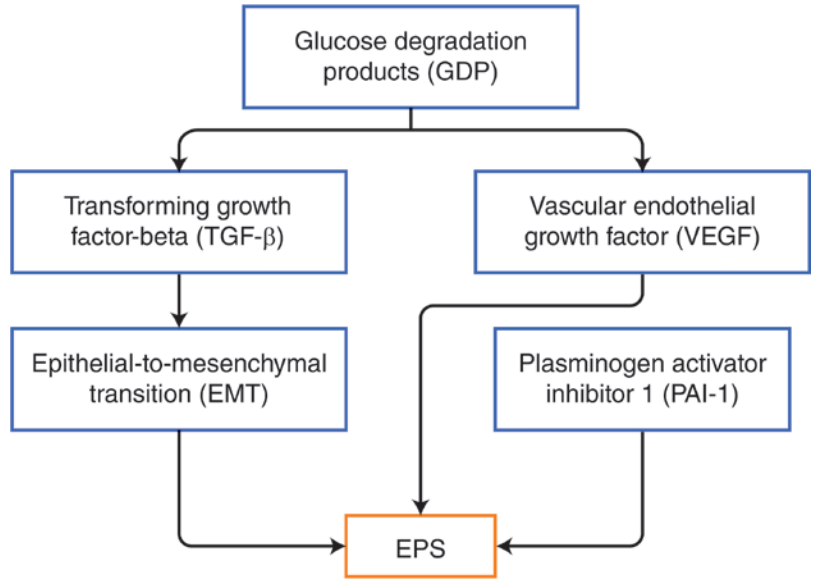


Fig. 39.11 Pathogenesis of encapsulating peritoneal sclerosis (EPS)

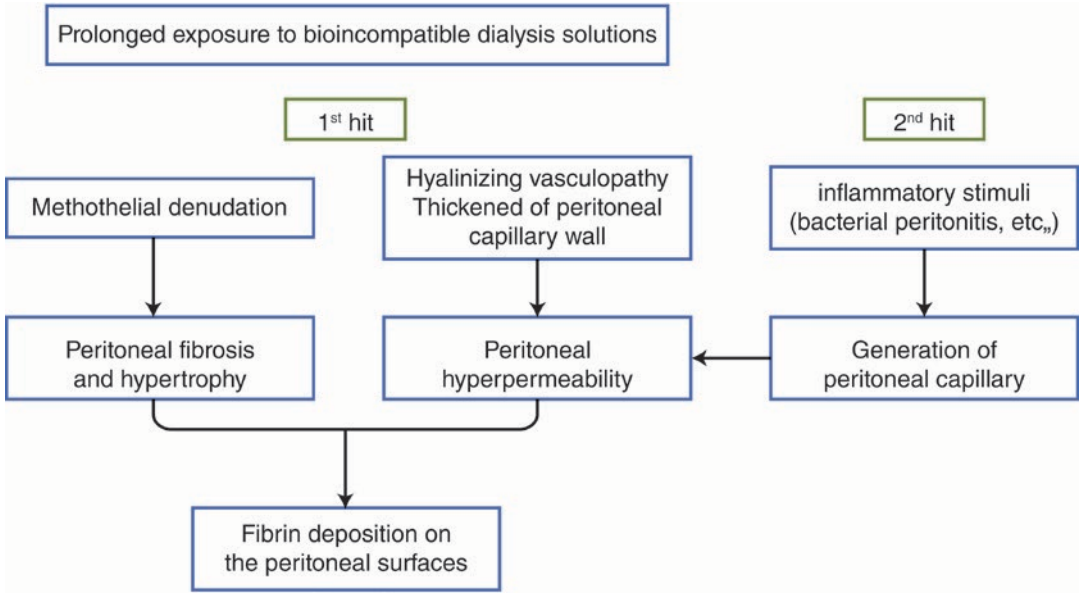


Fig. 39.12 Two-hit theory of pathogenesis of encapsulating peritoneal sclerosis (EPS)

mentioned effluent markers. To summarize, no measure is an independent, absolute diagnostic marker that can be used alone to detect peritoneal dysfunction or morphological change that may lead to EPS. It is recommended to make a comprehensive assessment based on the findings from multiple measures.

Risk Factors

As stated above, numerous factors are likely involved in the development of EPS. Possible causal factors include PD duration, peritonitis, acetate dialysate, high-glucose dialysate, bioincompatible dialysate, chlorhexidine, and plasticizers [30, 109]. Additionally, some

Table 39.12 Relationship between long-term PD and EPS incidence

EPS incidence (%)	PD duration	Country	Adult or children	Reference
6.6 12	5 years or more 8 years or more	Japan	Children	Hoshii S et al. [95]
21.1	5 years or more	Italy	Children	Vidal et al. [103]
5 10.8 19.4	5 years or more 6 years or more 8 years or more	Australia	Adult	Rigby RJ et al. [160]
0.5 3.3	5–10 years 10 years or more	Japan	Adult	Kawanishi et al. [161]
0.7 2.1 5.9 5.8 17.2	5 years 8 years 10 years 15 years 15 years or more	Japan	Adult	Kawanishi et al. [123]
8.8 5	5–6 years 6 years or more	Scotland	Adult	Brown et al. [93]
0.8 3.9	5 years or more 8 years or more	Australia and New Zealand	Adult	Johnson et al. [96]
20 100	6 years or more 8 years or more	Ireland	Adult	Phelan et al. [162]
15 38	6 years or more 9 years or more	USA	Adult	Bansal et al. [163]
0.6 2.3 1.2	5 years 8 years 8 years or more	Japan	Adult	Nakayama et al. [116]
6 8 18 75 67	6–8 years 8–10 years 10–12 years 12–14 years 14 years or more	Italy	Adult	Vizzardi et al. [164]
9.4 22.2	5 years or more 7 years or more	Scotland	Adult	Petrie et al. [165]
10.8 23.3 25	5 years or more 6 years or more 7 years or more	Iran	Adult	Alatab et al. [166]

EPS encapsulating peritoneal sclerosis, *PD* peritoneal dialysis

patients might have a genetic predisposition to EPS [92, 109].

PD Duration

The most important risk factor for EPS is long-term exposure to peritoneal dialysate. The Japanese registry of pediatric peritoneal dialysis patients reported that all patients with EPS had been on PD for 5 years or more [95]. Additionally, the incidence of EPS was 6.6% after 5 years or more of PD and 12% after 8 years or more of PD. The Italian Registry of Pediatric Chronic Dialysis reported that the incidence of EPS was 21.1% in patients who had received PD for more than 5 years compared with 0.4% for those who had received PD for less than 5 years [103]. The European Pediatric Dialysis Working Group (EPDWG) reported that the median duration of PD was 5.9 (range, 1.6–10.2) years in patients with EPS and 1.7 (range, 0.7–7.7) years in patients without EPS [94].

Many studies in adults have also shown that the incidence of EPS increases as the PD duration becomes longer (Table 39.12).

Composition of Dialysate

As a result of the reported association between acetate-buffered dialysate and the development

of EPS [110], lactate-buffered dialysates are currently used in many PD patients. Additionally, exposure to bioincompatible dialysate containing high concentrations of glucose and GDPs may be a risk factor [92].

Icodextrin has also been shown to be associated with an increase in local inflammatory markers such as IL-6 [111, 112], and an association between the long-term use of icodextrin and the development of EPS has been reported [113]. However, no differences in the prescription of icodextrin between patients with and without EPS have been reported [114]. In fact, icodextrin has also been reported to be involved in the protection of mesothelial cells and peritoneal function [115]. Thus, no conclusive evidence that icodextrin contributes to the development of EPS is available.

In contrast, neutral pH peritoneal dialysis solutions containing fewer GDPs are being used by an increasing percentage of PD patients globally (but not in the USA), and this has resulted in a reduction in EPS, based on an observational study [116]. In patients using neutral pH dialysate, the incidence of EPS decreased to 1.0% with an incidence rate of 2.3/1000 patient-years, and clinical symptoms of EPS were often mild. Studies with parietal peritoneal biopsy tissues have also provided evidence of a lower incidence of peritoneal vascular degeneration in the neutral pH dialysate group [117, 118].

Peritonitis

Severe peritonitis, especially when caused by *Staphylococcus aureus*, *Pseudomonas*, or fungi, might be a risk factor for EPS [93]. It is unclear whether the frequency of peritonitis is a risk factor for EPS [94, 103]. It has been reported that patients with severe peritonitis episodes developed progressive EPS after switching from PD to HD [119], whereas mild recurrent peritonitis was not a risk factor for EPS [96]. While peritonitis may be strongly associated with the development of EPS [120], the degree of association differs between patients on short-term PD and those on long-term PD. Patients on PD for as long as 5 years or more are more likely to develop EPS when peritonitis occurs [30, 121, 122].

Discontinuation of PD

EPS has also been reported to occur after renal transplantation or after switching from PD to HD [123–126]. Post-transplantation EPS has occurred mostly within 1 year of transplant, presumably because of the profibrotic effects of calcineurin inhibitors (CNIs) [124, 126]. CNIs, especially tacrolimus, increase TGF-β mRNA expression and extracellular matrix production [126, 127]. A steroid reduction protocol might also increase the risk of EPS by reducing the anti-inflammatory effects of steroids [128]. However, mammalian target of rapamycin inhibitors may reduce angiogenesis and fibrosis [129, 130].

In Japan, EPS has often occurred after switching from PD to HD, with a reported incidence of 69% in adults [96] and 29% in children [30, 95]. Discontinuation of PD might result in an increase in inflammatory mediators and the intraperitoneal fibrin concentration, and there have been conflicting reports about the benefits of peritoneal lavage after discontinuing PD. Some studies have reported that the lavage prevented EPS [106, 131], whereas others pointed out that the lavage might increase the risk of EPS [92].

Drugs

Besides the abovementioned CNIs, treatment with β-blockers has been reported to be a risk factor for EPS [132]. An association between the use of chlorhexidine to sterilize tubing connections for PD and development of EPS has also been reported [133].

Diagnosis of EPS

The diagnosis of EPS is based on a combination of structural (e.g., CT scan appearance) and functional features (intermittent, subacute bowel obstruction) [134].

Clinical Diagnosis

EPS develops gradually and progresses slowly [135]. The pre-EPS clinical picture is characterized by UF failure and mild ascites. In early EPS, findings that are suggestive of a systemic inflammatory response are sometimes noted. Late EPS is characterized by symptoms of intestinal obstruc-

tion that are caused by the encapsulating peritoneum. Digestive symptoms including abdominal pain, nausea, vomiting, constipation, and diarrhea, which are symptoms of small intestinal obstruction, are noted. Finally, symptoms of complete intestinal obstruction may occur, including abdominal mass, low-grade fever, hemorrhagic effluent, anorexia, weight loss, and malnutrition. Increased CRP [95, 103], as well as failure of UF (or decrease in UF), and increased peritoneal permeability are noted. It has been reported that EPS occurred in 50% of patients who continued PD after a decrease in UF [136], and the EPDWG reported that failure of UF was observed in 90% or more of children with EPS [94]. However, these changes in membrane function are also observed in many patients on chronic PD without EPS.

Radiological Diagnosis

Radiographic examinations which are often conducted to diagnose EPS include ultrasonography and CT. Ultrasonography reveals the formation of a mass in the intestinal tract, with a thickened peritoneum, and CT reveals peritoneal thickening and encapsulation, which are findings of intestinal obstruction, in addition to peritoneal calcification (Fig. 39.13) [137–139]. However, because these imaging findings are infrequently seen in the early stages of this disorder, neither ultrasonography nor CT is suitable for screening.

Pathological Diagnosis

Peritoneal biopsy is recommended for children who have been on PD for 8 years or more with failure of UF and/or peritoneal calcification on CT [140]. If biopsy reveals a loss of mesothelial cells, thickened submesothelial connective tissue, denatured collagen fibers, and/or a markedly thickened microvascular wall with vascular lumen narrowing (Fig. 39.14), a diagnosis of peritoneal sclerosis is made [75], and PD should be discontinued; this approach protected all of six reported pediatric PD patients diagnosed with peritoneal sclerosis from EPS [140]. Peritoneal biopsy is helpful and practical in diagnosing EPS as mentioned above, but is not recommended to be performed on a routine basis because it is highly invasive.

Treatment

The International Society for Peritoneal Dialysis (ISPD) position paper on EPS recommends that treatment of EPS includes discontinuation of PD, nutritional support, and surgical therapy [134]. However, there are no consensus guidelines on the management of EPS.

Corticosteroids are used in Japan as the first treatment option after the onset of EPS [141, 142]. Corticosteroids may act by inhibiting inflammation to prevent ascites and fibrin deposition. Treatment should be initiated immediately after EPS onset; dose reduction following a good response is also important. Additionally, the necessity for prolonged high-dose steroid therapy for patients with a continuously increasing CRP has been reported [143]. However, reports about the efficacy of corticosteroids are insufficient, so there is currently no consensus on the use of this therapy.

Tamoxifen, a selective estrogen receptor modulator [144], is widely used in Europe for the treatment of EPS. Tamoxifen may prevent peritoneal dysfunction and morphological changes by inhibiting profibrotic factor gene expression, inhibiting mesothelial stromal cell transformation, and promoting denatured collagen removal [145, 146]. Treatment with tamoxifen has resulted in resolution of EPS-related symptoms [147], and an EPS registry study in the Netherlands reported a significant improvement in the survival rate in the tamoxifen group [148]. EPS treatment guidelines published in the Netherlands in 2011 contain recommendations for the use of steroids and tamoxifen and the timing of surgery [143]. However, because drug therapies have been evaluated only in case series or in small case-control studies, no definite conclusions can currently be drawn about the clinical efficacy of these therapies. In the United Kingdom (UK), the National Institute for Health and Care Excellence Guideline [149] stated that drug therapy should be used at the discretion of individual physicians because there is no conclusive evidence regarding its utility.

Surgery

While surgical treatment was initially contraindicated for EPS [150], favorable results of intesti-

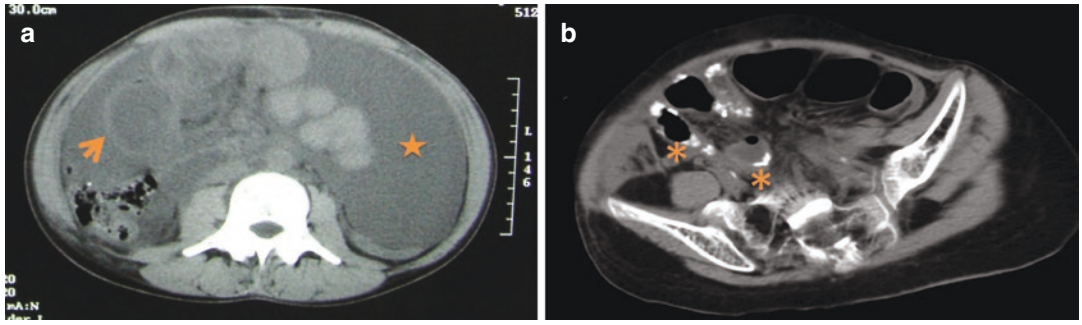


Fig. 39.13 (**a**) CT scan findings of EPS. Thickened bowel wall (arrow) and loculation of ascitic fluid (star). (**b**) CT scan findings of the peritoneum with calcifications (*)

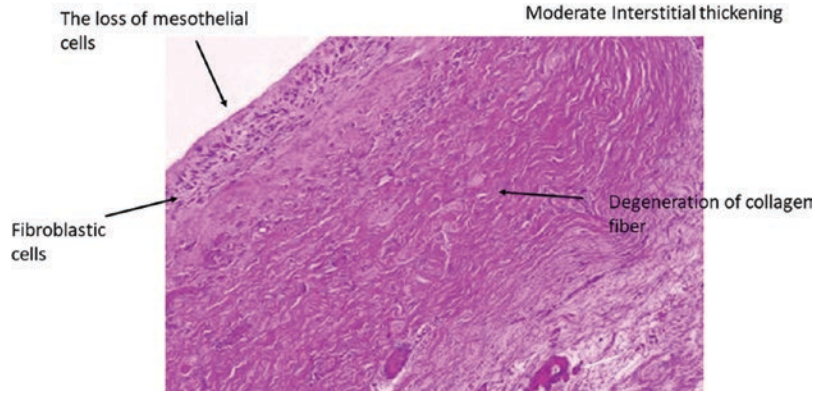


Fig. 39.14 Peritoneal biopsy of EPS

nal adhesiolysis have been reported in Japan [151–153]. Surgical treatment is required for patients with an acute abdomen resulting from complete intestinal obstruction, intestinal perforation, or intra-abdominal hemorrhage, as well as those with no response to drug therapy. Surgical treatment administered by an experienced team should be considered for complete EPS as soon as possible after a reduction in inflammation has been accomplished. Based on reports in Japan [152], the UK [154], Germany [155], and the Netherlands [156], the mortality rate for surgery ranges from 32% to 35%, which is better than the results associated with conservative therapy (39–56%) [96, 97].

Nutritional Support

Malnutrition is of great concern in patients with severe EPS, and nutritional support is extremely important for these patients. Adequate enteral or parenteral nutritional support restores the nutritional status in many patients [157, 158]. Nutritional support should be initiated early to prevent malnutrition and ideally to decrease mortality risk.

Outcome

Based on a report in adults, the mortality rate of EPS is as high as 25–56%, and many PD patients have died within 2 years of the diagnosis of EPS. The pediatric registries have reported mortality rates of 13–27% [94, 95, 159], which are lower compared with those in adults, but the reason for this is unknown. Normal intestinal function has been reported after recovery from EPS [94], showing that early diagnosis and appropriate management are extremely important for the patient's prognosis.

Prevention

Currently, there are no recommended strategies to prevent EPS. Kawaguchi et al. recommended

that for patients on PD for more than 8 years, the therapy can be continued under certain conditions, specifically if there is a stable D/P Cr on PET test, no development of a high-transport membrane status or requirement for the frequent use of hypertonic solutions, clinical stability with a good appetite and stable body weight, no signs of overhydration, stable serum CRP, and the absence of recurrent episodes of peritonitis [92]. Earlier discontinuation of PD may be considered for the patient who has been on PD for 5 years or more with an increased D/P Cr or worsening UF capacity/development of UF failure.

Cognitive Functioning

Impaired neurocognitive development and functioning are important, but not well-understood complications of pediatric CKD. There is evidence that dialysis treatment is a prominent determinant. Many have found evidence of several neuropsychological deficits in children with ESKD, including impairment in IQ, academic achievement, memory, and executive functioning [167–169]. This may not be completely reversible after transplantation and can result in cognitive dysfunction in adulthood. Cognitive and learning impairment is more prevalent in middle-aged adult patients with childhood ESKD than in the age-matched population [170, 171].

These issues have been uniquely addressed in the aforementioned longitudinal Dutch initiative, LERIC study [171]. As noted previously, the LERIC study comprises all Dutch patients who started RRT at age 0–15 years between 1972 and 1992. Information was obtained by reviewing all available charts from all patients in 2000 and 2010 and inviting all living patients to return for cross-sectional investigation. While the LERIC study is predominantly an analysis of long-term RRT with a functioning kidney transplant, because these patients began RRT as children, the study offers important insights into the future for children who have received long-term dialysis.

In the LERIC study, the mean IQ scores of adults aged 20–40 years with childhood ESKD were on average ten points lower than in the aged-matched Dutch population, which is in line with the results of recent intelligence quotient (IQ) studies performed in children [171–173]. Impaired schooling and cognition appear to have been induced by a long period of dialysis during youth. The LERIC study found no difference in intellectual performance between patients who were on dialysis and those who were transplanted at the time of the investigation [171], *which is in line with comparable outcomes* of recent IQ studies in ESKD. Most deficits were found in tasks requiring memory, concentration, and general knowledge [171].

In contrast to the finding of the LERIC study, pediatric transplanted patients with a median age of 25.7 years in a Swedish study reached the same level of academic achievement as in the general population. The limitation of this study was that 40% of the overall cohort did not participate and no information about the characteristics of these non-participants was provided [174].

Other studies on cognition in pediatric patients with CKD suggest that toddlers and young children with CKD are at greatest risk for impaired neurocognitive development [175]. In a large North American study from the Chronic Kidney Disease in Children (CKiD) cohort, of the 386 children with CKD stages 2–4 (mean glomerular filtration rate 41 mL/min/1.73 m^2) studied, the overall neurocognitive functioning was within the average range for the entire group, but 21% to 40% of participants scored at least one SD below the mean on measures of IQ, academic achievement, attention regulation, or executive functioning. A higher glomerular filtration rate was associated with a lesser risk for poor performance on measures of executive function [176].

Early detection of neurocognitive impairment in children on long-term dialysis is of extreme importance; an individualized adapted school program may significantly improve academic performance and lead to greater autonomy and a skilled job as an adult that better matches the subject's capabilities and expectations.

Quality of Life

In the LERIC study, patients aged 20–40 years with pediatric onset of ESKD and who were on

dialysis at the time of assessment indicated the presence of an impaired quality of life more often than the general population in all physical domains: in activities that require good physical condition (physical functioning), in social activities that require a good physical condition (role physical), in social functioning, and in general health perception. These same patients, however, reported equally or even less often an impaired quality of life for mental domains [177] compared to age-matched Dutch citizens. This was sharply in contrast with data from dialysis patients of the same age with onset of ESKD in adulthood, who scored substantially lower on all physical and mental domains compared to healthy individuals [178–180].

The high mental health scores in LERIC are in line with data from other studies in adolescents and adults with chronic illness since childhood, including cystic fibrosis, sickle cell disease, and asthma [181–183]. Different life expectations and coping strategies between children and adults may explain the different mental status of patients with adult and those with pediatric onset of disease. Health-related quality of life reflects the difference between health experiences and health expectations; children may be far superior to adults in successfully using coping strategies [184, 185]. Although transplanted patients showed the most favorable outcomes with respect to the physical domains, "early" aging seems to become a problem after more than 30 years of RRT. Finally, consideration of the sociodemographic variables is also important, and being employed appeared to be associated with a lower risk of impaired QoL in the domains of physical functioning, vitality, and general health perception. Having offspring was also associated with a lower risk of impaired QoL [186].

Social Outcome

Employment In the LERIC study, social outcome was assessed in 2000 (mean age 30) and 2010 (mean age 40). In 2000 and 2010, 67.4% and 61.8%, respectively, of subjects were employed, 85% (81.8% in 2010) for more than 50% time equivalent [187, 188]. Involuntary unemployment occurred in 19.1% vs. 6.4% in the Dutch population at large. Low-skilled professions were most prevalent (53%); only 10% of patients had high-skilled professions [187, 188]. In 2010, there was a very significant difference between patients on dialysis, of whom only 31.3% were still employed, and transplanted patients. Dialysis as the RRT modality and having motor disabilities were the most important risk factors for unemployment. Increasing chronic fatigue was also often mentioned as a reason for becoming unemployed. Others, however, reported that their employment contract was not renewed as a direct result of the disclosure of their dialysis patient status to the employer. Unemployment was more often related to the patients' low subjective health perception, rather than to their objective physical condition, or to whether they were transplanted or on dialysis. Between 2000 and 2010, there was a trend toward more highly educated occupations and an increase in the educational level within the cohort. In 2010, 22.1% of subjects had completed a high vocational training or scientific degree, compared to 31.2% in the general Dutch population ($P > 0.05$). 34.8% of the patients had an income equal to or above the national modal income of €2500 (about US$ 3200) gross per month, a significantly smaller proportion compared to the general population (61.1%) [188].

In a French outcome study on 624 patients transplanted at childhood, fewer subjects than expected had a high-level degree (14.8% vs. 30.2% general population) and fewer women had a baccalaureate degree (49.2% vs. 76.5%), but these differences were less marked than in LERIC [170]. Mean incomes were much lower than in the overall French population and more patients were unemployed (18.5% vs. 10.4%, $p < 0.01$). A low educational level of the parents or patient, female gender and being on dialysis at the time of assessment, ESKD onset in infancy, and the presence of comorbidities and disabilities were all independent risk factors for a poor social outcome. Interestingly, patients less often had a per-

manent contract than the average French employee (66.8% vs. 81.8%) [170].

The relatively good overall outcome reported from the French study might be slightly biased by the fact that more non-responders than responders had graft failure at the time of investigation and that the cumulative duration on dialysis was also higher in the non-responder group. Nearly 50% of the French patients mentioned having suffered from discrimination, either from employers (27.8%), work colleagues (19.9%), or at school (60.8%) and even from friends (19.3%) (212). In LERIC, 35.2% of subjects lost their job between 2000 and 2010; 32.3% were fired – sometimes as part of a "reorganization," and 45.2% stopped working for medical reasons. In 12.1%, employers indicated that the disease state of the patient influenced their achievements. About 21% of patients felt that their disease had a significant negative influence on their professional achievements and career [188].

Partnership and Independency In 2000, many LERIC patients mentioned significant difficulties in finding a partner. At age 20–40 years, 31.9% lived alone, 34% with a partner, and 49 (34%) with their parents. The odds ratio of living with parents, as a measure of autonomy, versus living alone or with a partner was 3.3 (95% CI, 2.3–4.7) for LERIC patients compared with age-matched Dutch inhabitants [187]. This is in line with data from the French follow-up study of pediatric transplanted patients of the same age as in LERIC at the time of assessment (31.1% partnership, 35.7% living with parents) [170]. Between 2000 and 2010, the situation in the LERIC cohort completely changed: in 2010, 67.4% of subjects were married or lived with a partner, and 28 (31.5%) had offspring compared to values of 74.4% ($P > 0.05$) and 64.8% ($P < 0.05$), respectively, in the general population . This delay in starting a relationship could reflect a genuine delay in sexual or "social maturity" as previously has been described in patients with a chronic disease [174, 189]. These patterns also seem to be culturally determined: for instance, impaired autonomy development in disabled patients is more prevalent in Southern than in Northern European countries [170, 185, 189–193]. Men appear to have problems finding a life partner more often than women [170, 192].

Conclusion

Children with ESKD and especially those with long-time dialysis treatment are at risk for long-term medical complications and impaired autonomy, development, and educational attainment. Early recognition and intervention may be of extreme importance in order to optimize their long-term survival with as few comorbidities as possible and prepare them for a successful career as partner, parent, and functional member of society.

References

1. SR A. VIII. Pediatric end-stage renal disease. Am J Kidney Dis. 1999;34:S102–13.
2. Neu AM, Ho PL, McDonald RA, Warady BA. Chronic dialysis in children and adolescents. The 2001 NAPRTCS annual report. Pediatr Nephrol. 2002;17:656–63.
3. Vats AN, Donaldson L, Fine RN, Chavers BM. Pretransplant dialysis status and outcome of renal transplantation in North American children: a NAPRTCS study. North American Pediatric Renal Transplant Cooperative Study. Transplantation. 2000;69:1414–9.
4. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350:2654–62.
5. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, Wolff ED, Davin JC, Heymans HS. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002 Feb;61(2):621–9. https://doi.org/10.1046/j.1523-1755.2002.0015.
6. Shroff R, Ledermann S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2009;24:463–74.
7. United State Renal Data System 2016 annual data report. Chapter 8: ESRD Among Children, Adolescents, and young Adults, 2016.
8. Kramer A, Pippias M, Noordzij M, Stel VS, Afentakis N, Ambuhl PM, Andrusev AM, Fuster EA, Arribas Monzon FE, Asberg A, Barbullushi M, Bonthuis M, Caskey FJ, Castro de la Nuez P, Cernevskis H, des Grottes JM, Garneata L, Golan E, Hemmelder MH,

Ioannou K, Jarraya F, Kolesnyk M, Komissarov K, Lassalle M, Macario F, Mahillo-Duran B, Martin de Francisco AL, Palsson R, Pechter U, Resic H, Rutkowski B, Santiuste de Pablos C, Seyahi N, Simic Ogrizovic S, Slon Roblero MF, Spustova V, Stojceva-Taneva O, Traynor J, Massy ZA, Jager KJ. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. Clin Kidney J. 2018;11:108–22.

9. United States renal data system. 2017 annual data report. 2017;2; End-Stage Renal Disease in the United States.
10. United States renal data system. 2018 annual data report. 2018; 2: End-Stage Renal Disease in the United States.
11. ESPN/ERA-EDTA Registry. 2018.
12. ERA-EDTA Registry Annual Report 2016.
13. Zagozdzon I, Zurowska A, Prokurat S, Rubik J, Drozdz D, Szczepanska M, Warzywoda A, Jander A, Ziolkowska H, Makulska I, Bienias B, Kipigroch H, Wiercinski R, Siten G. Do children with end-stage renal disease live shorter? Analysis of mortality on the basis of data from the Polish Registry of Renal Replacement Therapy in Children. Adv Med Sci. 2015;60:13–7.
14. Hattori M, Sako M, Kaneko T, Ashida A, Matsunaga A, Igarashi T, Itami N, Ohta T, Gotoh Y, Satomura K, Honda M, Igarashi T. End-stage renal disease in Japanese children: a nationwide survey during 2006-2011. Clin Exp Nephrol. 2015;19:933–8.
15. Plumb L, Wong E, Casula A, Braddon F, Lewis M, Marks SD, Shenoy M, Sinha MD, Maxwell H. Chapter 4 demography of the UK Paediatric renal replacement therapy population in 2016. Nephron. 2018;139(Suppl 1):105–16.
16. Australia and New Zealand Dialysis and Transplantation Registry Annual Report. 2017;Chapter 11; End-stage kidney disease in pediatrics.
17. CORR Annual report: treatment of end-stage organ failure in Canada, 2004 to 2013. 2015.
18. Samuel SM, Tonelli MA, Foster BJ, Alexander RT, Nettel-Aguirre A, Soo A, Hemmelgarn BR. Survival in pediatric dialysis and transplant patients. Clin J Am Soc Nephrol. 2011;6:1094–9.
19. Verrina E, Edefonti A, Gianoglio B, Rinaldi S, Sorino P, Zacchello G, Lavoratti G, Maringhini S, Pecoraro C, Calevo MG, Turrini Dertenois L, Perfumo F. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
20. Adamczuk D, Roszkowska-Blaim M. Long-term outcomes in children with chronic kidney disease stage 5 over the last 40 years. Arch Med Sci. 2017;13:635–44.
21. Vogelzang JL, van Stralen KJ, Jager KJ, Groothoff JW. Trend from cardiovascular to non-cardiovascular late mortality in patients with renal replacement therapy since childhood. Nephrol Dial Transplant. 2013;28(8):2082–9. https://doi.org/10.1093/ndt/gft048. Epub 2013
22. Chesnaye NC, Schaefer F, Groothoff JW, Bonthuis M, Reusz G, Heaf JG, Lewis M, Maurer E, Paripovic D, Zagozdzon I, van Stralen KJ, Jager KJ. Mortality risk in European children with end-stage renal disease on dialysis. Kidney Int. 2016;89:1355–62.
23. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. JAMA. 2013;309:1921–9.
24. Lin HH, Tsai CW, Lin PH, Cheng KF, Wu HD, Wang IK, Lin CY, Chen W, Huang CC. Survival analysis of pediatric dialysis patients in Taiwan. Nephrology (Carlton). 2012;17:621–7.
25. North American Pediatric Renal Trial and Collaboration Studies. NAPRTCS Annual Report 2011.
26. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, Mehls O, Schaefer F. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation. 2002;106:100–5.
27. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62:648–53.
28. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
29. North American Pediatric Renal Trial and Collaboration Studies. NAPRTCS Annual Report: renal transplantation, dialysis, chronic renal insufficiency. 2008.
30. Honda M, Warady BA. Long-term peritoneal dialysis and encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2010;25:75–81.
31. Youssef DM, Neemat-Allah MA. Hemodialysis in children: eleven years in a single center in Egypt. Iran J Kidney Dis. 2013;7(6):468–74. [26].
32. Chesnaye NC, Schaefer F, Bonthuis M, Holman R, Baiko S, Baskın E, Bjerre A, Berbeca O, Cloarec S, Cornelissen EAM, Espinosa L, Heaf J, Stone R, Shtiza D, Zagozdzon I, Harambat J, Jager KJ, Groothoff JW, van Stralen KJ. Mortality risk disparities in children receiving chronic renal replacement therapy for the treatment of end-stage renal disease across Europe. An ESPN-ERA/EDTA Registry analysis. Lancet. 2017;389:pii: S0140-6736(17)30063-6.
33. Schoenmaker NJ, Tromp WF, van der Lee JH, Adams B, Bouts AH, Collard L, Cransberg K, Van Damme-Lombaerts R, Godefroid N, Van Hoeck KJ, Koster-Kamphuis L, Lilien MR, Ann Raes A, Groothoff JW. Disparities in dialysis treatment and outcomes for Dutch and Belgian children with immigrant parents. Pediatr Nephrol. 2012;27:1369–79;
34. Tjaden LA, Noordzij M, van Stralen KJ, Kuehni CE, Raes A, Cornelissen EA, O'Brien C, Papachristou F, Schaefer F, Groothoff JW, Jager KJ, ESPN/ERA-EDTA Registry Study Group. Racial disparities in access to and outcomes of kidney transplantation

in children, adolescents, and young adults: results from the ESPN/ERA-EDTA (European Society of Pediatric Nephrology/European renal association-European Dialysis and Transplant Association) registry. Am J Kidney Dis. 2016;67(2):293–301.
35. Vidal E, van Stralen KJ, Chesnaye NC, Bonthuis M, Holmberg C, Zurowska A, Trivelli A, Da Silva JEE, Herthelius M, Adams B, Bjerre A, Jankauskiene A, Miteva P, Emirova K, Bayazit AK, Mache CJ, Sanchez-Moreno A, Harambat J, Groothoff JW, Jager KJ, Schaefer F, Verrina E. Infants requiring maintenance dialysis: outcomes of hemodialysis and peritoneal dialysis. Am J Kidney Dis. 2017;69:617–25.
36. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32:2319–30.
37. Honda M. The 1997 report of the Japanese National Registry data on pediatric peritoneal dialysis patients. Perit Dial Int. 1999;19(Suppl 2):S473–8.
38. Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. Kidney Int. 2005;68:818–25.
39. Myerburg RJ, Mitrani R, Interian A Jr, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation. 1998;97:1514–21.
40. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol. 1998;9:S16–23.
41. Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, Grimm R, Liu J, Louis T, Manning W, Matas A, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li S, Li S, Roberts T, Snyder J, Solid C, Wang C, Weinhandl E, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Johnson R, Sheets D, Forrest B, Berrini D, Constantini E, Everson S, Frederick P, Eggers P, Agodoa L. Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2005;45:A5–7, s1–280.
42. European Best Practice Guidelines Expert Group on Hemodialysis Section VII. Vascular disease and risk factors. Nephrol Dial Transplant. 2002;17(Suppl 7):88–109.
43. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45:S1–153.
44. Wang AY, Sanderson JE. Current perspectives on diagnosis of heart failure in long-term dialysis patients. Am J Kidney Dis. 2011;57:308–19.
45. Nolan CR. Strategies for improving long-term survival in patients with ESRD. J Am Soc Nephrol. 2005;16(Suppl 2):S120–7.
46. Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, Acquistapace I, Stella A, Bonforte G, DeVecchi A, DeCristofaro V, Buccianti G, Vincenti A. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. Am J Kidney Dis. 2005;46:897–902.
47. Wang AY, Wang M, Woo J, Lam CW, Li PK, Lui SF, Sanderson JE. Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. J Am Soc Nephrol. 2003;14:159–68.
48. Straumann E, Meyer B, Misteli M, Blumberg A, Jenzer HR. Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis. Br Heart J. 1992;67:236–9.
49. Litwin M, Wuhl E, Jourdan C, Niemirska A, Schenk JP, Jobs K, Grenda R, Wawer ZT, Rajszys P, Mehls O, Schaefer F. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant. 2008;23:2552–7.
50. Goothoff JW, Gruppen MP, Offringa M, de Groot E, Stok W, Bos WJ, Davin JC, Lilien MR, Van de Kar NC, Wolff ED, Heymans HS. Increased arterial stiffness in young adults with end-stage renal disease since childhood. J Am Soc Nephrol. 2002;13(12):2953–61. https://doi.org/10.1097/01.asn.0000037677.16961.df.
51. Xie Q, Ge X, Shang D, Li Y, Yan H, Tian J, Hao CM, Zhu T. Coronary artery calcification score as a predictor of all-cause mortality and cardiovascular outcome in peritoneal Dialysis patients. Perit Dial Int. 2016;36:163–70.
52. Querfeld U, Schaefer F. Cardiovascular risk factors in children on dialysis: an update. Pediatr Nephrol. 2018;35:41–57.
53. Al-Biltagi M, ElHafez MAA, El Amrousy DM, El-Gamasy M, El-Serogy H. Evaluation of the coronary circulation and calcification in children on regular hemodialysis. Pediatr Nephrol. 2017;32:1941–51.
54. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478–83.
55. Srivaths PR, Silverstein DM, Leung J, Krishnamurthy R, Goldstein SL. Malnutrition-inflammation-coronary calcification in pediatric patients receiving chronic hemodialysis. Hemodial Int. 2010;14:263–9.
56. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, Zambrano P, Ahlenstiel T, Bakkaloglu SA, Spizzirri AP, Lopez L, Ozaltin F, Printza N, Hari P, Klaus G, Bak M, Vogel A, Ariceta G, Yap HK, Warady BA, Schaefer F. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78:1295–304.
57. Groothoff JW, Offringa M, Van Eck-Smit BL, Gruppen MP, Van De Kar NJ, Wolff ED, Lilien MR, Davin JC, Heymans HS, Dekker FW. Severe bone disease and low bone mineral density after juvenile renal failure. Kidney Int. 2003;63:266–75.

58. Rennenberg RJ, Kessels AG, Schurgers LJ, van Engelshoven JM, de Leeuw PW, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. Vasc Health Risk Manag. 2009;5:185–97.
59. Harambat J, Bonthuis M, van Stralen KJ, Ariceta G, Battelino N, Bjerre A, Jahnukainen T, Leroy V, Reusz G, Sandes AR, Sinha MD, Groothoff JW, Combe C, Jager KJ, Verrina E, Schaefer F, ESPN/ERA-EDTA Registry. Adult height in patients with advanced CKD requiring renal replacement therapy during childhood. Clin J Am Soc Nephrol. 2014;9(1):92–9.
60. van Huis M, Bonthuis M, Sahpazova E, Mencarelli F, Spasojević B, Reusz G, Caldas-Afonso A, Bjerre A, Baiko S, Vondrak K, Molchanova EA, Kolvek G, Zaikova N, Böhm M, Ariceta G, Jager KJ, Schaefer F, van Stralen KJ, Groothoff JW. Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries-a report from the ESPN/ERA-EDTA registry. Nephrol Dial Transplant. 2015;31(4):609–19. pii: gfv105
61. Tanno Y, Yokoyama K, Hosoya T. Laparoscopic approach for the evaluation of peritoneal injury. Kidney Int. 2012;82:244–5.
62. Honda K, Hamada C, Nakayama M, Miyazaki M, Sherif AM, Harada T, Hirano H. Impact of uremia, diabetes, and peritoneal dialysis itself on the pathogenesis of peritoneal sclerosis: a quantitative study of peritoneal membrane morphology. Clin J Am Soc Nephrol. 2008;3:720–8.
63. Tawada M, Ito Y, Hamada C, Honda K, Mizuno M, Suzuki Y, Sakata F, Terabayashi T, Matsukawa Y, Maruyama S, Imai E, Matsuo S, Takei Y. Vascular endothelial cell injury is an important factor in the development of encapsulating peritoneal sclerosis in long-term peritoneal dialysis patients. PLoS One. 2016;11:e0154644.
64. Yamamoto T, Izumotani T, Otoshi T, Kim M. Morphological studies of mesothelial cells in CAPD effluent and their clinical significance. Am J Kidney Dis. 1998;32:946–52.
65. Johnson DW, Mudge DW, Blizzard S, Arndt M, O'Shea A, Watt R, Hamilton J, Cottingham S, Isbel NM, Hawley CM. A comparison of peritoneal equilibration tests performed 1 and 4 weeks after PD commencement. Perit Dial Int. 2004;24:460–5.
66. Rubin J, Ray R, Barnes T, Bower J. Peritoneal abnormalities during infectious episodes of continuous ambulatory peritoneal dialysis. Nephron. 1981;29:124–7.
67. Albrektsen GE, Wideroe TE, Nilsen TI, Romundstad P, Radtke M, Hallan S, Aasarod K, Oien C, Laegreid IK. Transperitoneal water transport before, during, and after episodes with infectious peritonitis in patients treated with CAPD. Am J Kidney Dis. 2004;43:485–91.
68. Krediet RT, Zuyderhoudt FM, Boeschoten EW, Arisz L. Alterations in the peritoneal transport of water and solutes during peritonitis in continuous ambulatory peritoneal dialysis patients. Eur J Clin Investig. 1987;17:43–52.
69. Lai KN, Leung JC. Inflammation in peritoneal dialysis. Nephron Clin Pract. 2010;116:c11–8.
70. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. Kidney Int. 2004;66:2437–45.
71. Holtta TM, Ronnholm KA, Holmberg C. Influence of age, time, and peritonitis on peritoneal transport kinetics in children. Perit Dial Int. 1998;18:590–7.
72. Warady BA, Fivush B, Andreoli SP, Kohaut E, Salusky I, Schlichting L, Pu K, Watkins S. Longitudinal evaluation of transport kinetics in children receiving peritoneal dialysis. Pediatr Nephrol. 1999;13:571–6.
73. Yoshino A, Honda M, Fukuda M, Araki Y, Hataya H, Sakazume S, Tanaka Y, Kawamura K, Murai T, Kamiyama Y. Changes in peritoneal equilibration test values during long-term peritoneal dialysis in peritonitis-free children. Perit Dial Int. 2001;21:180–5.
74. Kaku Y, Honda M. Standardized peritoneal equilibration test in Japanese children and the influence of long-term peritoneal dialysis. Perit Dial Int. 2008;28(Suppl 3):S150–2.
75. Honda K, Oda H. Pathology of encapsulating peritoneal sclerosis. Perit Dial Int. 2005;25(Suppl 4):S19–29.
76. Van Overmeire L, Goffin E, Krzesinski JM, Saint-Remy A, Bovy P, Cornet G, Bovy C. Peritoneal equilibration test with conventional 'low pH/high glucose degradation product' or with biocompatible 'normal pH/low glucose degradation product' dialysates: does it matter? Nephrol Dial Transplant. 2013;28:1946–51.
77. Choi HY, Kim DK, Lee TH, Moon SJ, Han SH, Lee JE, Kim BS, Park HC, Choi KH, Ha SK, Han DS, Lee HY. The clinical usefulness of peritoneal dialysis fluids with neutral pH and low glucose degradation product concentration: an open randomized prospective trial. Perit Dial Int. 2008;28:174–82.
78. Ayuzawa N, Ishibashi Y, Takazawa Y, Kume H, Fujita T. Peritoneal morphology after long-term peritoneal dialysis with biocompatible fluid: recent clinical practice in Japan. Perit Dial Int. 2012;32:159–67.
79. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, Passlick-Deetjen J. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int. 2004;66:408–18.
80. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, Jones B, Kulkarni H, Langham R, Ranganathan D, Schollum J, Suranyi M, Tan SH, Voss D. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol. 2012;23:1097–107.
81. Yamagata K, Tomida C, Koyama A. Intraperitoneal hyaluronan production in stable continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1999;19:131–7.

82. Kawanishi H, Moriishi M. Epidemiology of encapsulating peritoneal sclerosis in Japan. Perit Dial Int. 2005;25(Suppl 4):S14–8.
83. Hirahara I, Inoue M, Okuda K, Ando Y, Muto S, Kusano E. The potential of matrix metalloproteinase-2 as a marker of peritoneal injury, increased solute transport, or progression to encapsulating peritoneal sclerosis during peritoneal dialysis–a multicentre study in Japan. Nephrol Dial Transplant. 2007;22:560–7.
84. Do JY, Kim YL, Park JW, Chang KA, Lee SH, Ryu DH, Kim CD, Park SH, Yoon KW. The association between the vascular endothelial growth factor-to-cancer antigen 125 ratio in peritoneal dialysis effluent and the epithelial-to-mesenchymal transition in continuous ambulatory peritoneal dialysis. Perit Dial Int. 2008;28(Suppl 3):S101–6.
85. Homma S, Masunaga Y, Kurosu M, Inoue M, Sakurai T, Asano Y. Changes in peritoneal coagulation and fibrinolysis after discontinuation of chronic peritoneal dialysis. Perit Dial Int. 2002;22:178–83.
86. Morelle J, Sow A, Hautem N, Bouzin C, Crott R, Devuyst O, Goffin E. Interstitial fibrosis restricts osmotic water transport in encapsulating peritoneal sclerosis. J Am Soc Nephrol. 2015;26:2521–33.
87. Yokoyama K, Yoshida H, Matsuo N, Maruyama Y, Kawamura Y, Yamamoto R, Hanaoka K, Ikeda M, Yamamoto H, Nakayama M, Kawaguchi Y, Hosoya T. Serum beta2 microglobulin (beta2MG) level is a potential predictor for encapsulating peritoneal sclerosis (EPS) in peritoneal dialysis patients. Clin Nephrol. 2008;69:121–6.
88. Izumotani T, Ishimura E, Yamamoto T, Otoshi T, Okuno S, Inaba M, Kim M, Nishizawa Y. Correlation between peritoneal mesothelial cell cytology and peritoneal histopathology with respect to prognosis in patients on continuous ambulatory peritoneal dialysis. Nephron. 2001;89:43–9.
89. Nishina M, Endoh M, Suzuki D, Tanabe R, Endoh H, Hirahara I, Sakai H. Neutral-pH peritoneal dialysis solution improves peritoneal function and decreases matrix metalloproteinase-2 (MMP-2) in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Clin Exp Nephrol. 2004;8:339–43.
90. Kawanishi H, Fujimori A, Tsuchida K, Takemoto Y, Tomo T, Minakuchi J, Yamamoto T, Kim M, Numata A, Choh S, Naito H. Markers in peritoneal effluent for withdrawal from peritoneal dialysis: multicenter prospective study in Japan. Adv Perit Dial Conf Perit Dial. 2005;21:134–8.
91. Ho-dac-Pannekeet MM, Hiralall JK, Struijk DG, Krediet RT. Longitudinal follow-up of CA125 in peritoneal effluent. Kidney Int. 1997;51:888–93.
92. Kawaguchi Y, Saito A, Kawanishi H, Nakayama M, Miyazaki M, Nakamoto H, Tranaeus A. Recommendations on the management of encapsulating peritoneal sclerosis in Japan, 2005: diagnosis, predictive markers, treatment, and preventive measures. Perit Dial Int. 2005;25(Suppl 4):S83–95.
93. Brown MC, Simpson K, Kerssens JJ, Mactier RA. Encapsulating peritoneal sclerosis in the new millennium: a national cohort study. Clin J Am Soc Nephrol. 2009;4:1222–9.
94. Shroff R, Stefanidis CJ, Askiti V, Edefonti A, Testa S, Ekim M, Kavaz A, Ariceta G, Bakkaloglu S, Fischbach M, Klaus G, Zurowska A, Holtta T, Jankauskiene A, Vondrak K, Vande Walle J, Schmitt CP, Watson AR. Encapsulating peritoneal sclerosis in children on chronic PD: a survey from the European Paediatric Dialysis Working Group. Nephrol Dial Transplant. 2013;28:1908–14.
95. Hoshii S, Honda M. High incidence of encapsulating peritoneal sclerosis in pediatric patients on peritoneal dialysis longer than 10 years. Perit Dial Int. 2002;22:730–1.
96. Johnson DW, Cho Y, Livingston BE, Hawley CM, McDonald SP, Brown FG, Rosman JB, Bannister KM, Wiggins KJ. Encapsulating peritoneal sclerosis: incidence, predictors, and outcomes. Kidney Int. 2010;77:904–12.
97. Balasubramaniam G, Brown EA, Davenport A, Cairns H, Cooper B, Fan SL, Farrington K, Gallagher H, Harnett P, Krausze S, Steddon S. The Pan-Thames EPS study: treatment and outcomes of encapsulating peritoneal sclerosis. Nephrol Dial Transplant. 2009;24:3209–15.
98. Kawanishi K, Honda K, Hamada C. Recommendations for pathological diagnosis on biopsy samples from peritoneal dialysis patients. Pleura Peritoneum. 2017;2:3–15.
99. Io H, Hamada C, Ro Y, Ito Y, Hirahara I, Tomino Y. Morphologic changes of peritoneum and expression of VEGF in encapsulated peritoneal sclerosis rat models. Kidney Int. 2004;65:1927–36.
100. Schilte MN, Celie JW, Wee PM, Beelen RH, van den Born J. Factors contributing to peritoneal tissue remodeling in peritoneal dialysis. Perit Dial Int. 2009;29:605–17.
101. Aguilera A, Yanez-Mo M, Selgas R, Sanchez-Madrid F, Lopez-Cabrera M. Epithelial to mesenchymal transition as a triggering factor of peritoneal membrane fibrosis and angiogenesis in peritoneal dialysis patients. Curr Opin Investig Drugs (London, England: 2000). 2005;6:262–8.
102. Holmdahl L, Kotseos K, Bergstrom M, Falk P, Ivarsson ML, Chegini N. Overproduction of transforming growth factor-beta1 (TGF-beta1) is associated with adhesion formation and peritoneal fibrinolytic impairment. Surgery. 2001;129:626–32.
103. Vidal E, Edefonti A, Puteo F, Chimenz R, Gianoglio B, Lavoratti G, Leozappa G, Maringhini S, Mencarelli F, Pecoraro C, Ratsch IM, Cannavo R, De Palo T, Testa S, Murer L, Verrina E. Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients: the experience of the Italian Registry of Pediatric Chronic Dialysis. Nephrol Dial Transplant. 2013;28:1603–9.
104. Otsuka Y, Nakayama M, Ikeda M, Sherif AM, Yokoyama K, Yamamoto H, Kawaguchi Y. Restoration of peritoneal integrity after withdrawal of peritoneal dialysis: characteristic features

of the patients at risk of encapsulating peritoneal sclerosis. Clin Exp Nephrol. 2005;9:315–9.
105. Lambie ML, John B, Mushahar L, Huckvale C, Davies SJ. The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis is made. Kidney Int. 2010;78:611–8.
106. Yamamoto T, Nagasue K, Okuno S, Yamakawa T. The role of peritoneal lavage and the prognostic significance of mesothelial cell area in preventing encapsulating peritoneal sclerosis. Perit Dial Int. 2010;30:343–52.
107. Barreto DL, Coester AM, Struijk DG, Krediet RT. Can effluent matrix metalloproteinase 2 and plasminogen activator inhibitor 1 be used as biomarkers of peritoneal membrane alterations in peritoneal dialysis patients? Perit Dial Int. 2013;33:529–37.
108. Sampimon DE, Korte MR, Barreto DL, Vlijm A, de Waart R, Struijk DG, Krediet RT. Early diagnostic markers for encapsulating peritoneal sclerosis: a case-control study. Perit Dial Int. 2010;30:163–9.
109. Kawaguchi Y, Kawanishi H, Mujais S, Topley N, Oreopoulos DG. Encapsulating peritoneal sclerosis: definition, etiology, diagnosis, and treatment. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int. 2000;20(Suppl 4):S43–55.
110. Rottembourg J, Brouard R, Issad B, Allouache M, Ghali B, Boudjemaa A. Role of acetate in loss of ultrafiltration during CAPD. Contrib Nephrol. 1987;57:197–206.
111. Parikova A, Zweers MM, Struijk DG, Krediet RT. Peritoneal effluent markers of inflammation in patients treated with icodextrin-based and glucose-based dialysis solutions. Adv Perit Dial Conf Perit Dial. 2003;19:186–90.
112. Moriishi M, Kawanishi H. Icodextrin and intraperitoneal inflammation. Perit Dial Int. 2008;28(Suppl 3):S96–s100.
113. Kawanishi H, Shintaku S, Shishida M, Morrishi M, Tsuchiya S, Dohi K. A case of encapsulating peritoneal sclerosis suspected to result from the use of icodextrin peritoneal solution. Adv Perit Dial Conf Perit Dial. 2009;25:45–9.
114. Habib AM, Preston E, Davenport A. Risk factors for developing encapsulating peritoneal sclerosis in the icodextrin era of peritoneal dialysis prescription. Nephrol Dial Transplant. 2010;25:1633–8.
115. Klink CD, Schickhaus P, Binnebosel M, Jockenhoevel S, Rosch R, Tolba R, Neumann UP, Klinge U. Influence of 4% icodextrin solution on peritoneal tissue response and adhesion formation. BMC Surg. 2013;13:34.
116. Nakayama M, Miyazaki M, Honda K, Kasai K, Tomo T, Nakamoto H, Kawanishi H. Encapsulating peritoneal sclerosis in the era of a multi-disciplinary approach based on biocompatible solutions: the NEXT-PD study. Perit Dial Int. 2014;34:766–74.
117. Kawanishi K, Honda K, Tsukada M, Oda H, Nitta K. Neutral solution low in glucose degradation products is associated with less peritoneal fibrosis and vascular sclerosis in patients receiving peritoneal dialysis. Perit Dial Int. 2013;33:242–51.
118. Hamada C, Honda K, Kawanishi K, Nakamoto H, Ito Y, Sakurada T, Tanno Y, Mizumasa T, Miyazaki M, Moriishi M, Nakayama M. Morphological characteristics in peritoneum in patients with neutral peritoneal dialysis solution. J Artif Organs. 2015;18:243–50.
119. Hoshii S, Honda M, Itami N, Oh S, Matsumura C, Moriya S, Mori M, Hatae K, Ito Y, Karashima S. Sclerosing encapsulating peritonitis in pediatric peritoneal dialysis patients. Pediatr Nephrol. 2000;14:275–9.
120. Nomoto Y, Kawaguchi Y, Kubo H, Hirano H, Sakai S, Kurokawa K. Sclerosing encapsulating peritonitis in patients undergoing continuous ambulatory peritoneal dialysis: a report of the Japanese Sclerosing Encapsulating Peritonitis Study Group. Am J Kidney Dis. 1996;28:420–7.
121. Nakayama M. The greater incidence of encapsulating peritoneal sclerosis is not the result of overdiagnosis. Perit Dial Int. 2001;21(Suppl 3):S72–4.
122. Hsu YH, Hsia CC, Tsai DM, Tu HY, Hung KY, Huang JW. Development of encapsulating peritoneal sclerosis following bacterial peritonitis in a peritoneal dialysis patient. Am J Kidney Dis. 2010;55:198–202.
123. Kawanishi H, Kawaguchi Y, Fukui H, Hara S, Imada A, Kubo H, Kin M, Nakamoto M, Ohira S, Shoji T. Encapsulating peritoneal sclerosis in Japan: a prospective, controlled, multicenter study. Am J Kidney Dis. 2004;44:729–37.
124. van Westrhenen R, Aten J, Hajji N, de Boer OJ, Kunne C, de Waart DR, Krediet RT. Cyclosporin A induces peritoneal fibrosis and angiogenesis during chronic peritoneal exposure to a glucose-based, lactate-buffered dialysis solution in the rat. Blood Purif. 2007;25:466–72.
125. da Silva N, Rocha S, Rocha L, Faria S, Costa T, Mota C. Post-transplantation encapsulating peritoneal sclerosis in a pediatric patient. Pediatr Nephrol. 2012;27:1583–8.
126. Tan R, Betjes M, Cransberg K. Post-transplantation encapsulating peritoneal sclerosis in a young child. Nephrol Dial Transplant. 2011;26:3822–4.
127. Maluccio M, Sharma V, Lagman M, Vyas S, Yang H, Li B, Suthanthiran M. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. Transplantation. 2003;76:597–602.
128. Korte MR, Habib SM, Lingsma H, Weimar W, Betjes MG. Posttransplantation encapsulating peritoneal sclerosis contributes significantly to mortality after kidney transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2011;11:599–605.
129. Temple S, Zaltzman J, Perl J. Development of encapsulating peritoneal sclerosis in a renal transplant recipient on sirolimus immunotherapy. Perit Dial Int. 2010;30:475–7.

130. Sud R, Garry L, Spicer ST, Allen RD, Eris JM, Wyburn K, Verran D, Cooper CL, Chadban S. A role for everolimus in post-transplant encapsulating peritoneal sclerosis: first case report. Nephrology (Carlton). 2014;19(Suppl 1):27–30.
131. Moriishi M, Kawanishi H, Kawai T, Takahashi S, Hirai T, Shishida M, Watanabe H, Takahashi N. Preservation of peritoneal catheter for prevention of encapsulating peritoneal sclerosis. Adv Perit Dial Conf Perit Dial. 2002;18:149–53.
132. Brown P, Baddeley H, Read AE, Davies JD, McGarry J. Sclerosing peritonitis, an unusual reaction to a beta-adrenergic-blocking drug (practolol). Lancet (London, England). 1974;2:1477–81.
133. Oules R, Challah S, Brunner FP. Case-control study to determine the cause of sclerosing peritoneal disease. Nephrol Dial Transplant. 1988;3:66–9.
134. Brown EA, Bargman J, van Biesen W, Chang MY, Finkelstein FO, Hurst H, Johnson DW, Kawanishi H, Lambie M, de Moraes TP, Morelle J, Woodrow G. Length of time on peritoneal dialysis and encapsulating peritoneal sclerosis – position paper for ISPD: 2017 update. Perit Dial Int. 2017;37:362–74.
135. Nakamoto H. Encapsulating peritoneal sclerosis–a clinician's approach to diagnosis and medical treatment. Perit Dial Int. 2005;25(Suppl 4):S30–8.
136. Sampimon DE, Coester AM, Struijk DG, Krediet RT. The time course of peritoneal transport parameters in peritoneal dialysis patients who develop encapsulating peritoneal sclerosis. Nephrol Dial Transplant. 2011;26:291–8.
137. Goodlad C, Tarzi R, Gedroyc W, Lim A, Moser S, Brown EA. Screening for encapsulating peritoneal sclerosis in patients on peritoneal dialysis: role of CT scanning. Nephrol Dial Transplant. 2011;26:1374–9.
138. Tarzi RM, Lim A, Moser S, Ahmad S, George A, Balasubramaniam G, Clutterbuck EJ, Gedroyc W, Brown EA. Assessing the validity of an abdominal CT scoring system in the diagnosis of encapsulating peritoneal sclerosis. Clin J Am Soc Nephrol. 2008;3:1702–10.
139. Vlijm A, Stoker J, Bipat S, Spijkerboer AM, Phoa SS, Maes R, Struijk DG, Krediet RT. Computed tomographic findings characteristic for encapsulating peritoneal sclerosis: a case-control study. Perit Dial Int. 2009;29:517–22.
140. Araki Y, Hataya H, Tanaka Y, Fukuzawa R, Ikeda M, Kawamura K, Honda M. Long-term peritoneal dialysis is a risk factor of sclerosing encapsulating peritonitis for children. Perit Dial Int. 2000;20:445–51.141,142.
141. Kuriyama S, Tomonari H. Corticosteroid therapy in encapsulating peritoneal sclerosis. Nephrol Dial Transplant. 2001;16:1304–5.
142. Mori Y, Matsuo S, Sutoh H, Toriyama T, Kawahara H, Hotta N. A case of a dialysis patient with sclerosing peritonitis successfully treated with corticosteroid therapy alone. Am J Kidney Dis. 1997;30:275–8.
143. Habib SM, Betjes MG, Fieren MW, Boeschoten EW, Abrahams AC, Boer WH, Struijk DG, Ruger W, Krikke C, Westerhuis R, de Sevaux RG, van der Sande FM, Gaasbeek A, Korte MR. Management of encapsulating peritoneal sclerosis: a guideline on optimal and uniform treatment. Neth J Med. 2011;69:500–7.
144. van Bommel EF, Hendriksz TR, Huiskes AW, Zeegers AG. Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. Ann Intern Med. 2006;144:101–6.
145. Loureiro J, Sandoval P, del Peso G, Gonzalez-Mateo G, Fernandez-Millara V, Santamaria B, Bajo MA, Sanchez-Tomero JA, Guerra-Azcona G, Selgas R, Lopez-Cabrera M, Aguilera AI. Tamoxifen ameliorates peritoneal membrane damage by blocking mesothelial to mesenchymal transition in peritoneal dialysis. PLoS One. 2013;8:e61165.
146. Huang JW, Yen CJ, Wu HY, Chiang CK, Cheng HT, Lien YC, Hung KY, Tsai TJ. Tamoxifen downregulates connective tissue growth factor to ameliorate peritoneal fibrosis. Blood Purif. 2011;31:252–8.
147. Guest S. Tamoxifen therapy for encapsulating peritoneal sclerosis: mechanism of action and update on clinical experiences. Perit Dial Int. 2009;29:252–5.
148. Korte MR, Fieren MW, Sampimon DE, Lingsma HF, Weimar W, Betjes MG. Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study. Nephrol Dial Transplant. 2011;26:691–7.
149. Woodrow G, Fan SL, Reid C, Denning J, Pyrah AN. Renal Association Clinical Practice Guideline on peritoneal dialysis in adults and children. BMC Nephrol. 2017;18:333.
150. Kittur DS, Korpe SW, Raytch RE, Smith GW. Surgical aspects of sclerosing encapsulating peritonitis. Arch Surg (Chicago, Ill: 1960). 1990;125:1626–8.
151. Kawanishi H, Watanabe H, Moriishi M, Tsuchiya S. Successful surgical management of encapsulating peritoneal sclerosis. Perit Dial Int. 2005;25(Suppl 4):S39–47.
152. Kawanishi H, Shintaku S, Moriishi M, Dohi K, Tsuchiya S. Seventeen years' experience of surgical options for encapsulating peritoneal sclerosis. Adv Perit Dial Conf Perit Dial. 2011;27:53–8.
153. Kawanishi H. Surgical treatment for encapsulating peritoneal sclerosis. Adv Perit Dial Conf Perit Dial. 2002;18:139–43.
154. Campbell R, Augustine T, Hurst H, Pararajasingam R, van Dellen D, Armstrong S, Bartley C, Birtles L, Summers A. Anthropometrics identify wasting in patients undergoing surgery for encapsulating peritoneal sclerosis. Perit Dial Int. 2015;35:471–80.
155. Latus J, Ulmer C, Fritz P, Rettenmaier B, Biegger D, Lang T, Ott G, Scharpf C, Kimmel M, Steurer W, Alscher MD, Braun N. Encapsulating peritoneal sclerosis: a rare, serious but potentially curable complication of peritoneal dialysis-experience of a referral Centre in Germany. Nephrol Dial Transplant. 2013;28:1021–30.
156. Betjes MG, Habib SM, Boeschoten EW, Hemke AC, Struijk DG, Westerhuis R, Abrahams AC, Korte

MR. Significant decreasing incidence of encapsulating peritoneal sclerosis in the Dutch population of peritoneal dialysis patients. Perit Dial Int. 2017;37:230–4.
157. El-Sherbini N, Duncan N, Hickson M, Johansson L, Brown EA. Nutrition changes in conservatively treated patients with encapsulating peritoneal sclerosis. Perit Dial Int. 2013;33:538–43.
158. de Freitas D, Jordaan A, Williams R, Alderdice J, Curwell J, Hurst H, Hutchison A, Brenchley PE, Augustine T, Summers AM. Nutritional management of patients undergoing surgery following diagnosis with encapsulating peritoneal sclerosis. Perit Dial Int. 2008;28:271–6.
159. Stefanidis CJ, Shroff R. Encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2014;29:2093–103.
160. Rigby RJ, Hawley CM. Sclerosing peritonitis: the experience in Australia. Nephrol Dial Transplant. 1998;13:154–9.
161. Kawanishi H. Encapsulating peritoneal sclerosis in Japan: prospective multicenter controlled study. Perit Dial Int. 2001;21(Suppl 3):S67–71.
162. Phelan PJ, Walshe JJ, Al-Aradi A, Garvey JP, Finnegan K, O'Kelly P, McWilliams J, Ti JP, Morrin MM, Morgan N, Conlon PJ. Encapsulating peritoneal sclerosis: experience of a tertiary referral center. Ren Fail. 2010;32:459–63.
163. Bansal S, Sheth H, Siddiqui N, Bender FH, Johnston JR, Piraino B. Incidence of encapsulating peritoneal sclerosis at a single U.S. university center. Adv Perit Dial Conf Perit Dial. 2010;26:75–81.
164. Vizzardi V, Sandrini M, Zecchini S, Ravera S, Manili L, Cancarini G. Encapsulating peritoneal sclerosis in an Italian center: thirty-year experience. J Nephrol. 2016;29:259–67.
165. Petrie MC, Traynor JP, Mactier RA. Incidence and outcome of encapsulating peritoneal sclerosis. Clin Kidney J. 2016;9:624–9.
166. Alatab S, Najafi I, Pourmand G, Hosseini M, Shekarchian S. Risk factors of severe peritoneal sclerosis in chronic peritoneal dialysis patients. Ren Fail. 2017;39:32–9.
167. Brouhard BH, Donaldson LA, Lawry KW, et al. Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplant. 2000;4:261–7.
168. Gipson DS, Hooper SR, Duquette PJ, et al. Memory and executive functions in pediatric chronic kidney disease. Child Neuropsychol. 2006;12:391–405.
169. Qvist E, Pihko H, Fagerudd P, et al. Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant. 2002;6:53–62.
170. Broyer M, Le BC, Charbit M, et al. Long-term social outcome of children after kidney transplantation. Transplantation. 2004;77:1033–7.
171. Groothoff JW, Grootenhuis M, Dommerholt A, et al. Impaired cognition and schooling in adults with end stage renal disease since childhood. Arch Dis Child. 2002;87:380–5.
172. Bawden HN, Acott P, Carter J, et al. Neuropsychological functioning in end-stage renal disease. Arch Dis Child. 2004;89:644–7.
173. Duquette PJ, Hooper SR, Wetherington CE, et al. Brief report: intellectual and academic functioning in pediatric chronic kidney disease. J Pediatr Psychol. 2007;32:1011–7.
174. Karrfelt HM, Berg UB. Long-term psychosocial outcome after renal transplantation during childhood. Pediatr Transplant. 2008;12:557–62.
175. Johnson RJ, Warady BA. Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy. Pediatr Nephrol. 2013;28:1283–91.
176. Hooper SR, Gerson AC, Butler RW, et al. Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:1824–30.
177. Groothoff JW, Grootenhuis MA, Offringa M, Gruppen MP, Korevaar JC, Heymans HSA. Quality of life in adults with end-stage renal disease since childhood is only partially impaired. Nephrol Dial Transplant. 2003;18(2):310–7.
178. Fujisawa M, Ichikawa Y, Yoshiya K, et al. Assessment of health-related quality of life in renal transplant and hemodialysis patients using the SF-36 health survey. Urology. 2000;56:201–6.
179. Merkus MP, Jager KJ, Dekker FW, et al. Quality of life over time in dialysis: the Netherlands cooperative study on the adequacy of dialysis. NECOSAD Study Group. Kidney Int. 1999;56:720–8.
180. Merkus MP, Jager KJ, Dekker FW, et al. Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. The Necosad Study Group. Am J Kidney Dis. 1997;29:584–92.
181. Gee L, Abbott J, Conway SP, et al. Validation of the SF-36 for the assessment of quality of life in adolescents and adults with cystic fibrosis. J Cyst Fibros. 2002;1:137–45.
182. Lee TA, Hollingworth W, Sullivan SD. Comparison of directly elicited preferences to preferences derived from the SF-36 in adults with asthma. Med Decis Mak. 2003;23:323–34.
183. McClish DK, Penberthy LT, Bovbjerg VE, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005;3:50.
184. Rebollo P, Ortega F, Baltar JM, et al. Is the loss of health-related quality of life during renal replacement therapy lower in elderly patients than in younger patients? Nephrol Dial Transplant. 2001;16:1675–80. 200
185. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: is quality of life determined by expectations or experience? BMJ. 2001;322:1240–3.
186. Tjaden LA, Vogelzang J, Jager KJ, van Stralen KJ, Maurice-Stam H, Grootenhuis MA, et al. Long-term

quality of life and social outcome of childhood end-stage renal disease. J Pediatr. 2014;165(2):336–42.
187. Groothoff JW, Grootenhuis MA, Offringa M, et al. Social consequences in adult life of end-stage renal disease in childhood. J Pediatr. 2005;146:512–7.
188. Tjaden LA, Maurice-Stam H, Grootenhuis MA, Jager KJ, Groothoff JW. Impact of renal replacement therapy in childhood on long-term socioprofessional outcomes: a 30-year follow-up study. J Pediatr. 2016;171:189–95.e1-2. pii: S0022-3476(15)01527-9
189. Rees L, Shroff R, Hutchinson C, Fernando ON, Trompeter RS. Long-term outcome of Paediatric renal transplantation: follow-up of 300 children from 1973 to 2000. Nephron Clin Pract. 2007;105:c68–c7.
190. Rocha S, Fonseca I, Silva N, et al. Impact of pediatric kidney transplantation on long-term professional and social outcomes. Transplant Proc. 2011;43:120–4.
191. Tozzi AE, Mazzotti E, Di Ciommo VM, et al. Quality of life in a cohort of patients diagnosed with renal failure in childhood and who received renal transplant. Pediatr Transplant. 2012;16:840–5. 201
192. Mellerio H, Alberti C, Labeguerie M, et al. Adult social and professional outcomes of pediatric renal transplant recipients. Transplantation. 2014;97:196–205.
193. Offner G, Latta K, Hoyer PF, et al. Kidney transplanted children come of age. Kidney Int. 1999;55:1509–17.

40 Health-Related Quality of Life of Children and Adolescents on Dialysis

Rebecca J. Johnson and Susan L. Furth

Introduction

In addition to important indicators of health outcomes such as growth, cardiovascular health, and infection rates, healthcare providers are increasingly invested in evaluating and considering the quality of life (QOL) of patients on dialysis and their families. It is now considered important, and often required, to assess QOL as a key outcome alongside other measures of health outcomes. Indeed, for patients with end-stage renal disease (ESRD) in the United States, yearly assessment of QOL is mandated by the Centers for Medicaid and Medicare Services [3].

The World Health Organization defines quality of life as individuals' "perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" [48]. It is meant to be a broad concept that reflects an individual's physical health, psychological state, personal beliefs, social relationships, and his or her relationships to important features of the environment. It is widely recognized that chronic disease and its treatment may significantly impact patients' QOL, including psychological health (mood, attention, concentration, learning), social functioning (quality of relationships, participation in normative social activities), physical health, and educational or vocational outcomes (school attendance, academic achievement, and attainment of vocational goals). Within the context of disease, quality of life is often referred to as health-related quality of life (HRQOL), recognizing that disease may have a unique impact on a person's life, but still defining HRQOL as a multidimensional construct. Most measures include questions or ratings that tap into the aspects of physical, psychological, social, and educational or vocational functioning described above.

Historically, parents or caregivers have been relied upon to describe a child's HRQOL, but current practice emphasizes the importance of assessing both caregiver perceptions and the child's own perceptions of his or her HRQOL. One reason for this is that many studies have identified discrepancies between parent-proxy and youth self-report of HRQOL [2, 27–29], so gathering information from both sources is best practice and believed to provide a more comprehensive picture of HRQOL [4, 7, 21].

Information gathered about patient- and parent-perceived HRQOL is primarily used to assess individual patient outcomes and to

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evaluate how disease and treatment is impacting an individual child and sometimes his or her family. This allows providers to consider potential interventions to address areas of HRQOL that are suboptimal or poor. In addition to this individual level of assessment, more attention is being paid to HRQOL as an important measure of the success of a given treatment within a population. Indeed, WHO defines health as "a state of complete physical, mental, and social well-being, not merely the absence of disease." The value of treatment, even if successful clinically, is diminished if the patient does not perceive adequate HRQOL. Thus, information about HRQOL can be used to evaluate the impact of treatments or programs on groups of patients, to inform standards of care and policy for identified patient populations. One example of an effort within nephrology to standardize outcomes that include aspects of HRQOL is SONG-Kids (Standardised Outcomes in Nephrology – Children and Adolescents). The aim of this initiative is to enhance the relevance, transparency, and impact of research designed to improve the lives of children across all stages of CKD and their families and, importantly, includes patients and their caregivers in the process of identifying key outcomes [40].

Assessment of HRQOL

Measures of HRQOL can be categorized into three types: generic HRQOL measures, disease-specific measures, and measures of functional disability. The reported psychometric properties of available pediatric instruments tend to be fair to good, but the full psychometric picture is often incomplete [28]. An important weakness of current measures is the absence of empirically derived minimal clinically important difference scores; this would allow providers to better interpret the magnitude of change that is observed and identify thresholds for meaningful change [28]. Three measures of generic HRQOL and one disease-specific measure that have been used with children who have ESRD are presented below, with a brief description of each.

Child Health and Illness Profile (CHIP)

The Child Health and Illness Profile (CHIP) has child and adolescent self-report versions and a parent-proxy report. The adolescent version (CHIP-AE) is for ages 11–17 and has been used with youth who have CKD. It has 153 items, assesses six domains of health (discomfort, satisfaction, disorders, achievements, resilience, and risks), and requires approximately 20 minutes to complete. It has demonstrated test-retest and internal reliability and criterion and construct validity [30].

Child Health Questionnaire

The Child Health Questionnaire (CHQ; [24]) is a generic HRQOL measure that includes both parent-proxy report for children ages 5–18 and child self-report for ages 10–18 years. This measure requires approximately 20 minutes to complete and assesses 12 domains of health (physical functioning, limitations in schoolwork and activities with friends, general health, bodily pain and discomfort, limitations in family activities, emotional/time impact on the parent, impact of emotional or behavior problems on schoolwork and other daily activities, self-esteem, mental health, behavior, family cohesion, and change in health). This measure has demonstrated internal consistency and concurrent validity [24].

PedsQL Generic Core Scales

The Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales is a 23-item generic (not disease-specific) measure of health-related quality of life [45]. It assesses four domains of health (physical functioning, emotional functioning, social functioning, and school functioning), and scores from these four domains are used to calculate three summary scores: psychosocial health, physical health, and a total scale score. The PedsQL was developed for youth and young adults 2–25 years; self-report forms for ages 5–18 years are avail-

able, as well as parent-proxy forms for children ages 2–18. The PedsQL takes approximately 4 minutes to complete and has been translated into several languages. It has demonstrated feasibility, reliability, and validity for use with children broadly, including those who have ESRD [17]. The parent-proxy report has also been shown to be feasible, reliable, and valid with youth 2–16 years of age [44].

PedsQL ESRD Module

In addition to the generic form of the PedsQL, a 34-item PedsQL End-Stage Renal Disease Module was developed for use with children who have ESRD [17]. This measure has seven scales relevant to ESRD: general fatigue, side effects of kidney disease, treatment problems, family and peer interactions, worry, perceived physical appearance, and communication. Child self-report and parent-proxy reports are available for patients ages 5–18 years, and a parent-proxy report is available for children 2–4 years. The format is similar to the PedsQL Generic Core Scales. Goldstein et al. reported initial support for the use of the ESRD module with children who have ESRD. Several scales demonstrated acceptable internal consistency reliability, and the measure demonstrated good construct validity. Ideally, the ESRD module would be used in conjunction with the Generic Core Scales, with both patient and parent informants, in order to capture comprehensively the child's HRQOL from both patient and parent perspectives.

Early Investigations of the Quality of Life of Youth on Dialysis

The first study to evaluate HRQOL in pediatric dialysis patients using a multidimensional, standardized measure of HRQOL was published in 1994 by Kurtin et al. [23]. In this pilot study, a measure of HRQOL was administered to 20 adolescents on hemodialysis. Overall, youth on hemodialysis reported impaired HRQOL. Those who were rated as less adherent by their healthcare providers reported more pain, poorer general and mental health, and lower family cohesion.

This pilot study led to the first multicenter, longitudinal study of QOL of children with chronic kidney disease (CKD) in the United States, initiated by Furth et al. The study expanded on Kurtin et al.'s pilot research to validate two multidimensional generic quality of life measures (the CHQ-Parent Form and the CHIP-AE) for use with children who have CKD. The parents of 78 patients with CKD completed the CHQ longitudinally (over 4 years); results indicated that parents reported poorer physical health for their children as their estimated glomerular filtration rate (eGFR) declined and that height gain was associated with better parent ratings of the physical and psychosocial functioning of their children [9]. This same study also examined adolescent self-report of HRQOL using the CHIP-AE. The sample included adolescents across multiple stages of CKD, including those on dialysis and post-transplant, with age-, socioeconomic-, and gender-matched controls. They found that the CHIP-AE distinguished between adolescents with kidney disease and the healthy control group in several domains [14]. Children with CKD reported lower satisfaction with health and more restriction in activity, with those on dialysis reporting the lowest levels of functional health.

Current Findings: Quality of Life of Youth on Dialysis

A number of cross-sectional studies have reported poorer HRQOL for children with CKD and in particular for youth on dialysis. Goldstein et al. [16] evaluated the HRQOL of 85 children on dialysis or with a renal transplant using both parent-proxy and self-report data from the PedsQL Generic Core Scales. Ratings derived from this patient group were compared to the ratings of a matched control group of healthy children. Results indicated that children with ESRD had worse HRQOL across domains – physical, emotional, social, and school – than the healthy control group, with dialysis patients reporting worse HRQOL than transplant patients. McKenna

et al. [25] reported both parent-proxy and self-reported HRQOL for patients with a range of CKD, including dialysis and transplant, and compared self- and parent-reported HRQOL to published norms. Patients on dialysis reported lower physical and school functioning ratings compared to a healthy control group but had similar ratings of emotional and social functioning. In contrast, parent-proxy ratings of youth on dialysis were lower than the healthy control group across all domains of the PedsQL. Dotis et al. [6] assessed the HRQOL of 55 children ages 8–18 years, a subset of whom were on dialysis (n = 14), and found that patients reported lower physical HRQOL than a healthy control group. In a study that assessed the HRQOL of 55 children with ESRD (dialysis or transplant), patients with ESRD had significantly lower scores than a healthy control group across all domains of HRQOL, for both self- and parent-proxy report, with patients on dialysis reporting poorer physical and school functioning than those with renal transplants [8]. Similar findings were reported by Kilicoglu et al. [22] for another group of dialysis and transplant patients; those receiving renal replacement therapy reported poorer HRQOL than a control group.

In addition to El Shafei et al., several other studies have indicated that patients on dialysis report poorer HRQOL than patients who have undergone renal transplant. In a study using the PedsQL ESRD module only, transplant patients (n = 37), versus those on dialysis (n = 55), reported better quality of life in one domain of self-report, and their parents reported better HRQOL in two domains [29]. In another study examining HRQOL in dialysis versus transplant, dialysis patients scored lower than healthy controls and transplant patients on a measure of health satisfaction [31]. Varni et al. [44] compared the parent-proxy and self-reports of HRQOL of children in ten disease groups, including ESRD, and found that compared to youth who had undergone renal transplant, children on hemodialysis reported significantly impaired physical and overall HRQOL and their parents reported poorer HRQOL across all domains for their children on hemodialysis compared to those who had received a transplant. For the subset of children on peritoneal dialysis, their parents reported lower emotional functioning for their children compared to children who had received a transplant.

In contrast, in a study of 192 youth, Splinter et al. [35] found that both dialysis and renal transplant patients self-reported impaired HRQOL compared to healthy controls and youth with other chronic health conditions. Those undergoing preemptive transplants reported higher physical HRQOL but otherwise had scores similar to those who underwent non-preemptive transplant. Rather than type of renal replacement therapy, it was presence of comorbidities that was the most important determinant of impaired HRQOL. In one of few studies to examine this question longitudinally, Wightman et al. [47] retrospectively examined the longitudinal HRQOL data for 56 children who were on dialysis before undergoing kidney transplant. They found that reported HRQOL improved over time for all scales on the PedsQL ESRD module; for patients with both pre- and post-transplant assessments, total scores increased on both self-report and parent-proxy reports. In another longitudinal study of HRQOL that included only patients on dialysis, Neul et al. [27] found that patients on dialysis longer, particularly females, had worse ratings of emotional functioning. Parents of older youth and youth on dialysis longer reported worse functioning for their children on multiple domains of HRQOL and perceived their children's school functioning as deteriorating over time.

With regard to long-term outcomes, Tjaden et al. [38] examined social outcomes 30 years later for all Dutch patients born before 1979 who started RRT at less than 15 years of age. These patients completed a measure of HRQOL and reported on other sociodemographic outcomes. Eighty-nine of 152 patients still alive responded; those on dialysis reported impaired physical HRQOL, but mental health scores were comparable to the general population. Those with a history of ESRD had fewer offspring, were less likely to have income equal to or above average, and were less likely to be employed than the general population. Lower

HRQOL was associated with disabilities, comorbidities, and unemployment.

A number of studies have used qualitative methods to evaluate the HRQOL of children with advanced CKD. Tong et al. [39] asked 27 adolescents and young adults awaiting transplant or on dialysis to keep a daily journal and complete interviews regarding their experiences and perspectives. This qualitative data indicated that these patients had impaired self-worth, perceived a precarious future, and felt limited with regard to their physical and psychosocial capacities; they did not perceive having the same opportunities and potential for success as their healthy peers. In the same sample, using cross-sectional methodology, Tong et al. [41] examined perceived HRQOL using a visual analogue scale and three utility-based measures of HRQOL. They found that these adolescents and young adults reported low HRQOL, and utility-based HRQOL scores suggested they were willing to trade considerable life expectancy for perfect health. Dialysis patients reported the highest burden of kidney disease (interference with daily life, time burden, and the feeling of being a burden to others).

Tjaden et al. [37] conducted a systematic review of 17 qualitative studies to describe the experiences and perspectives of adolescents on dialysis. The selected group of studies included 143 children and adolescents on dialysis and identified five main themes underlying these children's experience of dialysis. These included loss of control, restricted lifestyle, use of coping strategies, managing treatment, and feeling different. They concluded that children undergoing dialysis often have poor self-esteem and a pervasive sense of losing identity, body integrity, control, and independence, and these children perceive that their disease limits their opportunities in life.

Comorbidities and HRQOL

As reported above, the presence of increased comorbidities tends to negatively impact the HRQOL of children with ESRD. With regard to specific comorbidities, Stabouli et al. [34] examined sleep disorders in children with CKD, identifying seven relevant studies, five of which included children on dialysis. They found that the prevalence of sleep disorders ranged from 77% to 85% among patients on dialysis. Two of these studies also assessed HRQOL within the context of sleep disturbance. Davis et al. [5] found high rates of sleep disturbance among children with CKD and found that the presence of sleep disturbance correlated with a decline in HRQOL independent of disease group (pre-dialysis, dialysis, or transplant) or estimated GFR. Riar et al. [32] assessed children with CKD for restless legs syndrome (RLS) specifically, in a prospective, cross-sectional study that compared patients to a healthy control group and included assessment of HRQOL using the PedsQL Generic Core Scales. They found that RLS was more common in children with CKD, and there were no associations between CKD stage (pre-dialysis, dialysis, or transplant), etiology, or duration of disease and presence of RLS. Children with RLS were more likely to rate the quality of their sleep as "bad" or "very bad," and on parent-proxy report children with RLS had poorer psychosocial and total HRQOL scores.

Short stature, another comorbidity of CKD, has been associated with lower HRQOL. One study found that children with CKD who had short stature reported lower self-esteem and lower satisfaction with their overall health than those with more normal growth [31]. In studies of children with mild to moderate CKD, in one study short stature was associated with lower physical HRQOL [15], and in another it was associated with lower ratings of HRQOL by both parents and patients [19]. Tjaden et al. [36] reported in a 30-year follow-up study of childhood ESRD that short stature in adulthood was associated with less likelihood of having children. Another study found that both growth hormone use and height gains were associated with improved parent-proxy scores in the HRQOL domains of physical and social functioning [1]. Unfortunately, many children with CKD and short stature do not receive growth hormone therapy [43]; this is a potentially modifiable comorbidity, and improvement in height may lead to greater satisfaction with health and better quality of life.

Anemia is a common comorbidity of CKD and has been associated with reduced HRQOL. For children with mild to moderate CKD, anemia has been associated with lower parent-proxy scores on the social functioning scale of the PedsQL [15]. In a study of 105 adolescents with CKD stages 1–5, the parents of patients with hematocrit less than 36% (n = 75) reported that their children were less likely to participate in activities at school and with their friends and rated them as being less physically active than children with hematocrit greater than 36% [13]. In another study of children on dialysis, those who were anemic reported a negative impact on HRQOL in the areas of sleep, alertness, emotions, and daily activities [42]. In contrast, in a study that used level of hemoglobin to define anemia (<11 g/dl defined as anemic), there were no differences in HRQOL between the anemic and non-anemic groups.

To better manage comorbidities associated with ESRD, a number of studies have investigated the benefits of more frequent hemodialysis or variations on how hemodialysis is administered (e.g., at home, nocturnally). Initial findings included several positive outcomes that may affect HRQOL, including allowance of unrestricted diets and fluid intake, lack of need for phosphate binders, improved metabolic and blood pressure control, and in some cases improved growth [10, 26, 46]. Studies of adults have demonstrated improvements in blood pressure, phosphate control, and health-related quality of life through use of nocturnal hemodialysis [11, 33]. With regard to the pediatric literature, a small study (n = 4) examined outcomes of more frequent HD, including three patients who received more frequent HD at home. Results revealed no change in the total HRQOL score via parent-proxy or patient report, but the parents of the patients who completed HD at home reported improved emotional and psychosocial scores for their children (Goldstein et al. 2008). Geary et al. [12] reported that three of four adolescents in a trial of home nocturnal hemodialysis had improved HRQOL ratings, increased school attendance, and more positive teacher assessments. Difficulties associated with this treatment modality included increased burden for parents, disruption for other family members, and the need to establish a new routine. Hoppe et al. [20] prospectively examined 16 patients (ages 0.5 to 17 years) who transitioned from conventional hemodialysis to hospital-based intermittent nocturnal hemodialysis. In addition to improvements in several uremia-associated measures, perceived QOL improved and school absence decreased for all patients.

Conclusions

Along with other health outcomes, such as growth and cardiovascular health, it is important to assess and prioritize the HRQOL of children on dialysis. Cross-sectional, longitudinal, and qualitative studies all indicate that the HRQOL of children and adolescents on dialysis is significantly impaired compared to healthy children. Thus, comprehensive assessment of HRQOL, which may include both generic and disease-specific measures, is of key importance so that opportunities to improve HRQOL can be identified and pursued. Several different measures of HRQOL exist (see [28], for a review). In addition, discrepancies between parent-proxy and child self-report have been identified in the literature, so gathering both perspectives will improve our understanding of patients' HRQOL. Comorbidities, such as short stature, anemia, and sleep disturbance, are important drivers of HRQOL and are associated with poorer HRQOL. Alternative modalities that reduce comorbidities and improve engagement in normative activities, such as school attendance, may improve HRQOL. The literature on HRQOL in children and adolescents on dialysis would benefit from additional clarity regarding correlates of HRQOL and testing of interventions to improve this important health outcome.

References

1. Al-Uzri A, Matheson M, Gipson DS, Mendley SR, Hooper SR, Yadin O, Rozansky DJ, Moxey-Mims M, Furth SL, Warady BA, Gerson AC, Chronic Kidney Disease in Children Study Group. The impact of short stature on health-related quality of life in children with chronic kidney disease. J Pediatr. 2013;163:736–41.

2. Baek HE, et al. Health-related quality of life of children with pre-dialysis chronic kidney disease. Pediatr Nephrol. 2017;32:2097–105.
3. Centers for Medicare & Medicaid Services. Conditions for coverage (CFCs) & conditions of participations (CoPs) for end-stage renal disease facilities. Baltimore: Center for Medicare & Medicaid Services; 2008. Available at www.cms.gov
4. Cremeens J, Eiser C, Blades M. Brief report: assessing the impact of rating scale type, types of items, and age on the measurement of school-age children's self-reported quality of life. J Pediatr Psychol. 2007;32:132–8.
5. Davis ID, Greenbaum LA, Gipson D, Ling Wu L, Sinha R, Matsuda-Abedini M, Emancipator JL, Lane JC, Hodgkins K, Nailescu C, Barletta GM, Arora S, Mahan JD, Rosen CL. Prevalence of sleep disturbances in children and adolescents with chronic kidney disease. Pediatr Nephrol. 2012;27:451–9.
6. Dotis J, Pavlaki A, Printza N, Stabouli S, Antoniou S, Gkogka C, Kontodimopoulos N, Papachristou F. Quality of life in children with chronic kidney disease. Pediatr Nephrol. 2016;31:2309–16.
7. Eiser C. Commentary on evidence-based assessment of health-related quality of life and functional impairment in pediatric psychology. J Pediatr Psychol. 2008;33:997–8.
8. El Shafei A, Hegazy IS, Fadel FI, Nagy EM. Assessment of quality of life among children with end-stage renal disease: a cross-sectional study. J Environ Public Health. 2018; https://doi.org/10.1155/2018/8565498.
9. Fadrowski J, Cole S, Hwang W, Fiorenza J, Weiss R, Gerson A, Furth S. Changes in physical and psychosocial functioning among adolescents with chronic kidney disease. Pediatr Nephrol. 2006;21:394–9.
10. Fischbach M, Fothergill H, Zaloszyc A, Menouer S, Terzic J. Intensified daily dialysis: the best chronic dialysis option for children? Semin Dial. 2011;24:640–4.
11. Frequent Hemodialysis Network (FHN) Trial Group. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363:2287–300.
12. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, Harvey EA. Home nocturnal hemodialysis in children. J Pediatr. 2005;147:383–7.
13. Gerson AC, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush B, Furth S for the Council on Pediatric Nephrology and Urology of New York/New Jersey and the Kidney and Urology Foundation of America. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis. 2004;44:1017–23.
14. Gerson AC, Riley A, Fivush BA, Pham N, Fiorenza J, Robertson J, Chandra M, Trachtman H, Weiss R. Furth SL for the Council on Pediatric Nephrology and Urology of New/New Jersey and the Kidney and Urology Foundation of America. Assessing health status and health care utilization in adolescents with chronic kidney disease. J Am Soc Nephrol. 2005;16:1427–32.
15. Gerson AC, Wentz A, Abraham AG, Mendley SR, Hooper SR, Butler RW, Gipson DS, Lande MB, Shinnar S, Moxey-Mims MM, Warady BA, Furth SL. Health-related quality of life of children with mild to moderate chronic kidney disease. Pediatrics. 2010;125:e349–57.
16. Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW. Health-related quality of life in pediatric patients with ESRD. Pediatr Nephrol. 2006;21:846–50.
17. Goldstein SL, Graham N, Warady BA, Seikaly M, McDonald R, Burwinkle TM, Limbers CA, Varni JW. Measuring health-related quality of life in children with ESRD: performance of the generic and ESRD-specific instrument of the Pediatric Quality of Life Inventory (PedsQL). Am J Kidney Dis. 2008a;51:285–97.
18. Goldstein SL, Silverstein DM, Leung JC, Feig DI, Soletsky B, Knight C, Warady BA. Frequent hemodialysis with NxStage™ system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008b;23:129–35.
19. Harmer M, Wootton S, Gilbert R, Anderson C. Association of nutritional status and health-related quality of life in children with chronic kidney disease. Qual Life Res. 2019;28:1565–73.
20. Hoppe A, von Puttkamer C, Linke U, Kahler C, Boob M, Braunauer-Kolberg R, Hofmann K, Joachimsky P, Hirte I, Schley S, Utsch B, Thamfart J, Briese S, Gellermann J, Zimmering M, Querfeld U, Muller D. A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr. 2011;158:95–9.
21. Huang IC, Shenkman EA, Leite W, Knapp CA, Thompson LA, Revicki DA. Agreement was not found in adolescents' quality of life rated by parents and adolescents. J Clin Epidemiol. 2009;62:337–46.
22. Kilicoglu AG, Bahali K, Canpolat N, Bilgic A, Mutlu C, Yalçın Ö, Pehlivan G, Sever L. Impact of end-stage renal disease on psychological status and quality of life. Pediatr Int. 2016;58:1316–21.
23. Kurtin PS, Landgraf JM, Abetz L. Patient-based health status measurements in pediatric dialysis: expanding the assessment of outcome. Am J Kidney Dis. 1994;24:376–82.
24. Landgraf JM, Abetz LN, Ware JE. The Child Health Questionnaire (CHQ): A user's manual. 1st Printing, Boston, MA: New England Medical Center. 2nd Printing, Boston, MA: HealthAct; 1996, 1999.
25. McKenna AM, Keating LE, Vigneux A, Stevens S, Williams A, Geary DF. Quality of life in children with chronic kidney disease – patient and caregiver assessments. Nephrol Dial Transplant. 2006;21:1899–905.
26. Müller D, Zimmering M, Chan CT, McFarlane PA, Pierratos A, Querfeld U. Intensified hemodialysis regimens: neglected treatment options for children and adolescents. Pediatr Nephrol. 2008;23:1729–36.
27. Neul SK, Minard CG, Currier H, Goldstein SL. Health-related quality of life functioning over a 2-year period in children with end-stage renal disease. Pediatr Nephrol. 2013;28:285–93.

28. Palermo TM, Long AC, Lewandowski AS, Drotar D, Quittner AL, Walker LS. Evidence-based assessment of health-related quality of life and functional impairment in pediatric psychology. J Pediatr Psychol. 2008;33:983–96.
29. Park, et al. Quality of life in children with end-stage renal disease based on a PedsQL ESRD module. Pediatr Nephrol. 2012;27:2293–300.
30. Starfield B, Riley A. Profiling health and illness in children and adolescents. In: D Drotar measuring health-related quality of life in children and adolescents: implications for research and practice. Mahwah: Lawrence Erlbaum; 1998. p. 85–104.
31. Riaño-Galán I, Málaga S, Rajmil L, Ariceta G, Navarro M, Loris C, Vallo A. Quality of life of adolescents with end-stage renal disease and kidney transplant. Pediatr Nephrol. 2009;24:1561–8.
32. Riar SK, Leu RM, Turner-Green TC, Rye DB, Kendrick-Allwood SR, McCracken C, Bliwise DL, Greenbaum LA. Restless legs syndrome in children with chronic kidney disease. Pediatr Nephrol. 2013;28:773–95.
33. Rocco MV, Lockridge RS Jr, Beck GJ, Eggers PW, Gassman JJ, Greene T, Frequent Hemodialysis Network (FHN) Trial Group, et al. The effects of frequent nocturnal home hemodialysis: the frequent hemodialysis network nocturnal trial. Kidney Int. 2011;80:1080–91.
34. Stabouli S, Papadimitriou E, Printza N, Dotis J, Papachristou F. Sleep disorders in pediatric chronic kidney disease patients. Pediatri Nephrol. 2016;31:1221–9.
35. Splinter A, Tjaden LA, Haverman L, Adams B, Collard L, Cransberg K, van Dyck M, Van Hoeck KJ, Hoppe B, Koster-Kamphuis L, Lilien MR, Raes A, Taylan C, Grootenhuis MA, Groothoff JW. Children on dialysis as well as renal transplanted children report severely impaired health-related quality of life. Qual Life Res. 2018;27:1445–54.
36. Tjaden LA, Maurice-Stam H, Grootenhuis MA, Jager KJ, Groothoff JW. Impact of renal replacement therapy in childhood on long-term socioprofessional outcomes: a 30-year follow-up study. J Pediatr. 2016;171:189–95.
37. Tjaden L, Tong A, Henning P, Groothoff J, Craig JC. Children's experiences of dialysis: a systematic review of qualitative studies. Arch Dis Child. 2012;97:395–402.
38. Tjaden LA, Vogelzang J, Jager KJ, van Stralen KJ, Maurice-Stam H, Grootenhuis MA, Groothoff JW. Long-term quality of life and social outcome of childhood end-stage renal disease. J Pediatr. 2014;165:336–42.
39. Tong A, Henning P, Wong G, McTaggert S, Mackie F, Carroll RP, Craig JC. Experiences and perspectives of adolescents and young adults with advanced CKD. Am J Kidney Dis. 2013a;61:375–84.
40. Tong A, Saumuel S, Zappitelli M, Criag JC on behalf of the SONG-Kids Investigators. Standardised outcomes in nephrology – children and adolescents (SONG-Kids): a protocol for establishing a core outcome set for children with chronic kidney disease. Trials. 2016;17:401.
41. Tong A, Wong G, McTaggert S, Henning P, Mackie F, Carroll RP, Howard K, Craig JC. Quality of life of young adults and adolescents with chronic kidney disease. J Pediatr. 2013b;163:1179–85.
42. Van Damme-Lombaerts R, Broyer M, Businger J, Baldauf C, Stocker H. A study of recombinant human erythropoietin in the treatment of anaemia of chronic renal failure in children on hemodialysis. Pediatr Nephrol. 1994;8:338–42.
43. van Huis M, Bonthuis M, Sahpazova E, Mencarelli F, Spasojevic B, Reusz G, Caldas-Afonso A, Bjerre A, Baiko S, Vondrak K, Molchanova EA, Kolvek N, Zaikova N, Bohm M, Ariceta G, Jager KJ, Schaefer F, van Stralen KJ, Groothoff JW. Considerable variations in growth hormone policy and prescription in pediatric end-stage renal disease across European countries – a report from the ESPN/ERA-EDTA registry. Nephrol Dial Transplant. 2015; https://doi.org/10.1093/ndt/gfv105.
44. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007;5:43.
45. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37:126–39.
46. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14:297–303.
47. Wightman A, Bradford MC, Smith J. Health-related quality of life changes following renal transplantation in children. Pediatr Transplant. 2019; https://doi.org/10.1111/petr.13333.
48. World Health Organization. https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/

41 Transition and Transfer to Adult Care for Adolescents and Young Adults with Advanced Chronic Kidney Disease

Lorraine E. Bell and Dirk Bethe

Introduction

Experiencing chronic illness during adolescence or young adulthood is a major challenge. For patients with advanced chronic kidney disease (CKD), it can be overwhelming. If the onset of CKD is during adolescence, hopes and dreams for the future may be shattered. When it begins earlier, there may be lost opportunities for normal psychosocial milestones and development. These children and adolescents often miss out on typical peer activities, socially, academically, and vocationally. Generally, their transition to adult healthcare occurs during one of the most emotionally vulnerable stages of development, the period of emerging adulthood. The clinical vignettes below illustrate a number of the challenges involved in transition. In this chapter, we will examine these and other transition elements in greater detail.

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Clinical Vignettes

Sally was diagnosed with pauci-immune glomerulonephritis and pulmonary hemorrhage 9 months ago at the age of 16 years. Her treatment included plasma exchange, corticosteroids, and rituximab. Although she stabilized clinically, her renal function is declining, and she'll need dialysis within a month. Prior to her illness, she had no health issues and was an excellent student and musician. Her dream is to become a concert violinist.

Harry is 16 years old and has been on hemodialysis for 4 years. He received a kidney transplant 5 years ago for end-stage renal disease (ESRD) due to focal segmental glomerulosclerosis (FSGS), but his disease recurred aggressively, and despite intensive multifaceted treatment, his graft failed within 9 months. He lives in a foster family and is worried about what will happen when he turns 18. His dream is to be healthy and to have supportive friends and family.

Casey is almost 18 years old and has had chronic kidney disease (CKD) since infancy. She received a kidney transplant at the age of 6 years and did well until mid-adolescence. At the age of 16, she lost her transplanted kidney due to antibody-mediated rejection and has been on peritoneal dialysis since. She is now highly sensitized. Her home is 300 miles from the nearest pediatric dialysis and transplant center. She struggles with taking her medication and with following her diet restrictions. Two years ago she

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dropped out of school, because it was too great an effort. Her dream is to get a new kidney.

Jordan is 21 years old and recently transferred to an adult hemodialysis unit. He often arrives late, and he is commonly very fluid overloaded. While in pediatrics he was listed for a transplant but didn't get an offer; now the adult transplant center is considering withdrawing him from the active list because of adherence concerns. He finds it very difficult to be in a dialysis unit where patients are decades older and very ill-looking, and he avoids most social contact.

Simon is 18 years old and has had CKD since childhood. He started peritoneal dialysis a year ago and was recently transferred to an adult unit. His mother accompanies him to all of his healthcare appointments and provides most of the history. When questioned directly, he is unable to describe the nature of his underlying kidney condition, as well as the names of or the reasons for most of the medications he takes.

The personal and treatment challenges illustrated in the above vignettes include:

1. Coming to terms with the sudden onset of a life-threatening condition and complex treatment in the teenage years
2. Dealing with a serious disease for which there are limited treatment options
3. Treatment adherence
4. Poor psychosocial support
5. Living with kidney disease from an early age
6. Missed educational opportunities
7. Depression
8. Lack of patient autonomy in the understanding of their disease and its treatment
9. The change in environment from pediatric to adult care

These elements and more need to be considered in transitioning a patient from pediatric to adult care.

Overview

Transition is a purposeful multiyear process that begins during pediatric care and *continues after transfer*, until the patient is fully integrated into adult care. The goal is to maximize lifelong functioning and potential through comprehensive patient-centered, flexible, and developmentally appropriate care that is continuous from adolescence to adulthood [1]. For many patients with chronic illness, the process of transition may continue until they are in their mid-20s, for reasons discussed in section "Attention to Psychosocial Issues and Needs, Including Educational Challenges".

A number of publications have looked at *barriers to transition*, across a wide range of conditions [2–5]. Common themes are listed in Table 41.1. *Beneficial aspects of transition* to adult care have also been described by recently transferred youth; they appreciate the focus on responsibility and self-management, a business-like atmosphere, information relevant to adult issues, new treatment options, and the possibility to choose a hospital closer to home. The primary determinant of a positive transition experience was the patient-centeredness of the adult-oriented provider and collaboration between the adult and pediatric services [6].

Helping young people successfully transition into the adult world requires a multifaceted team approach that supports them from their early teenage years to at least their mid-20s.

Several excellent and comprehensive guidelines have been published on the adolescent to adult transition of care in the UK, USA, Canada, and other countries [7–12]. An outstanding website for transition resources is available at Got Transition [13]. However, successful implementation of guidelines requires support from multiple disciplines and very importantly from high-level hospital administration. Resources are needed in terms of healthcare professionals, organizational support, and information technology.

Table 41.1 Potential transition barriers [2–5, 9, 83]

Patient and family related potential barriers	Provider and system related potential barriers
1. Difficulty "letting go" of long-standing relationships with pediatric providers 2. Fear of poor outcomes in relinquishing control of the condition to the young person 3. Limited knowledge about their medication, illness, and the transition process 4. Insufficient self-management skills 5. Poor treatment adherence 6. Limitations in neurocognition and/or developmental immaturity 7. Difficulty developing trust in new adult site providers 8. Feeling overwhelmed by the adult environment (described as impersonal, unwelcoming, and difficult to navigate) 9. Psychosocial issues (e.g., depression, anxiety, denial of illness, mental health and substance issues, absent/unsupportive caregiver, unstable life circumstances) 10. Schooling and vocational issues 11. Competing life demands 12. Lack of peers with the same condition	1. Lack of institutional backing to effectively promote good transition practices 2. Inadequate transitional care funding and resources 3. Poor transition organization and support 4. Lack of coordination for patients with need for several subspecialty services 5. Inadequate communication from pediatric clinicians, including medical records and follow-up recommendations 6. Lack of sharing of protocols between the pediatric and adult sites 7. Limited availability of adult providers 8. Insufficient training of adult providers in adolescent medicine and pediatric-onset conditions 9. Shorter appointment times in adult healthcare system 10. Lack of mental health and support services in adult care 11. Change or loss of insurance coverage when reaching adult age

Key elements of all these published guidelines include the following:

1. Having a named healthcare worker responsible for the patient's transition process and a transition champion
2. Starting early
3. Timely attention to psychosocial issues and needs, including educational challenges, that patients may face
4. Regular evaluation of adherence, including barriers and facilitators
5. Patient and family engagement and empowerment
6. Regular assessment of transition preparation using standardized tools and development of individualized transition plans
7. Tracking progress of individual patients and of the clinic/program's transition process as a whole
8. Appropriate timing of transfer
9. A succinct relevant patient transfer summary
10. A personalized health passport or summary document for the patient
11. Open bidirectional communication between the pediatric and adult teams
12. Recognition by the adult team of the young adult's developmental needs
13. Continuation of the transition process after transfer to adult care, until the young person is fully integrated and able to function in the adult system
14. Education and training for healthcare professionals

There is also a need for research, quality improvement assessment, consideration of cost, and advocacy for health policy change. We will review each of these components in the following sections.

Named Healthcare Worker and Transition Champion

The named worker can be someone with a formal position such as a *patient navigator* [12, 14–21] or *transition coordinator* or can be a designated nurse in the renal unit. The importance of appointing someone to be responsible and providing them with sufficient time and resources cannot be overemphasized. If not, there is an ongoing challenge during clinic visits, or in the dialysis unit,

Table 41.2 Roles of transition navigator[a] or coordinator [12, 14–16, 18–21]

Clinical	Administrative
• Transition readiness assessments • Creation of medical passport • Patient education and self-management coaching • Screening for transition concerns such as psychosocial issues and comorbid diagnoses • Provide coaching on adherence • Encourage healthy lifestyle habits (diet, exercise) • Provide support for medical or mental health crisis management	• Track patients and outcome data • Develop and update educational material • Facilitate group encounters (e.g., peer mentorship, educational evenings, etc.) • Participate in quality improvement
Navigational	**Patient advocacy**
• Help establish relationships with primary care providers and appropriate specialty care providers • Work with patient and healthcare providers to promote continuity of care • Assist with data sharing between pediatric and adult service providers • Facilitate and accompany patient to first adult site appointment • Track follow-up appointments, medication refills, and laboratory tests to flag early for nonadherence • Assist with health system navigation at and between appointments	• Evaluation of whether the patient will need community navigational support (e.g., developmental services, mental health services, postsecondary education accommodations) • Assist patients and families navigate financial barriers to healthcare (e.g., health and medication insurance changes at transition, transportation issues) • Address concerns of autonomy and potential need for surrogate decision-maker • Engage patients and families (get their input) in the planning of transition interventions

[a]These tasks can be shared by several members of the multidisciplinary team, but a named person needs to coordinate and be responsible for the process

to balance planning for future events (transition and transfer) with day-to-day demands. In nephrology, the transition navigator could be responsible for children on dialysis as well as those with kidney transplants, advanced CKD, or milder CKD combined with other complex conditions or needs. Having one navigator for dialysis, transplant, and advanced CKD patients facilitates continuity of care during their transition preparation years. Typical roles of a transition navigator are listed in Table 41.2. These multiple tasks could be shared by several people, but there must be someone to oversee and coordinate the process. For programs with relatively small patient numbers, the coordinator or navigator position could be shared with other specialties, allowing for the development of expertise. There is also a very important need for a *transition champion*, a leader who advocates for and promotes optimal transition practices, within individual programs and at the broader hospital level. Often this person is a physician or nurse.

Starting Early

Most guidelines recommend formally starting the transition process at around the age of 12 to 14 years [10, 11, 13, 22]. However, thinking about this future task should begin much earlier; some would advise shortly after diagnosis [11]. This is because young people with chronic disease need to integrate the care and responsibility for their health into their daily lives and develop confidence in their abilities. Even small children can play an active role in their care, so that participation in their treatment becomes a natural part of their everyday life. Their parents are integral to this process. The active involvement of children and adolescents in their treatment also promotes their feeling of self-efficacy. A longitudinal study of adolescents and young adults with a variety of chronic conditions showed that perceived self-efficacy is associated with a better health-related quality of life (HRQoL) [23].

Attention to Psychosocial Issues and Needs, Including Educational Challenges

Young people with advanced CKD begin adolescence, and thus transition, in the context of a very serious disease. They and their family may have already had to deal with considerable psychosocial challenges before adolescence: these include incurability of the disease, threat to life, painful and unpleasant examinations and treatments, adherence to numerous medical prescriptions, instructions and restrictions, dependence on medical devices and healthcare providers, violation of body image, problems of social integration, neglect of parents' individual and marital needs as well as of siblings' needs, challenges with regular school attendance, cognitive delays associated with early-onset renal failure [24, 25], burdens for some of additional disabilities and comorbidities, and socioeconomic hardships. For other adolescent patients, advanced CKD and ESRD may seem to appear abruptly (e.g., patients with rapidly progressive glomerulonephritis or those with minimally symptomatic renal tubular and interstitial disease or dysplasia). They are suddenly struck with a serious disease and have not grown up with the idea that their life has limitations. This group of patients may have major difficulties in adapting to illness and treatment and need special attention.

Studies have shown that HRQoL in pediatric patients with CKD, especially dialysis patients, is lower compared to healthy peers [26] but also compared to patients with other chronic diseases [27, 28]. This is also reflected in mental health. For example, Clementi et al. [29] report increased rates of depression and anxiety disorders, lower self-esteem, and a higher level of social impairment in pediatric dialysis patients. Therefore, patients and their families often carry a heavy burden when they enter adolescence and the transition process begins.

Growing up is a challenge for everyone. Age-specific developmental tasks and challenges include identity formation, development of autonomy, identification with peer groups, emotional bonds, cognitive development, physical development, sexuality, forming one's own philosophy of life, and school and vocational training. Age-specific changes of brain structure and function have been shown in MRI studies. The developmental changes in the brain continue beyond the age of 18, well into the third decade of life. The brain develops asynchronously: the limbic system, associated with emotions, reward, impulsivity, and motivation, matures fairly early in adolescence, whereas the prefrontal cortex, involved in executive functions such as planning, problem-solving, and impulse control, doesn't reach maturity until the middle of the third decade of life [30]. Age-typical risk-taking behavior and sensation-seeking are associated with this asynchronous maturation (Fig. 41.1).

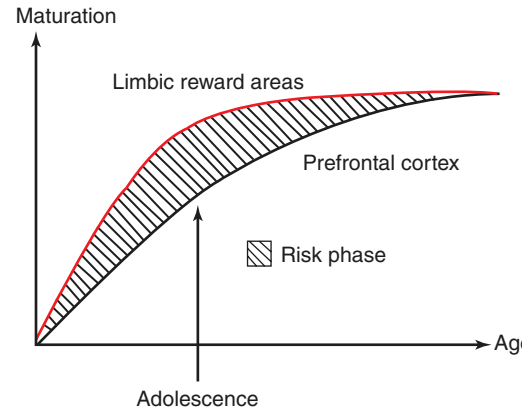

Fig. 41.1 Nonlinear maturation processes of subcortical and prefrontal brain areas lead to an imbalance of neural networks in adolescence. Age-typical risk-taking behavior and sensation-seeking are associated with this asynchronous maturation. (Modified from Casey et al. 2008 [30]; reproduced with permission of John Wiley and Sons)

Although these age-typical processes affect all young people, adolescents and young adults with a serious chronic disease such as CKD face particular challenges, including:

Adherence to Treatment, Despite Asynchronous Brain Development

In order not to endanger their health, they have the additional burden of adhering to their medical

treatment while coping with the same developmental, psychological, and neurobiological processes as other adolescents.

Acceptance That the Disease Does Not End with Childhood

As chronically ill youth grow out of childhood and adolescence, they are challenged to understand and cope with a difficult reality: that their disease is not a transitory aspect of their childhood but something that will always be a major part of their lives. Therefore, it is not surprising that some youth with a serious chronic disease, such as CKD, experience an identity crisis in late adolescence and early adulthood that requires psychotherapeutic treatment.

School and Vocational Training in Difficult Circumstances

Adolescents and young adults with advanced CKD often face hurdles with their education. Their health condition may lead to problems with concentration and memory, limitations in physical energy, and absenteeism due to clinic visits, hospitalizations, or dialysis treatments. Education is a very important determinant of future health; timely recognition of educational challenges is important so that processes can be put in place early to support the patient and optimize their potential. An additional consideration during vocational training and later employment is that CKD patients may need to accept restrictions in their choices of work and may have to give up their originally desired career.

Additional Challenges in Special Social Situations

Some youth with CKD exist in precarious situations that become even more difficult when they reach the age of majority, for example, those with emotionally unsupportive families, those with behavioral or mental health problems, those living in poverty, and those aging out of foster care [31–35]. Fragmented social support programs and idiosyncratic eligibility criteria may impede young adults getting the help they need and lead to lapses in care and stigmatization [35]. When these young people have a serious chronic disease, the hurdles can be overwhelming.

Some youth with CKD may not have the cognitive capacity to make informed decisions for themselves. In these situations, timely evaluation of decision-making capacity and the potential need for a surrogate decision-maker or official curatorship is essential. This should be started by the time the patient is 17 years of age, as the process can be lengthy. Conditions of guardianship or decision support need to be clearly documented in the patient's chart and communicated to the new adult clinicians [9].

Adolescents and young adults with CKD are in a vulnerable phase of life and therefore need regular evaluation of their psychosocial situation and a low threshold to access psychosocial support. It is also very important to provide support in school and vocational training in order to reconcile the requirements of medical treatment with educational needs. Having a psychologist and a social worker as part of the CKD and dialysis care team is key and should be the goal for all programs [36]. In general, the less support the family can provide, the more support by professionals is needed.

Unfortunately, psychosocial support services are less readily available in the adult medical system; this is an important argument in favor of individualized transfer timing. For patients that must be transferred while still needing psychosocial support, steps must be taken to either ensure services in the adult center or to connect the young person with a psychosocial counseling center near his or her home.

Table 41.3 The three "pillars" of adherence

	Communication between *P*atient/*F*amily (P/F) and *H*ealth-*C*are *T*eam (HCT)	Practical implementation in everyday life	Mental and emotional strength
Possible barriers to adherence	• HCT overestimates the P/F's health literacy or cognitive capacity, particularly when the care plan is complex • HCT fails to recognize limitations in language skills when the P/F's mother tongue is different • HCT overestimates the capacity of the P/F to absorb /retain information in certain settings, e.g., presence of distractions, emotionally taxing situations (*situational receptivity)* • P/F do not fully understand treatment and prescriptions • P/F disagree with (parts of) the treatment plan • Lack of clarity of medication prescriptions or other treatment regimen aspects	• Treatment requirement not practical for the P/F, e.g., "Take medication every 6 hours!" • Adverse side effects of medication • Forgetting medication • Competing priorities • Uncertainty in what to do with problems in medication taking, e.g., when realizing they forgot to take their medication, when they have vomiting or diarrhea • Difficulty adhering to diet and fluid restrictions • Financial-organizational aspects, e.g., high travel costs for outpatient consultations, difficulty missing work/school	• Stress and emotional exhaustion due to the long-term burden of the illness and treatment • Anxiety/psychological distress related to learning and responsibility for complex treatments (e.g., home dialysis) • Poor social support • Other forms of psychosocial issues • Denial of disease • Puberty
Support measures for improving adherence	• Provide information that takes into account the P/F's language ability and intellectual capacity • Be aware of potential problems with situational receptivity and the need to adapt or reschedule teaching • Age-appropriate education and regular involvement of the young person, from an early age • Provide complex regimens in writing, in "patient-friendly language," and keep them updated (e.g., medication prescription) • Develop a consensus on treatment that considers the P/F's views and ideas • Cultivate a relationship of trust between P/F and HCT	• Treatment regimens that, as much as possible, adapt to the everyday life of the P/F • Coaching, teaching, provision of practical aids (e.g., medicine dosettes, practical dietary information, phone or tablet apps for learning and reminders) • For medication side effects – Evaluate if the dose can be changed – Assess if something can be actively done to diminish the side effects – If not possible to make a change: Give extra appreciation for the "price" the patient is "paying" for the therapy • In case of financial problems: Consult a social worker	• Express appreciation for the coping efforts of the P/F – even if adherence is not yet satisfactory • Have an "open ear" for personal problems, if necessary calling professional psychosocial help • For patients in puberty: If necessary, help with the search for other fields for experimenting with sensation-seeking and risk-taking, e.g., advise on possible sports activities • Mediation of contacts to people who are equally affected; recommendation of participation in self-help activities, therapeutic camping, etc.

Checklist for assessing possible barriers to adherence and counseling tips to improve it. Each column ("pillar") is necessary but, on its own, is insufficient for acceptable adherence. If there are problems in one of the "pillars," the whole adherence-"building" becomes unstable (see also Fig. 41.2)

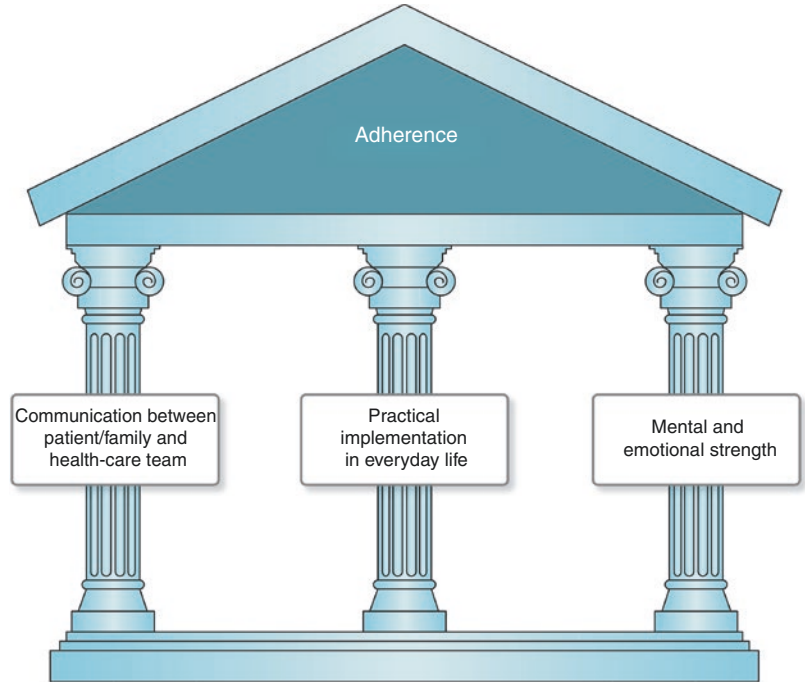

Fig. 41.2 The "three pillars of adherence" (see also Table 41.3)

Regular Evaluation of Adherence

Adherence to treatment is a challenge for almost all patients. "Satisfactory adherence" is attained when the difference between the patient's actual therapy (e.g., medication taken, dialysis performed, diet, etc.) and the prescribed therapy has no effect on the therapeutic outcome [37]. With the progression from childhood to adolescence and then young adulthood, satisfactory adherence usually becomes more challenging [37]. Most adolescents don't want to seem different from their peers and, as part of normal development, may resist the expectations of their parents and other adults. As they move into young adulthood, competing demands may contribute to poor adherence. Executive brain function, necessary for planning, good decision-making, and impulse control, is not fully developed until the mid-20s [30, 38, 39]. Among transplant recipients, the risk of graft failure is highest in adolescents and young adults aged 17–24 years and next highest in those aged 25–29 years; it is thought that nonadherence plays an important role in this outcome [40].

Regular support for adherence and nonjudgmental counseling are important for youth at all their outpatient visits. A partnership between the patient and healthcare team is essential. The "three pillars of adherence" (Table 41.3, Fig. 41.2) can serve as a checklist for regular adherence discussions, assessing possible barriers to adherence and jointly considering possibilities for improvement. Satisfactory adherence requires all three "pillars" to function: communication between the patient and healthcare team, practicality of implementation of the treatment regimen in everyday life, and mental and emotional strength. If one of the "pillars" develops cracks, the "adherence building" becomes "unstable."

Patient and Family Engagement and Empowerment

A well-functioning parent-young person relationship is central to the support of adolescents and young adults during the transition process. However, by the time their chronically ill chil-

dren reach adolescence, many parents have little strength remaining for the increased transition demands. A poignant statement from a systematic review of qualitative studies on parents' experiences sums it up: "In addition to 'normal' parental roles, being a parent of a child with chronic kidney disease demands a high-level healthcare provider, problem-solving, information seeking, and financial and practical skills at a time when the capacity to cope is threatened by physical tiredness, uncertainty, and disruption to peer support within and outside the family structure" [41].

Parents caring for a chronically ill child are at increased risk for depression, diminished quality of life, psychological stress, poor physical health, trauma symptoms, and financial burdens [41–44]. Despite this, most patient-family units adjust and jointly fulfill their tasks in treatment.

With the onset of adolescence, the challenges for patients and parents grow, with each taking on new roles. The patient must progressively assume more responsibility for his/her health management, and the parents must learn to gradually relinquish control over their child's adherence. The parents move from being the all-controlling "CEO" of their child's healthcare to a "consultant" in the background for support [45] (Fig. 41.3). Parents also need to understand that a teenager in an "adult" body doesn't yet have fully developed "adult-level" thought processes and decision-making judgment. Their task is a tightrope walk between under- and overprotectiveness, with a continued need for vigilant background oversight of treatment. The multidisciplinary healthcare team can play an important role in positively supporting these changes. Parent-child conflict may be greater for chronically ill AYA, compared to healthy peers [46].

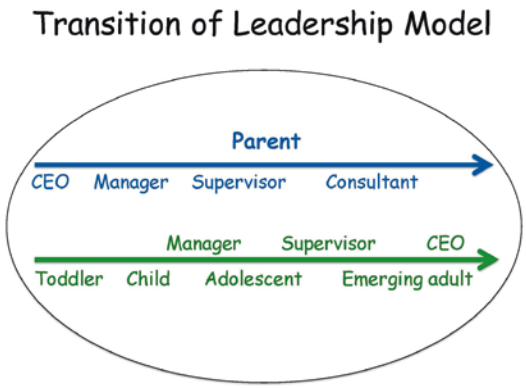

Fig. 41.3 A model of leadership transition for health management responsibility between parents and their children with special healthcare needs. (Image reproduced from Bell 2017, [84] with permission of Springer Nature)

Many parents and some patients are fearful of the transfer to adult care; concerns include potential deterioration in quality of care, diminished support, and the emotional challenge of leaving their long-established and trusted pediatric team [2, 47]. They find it easier if they are sufficiently prepared and actively involved in the transition process, including timing of the transfer of care and if they perceive a cooperative alliance between the pediatric and adult teams [48].

When no family is available to support the young person during their transition and transfer, there is a need to find someone who can fill this gap; possibilities include a relative, a residential group caregiver, or youth worker from a community psychosocial agency. Transfer to adult medicine without a close support person may overburden the young person and pose a risk to their health.

Regular Assessment of Transition Preparation Using Standardized Tools

There are a number of publicly available generic transition preparation tools, some more comprehensive than others. Most target older adolescents and their transfer readiness, and only a few have been validated. A list of currently validated tools is available on the Got Transition website [49]. When choosing a tool, it is important to ensure it covers all areas of transition preparation, including mental health, sexuality (fertility, pregnancy, contraception, and sexually transmitted infections), substance use, and healthy, active living. Many validated tools consist of simple checkboxes for the patient to fill out. However, unless these are carefully reviewed by a healthcare professional in an interview with the

adolescent, important items may be missed. There is also a need for transition tools for younger adolescents that assess age-appropriate milestones and tasks, because stepwise preparation for independence is recommended from the age of 12 years. For example, at the Montreal Children's Hospital, there are age-specific forms to promote progressive steps toward self-reliance. There are also questionnaires for parents, to help them better understand and foster their child's developing autonomy. All are publicly available on the hospital website [50]. Developmentally progressive checklists, entitled "Ready, Steady, Go," are also available on the website of a large UK teaching hospital [51, 52]. In addition, there is an outstanding set of tools developed for pediatric transplant recipients by the American Society of Transplant Pediatric Community of Practice which could easily be adapted for dialysis patients or those with advanced CKD [53].

Once these assessments are completed and reviewed with the healthcare professional, an individualized transition plan needs to be put in place for each patient that promotes their progressive independence and self-responsibility. It should be clearly labeled and easily accessible in the patient's medical chart. An excellent example from Got Transition [13] includes the following: (1) prioritized goals, (2) specific issues or concerns, (3) selected actions to take with consideration of both the target date and completion date, and (4) the name of the person responsible. These transition plans of action need to be periodically reviewed for progress and updates. For patients with intellectual disability who will never be independent, transition support needs to include, or focus on, the patient's parents. Important issues to address include legal information about surrogate decision-making, community resources, potential financial aid, and the changes that will occur in the adult healthcare system. Teaching and preparation of parents should also be documented and tracked in the patient's chart.

It can be difficult to find enough time at regular clinic visits to incorporate all the elements needed to prepare a patient for transition and transfer. A useful option is to have designated multidisciplinary transition preparation clinics. Patients can attend these clinics once or twice a year, starting a few years prior to the planned transfer date. At the Montreal Children's Hospital, transition preparation clinics are offered to all adolescents with complex renal disease, starting from the age of 12 to 14 years. Each patient is seen without their parent by the renal nurse, dietician, and social worker, as well as by a dedicated adolescent medicine physician and nephrologist. One or both parents also meet with the nephrology nurse, to help them prepare their adolescent for progressive autonomy.

Tracking Progress of Individual Patients and of the Clinic's Transition Process as a Whole

Keeping track of patients in need of transition preparation and their multiyear progress requires a systematic approach. An individual flow chart within a patient's medical file can facilitate this. Suggested items to include are the following: (1) the dates of (a) the patient's serial transition assessments, (b) updates of their medical summary and emergency care plan, (c) discussions about the adult model of care, (d) when the patient/family was advised regarding the need for a primary care physician (and the name of that person), and (e) the planned transfer time; (2) the names of the selected adult nephrologist and other adult specialists (if relevant); and (3) documentation of the preparation and content of the transfer package. An example of such of a form can be found in the Got Transition tools [54].

It is also important to monitor the clinic or program's transition process as a whole, and a registry/database is recommended, such as that shown on the Got Transition website [55]. For pediatric renal programs, it should include, at a minimum, patients on dialysis, kidney transplant recipients, adolescents with complex kidney disease, and those with advanced CKD. A program registry is important for overall program organization, quality improvement, and, potentially, future research initiatives.

Timing of Transfer

Transfer of care is a pivotal event in the transition process, and its timing should be optimized. The joint consensus statement of the International Pediatric Nephrology Association (IPNA) and the International Society of Nephrology (ISN) recommends individualized transfer timing, taking into account the patient's transition readiness, clinical and social stability, school milestones, and other subspecialty coordination [10].

However, in many pediatric nephrology centers, the age at transfer is fixed and nonnegotiable, usually at around 18 years of age, and determined by government regulation, health administration organizations, or insurance [56–58]. There is concern that a fixed transfer age may negatively impact outcome [56] and some evidence to suggest that transition readiness improves with increasing young adult age [59, 60]. In a landmark study using the United States Renal Data System (USRDS) to look at the association between age and graft failure rate, Foster and colleagues showed that the highest rate of graft failure was between the ages of 18 and 19 years – precisely when many centers have to transfer their patients to adult medicine [61]. An investigation of the correlation between age at transfer and kidney graft failure revealed that patients who were transferred under the age of 21 years had a significantly higher graft failure rate than those who were 21 years or older at the time of transfer [62].

For centers that are required to transfer their patients at the age of 18 years, systems are needed to support the young person during the vulnerable young adult (or emerging adult) period (approximately 18 to 25 years of age). These can include providing a phase of overlapping pediatric/adult care, having a designated nurse and physician interested in young adult care assigned to each young adult patient, organizing a young adult clinic, facilitating networking among peer patients, and involving external psychosocial counseling agencies and/or (if available) psychosocial staff at the adult center [11, 63]. A number of centers in Canada, Europe, and the USA have established young adult clinics in a variety of specialties, including diabetes, kidney transplant, respirology, and rheumatology [64–68]. Improved outcomes have been noted, but more studies are needed. Whatever the approach, an adult site champion is very important to lead and advocate for optimal transition processes, while a navigator/coordinator (see section "Named Healthcare Worker and Transition Champion" above) can help the young person make their way in the adult health system and prevent losses to follow-up.

Succinct Relevant Patient Transfer Summaries

Creating the transfer summary can often feel like a daunting task, particularly for patients followed for many years or with multiple health issues. An early start greatly simplifies the process. For example, an annual health summary for each patient with chronic kidney disease can be incrementally updated and edited. The final transfer summary should be succinct and highlight information that will be most pertinent to the patient's ongoing care. This summary should also include significant psychosocial aspects. The person receiving it will likely have time constraints and will need the most relevant information to be clearly available. Inclusion of appropriate contact information for the patient, including preferred modes of contact (e.g., cellphone, email, text message), is essential.

Another challenge is organizing the transition of patients followed by multiple services, each of whom needs to transfer care. For patients who will be followed in the same adult facility for all their health issues, the process is somewhat simpler; if this will not be the case, all the patient's relevant health documents/summaries need to be accessible to each service. A navigator or coordinator can play an important role in facilitating this process.

A Personalized Health Passport or Summary Document for the Patient

The patient should also receive a copy of their health summary in an easy-to-understand format, commensurate with their health literacy. Providing this a few years before transfer (and regularly updating it) can help empower the patient and assist them in learning about their health condition. A health passport is also useful; an excellent prototype can be found on the Good 2 Go Transition website, from the SickKids Hospital in Toronto [69]. A variety of passports are available on this site from a drop-down list, including one specifically for kidney disease. These passports are very comprehensive and once created can be printed into a wallet size card. They include the patient's medical conditions, past procedures, treatments, medications, allergies, and other health-related information. Healthcare providers or parents can assist the patient in completing their passport online, as needed.

Open Bidirectional Communication Between the Pediatric and Adult Teams

Both the pediatric and adult nephrology teams need to appreciate each other's approaches to care. This can enhance the pediatric team's preparation of their patients for transfer and the adult team's understanding of the expectations of the adolescents and young adults. For complex patients, like those on dialysis or with advanced CKD, it is very helpful for the healthcare professionals at each site to communicate by phone or in person, not just in writing. For patients with kidney diseases seen primarily in pediatric practice, a condition fact sheet can be very helpful for the adult care provider. This is particularly relevant for genetic conditions and congenital anomalies. It is also useful for the adult and pediatric teams to give each other feedback on how each patient's transition process went, in order to facilitate continuous improvement. Things to consider are how well the pediatric team prepared the patient for the adult model of care, the patient's attendance at follow-up visits, avoidable complications, and the patient and family's satisfaction and ideas for improvement.

Recognition by the Adult Team of the Young Adult's Developmental Needs

Many patients who transfer at the younger end of the transition age spectrum need ongoing support to achieve their potential. In Canada, a number of European countries, Australia, and New Zealand, the required age to transfer is at around 18 years of age, sometimes with little flexibility. During this vulnerable age, extra services are often needed by the patient to help address psychosocial issues, education, and the development of autonomy in their medical care [39, 70].

Continuation of the Transition Process After Transfer to Adult Care, Until the Young Person Is Fully Integrated and Able to Function in the Adult System

Following transfer to adult care, communication and collaboration between the pediatric and adult teams remains important. *Transition does not end with transfer* – it continues until the young person is fully integrated into adult care. Preparing the setting for the young person's entry to the adult site can make a substantial difference to the likelihood of success. Recommendations are for the adult site to have a welcome package that orients the young person to the new hospital and clinic [71]. For dialysis patients, this could include the following: the names and contact information for all the relevant healthcare professionals the patient will interact with in the dialysis unit (e.g., the nephrologists, dialysis nurses, nutritionist, social worker, psychologist, and administrative support staff), other relevant clinic information (e.g., the pretransplant evaluation clinic staff names and contact information), who (and how) to contact adult care providers for an

emergency outside of dialysis hours, location and contact information for medical imaging, the blood procurement center, the emergency department, and other logistics. A welcome tour of the new facility and hospital is also important, as is an intake meeting with the young person during which time issues important to them are discussed. Confidentiality and communication of information also needs to be addressed; whereas in the pediatric center the parent is often contacted to receive their child's test results or to set up appointments, the patient will almost always be the person contacted in the adult program.

Many adolescents and young adults with kidney failure have additional health problems and are followed by other specialty services. There is a need to facilitate continuity of care for all of the patient's healthcare issues. This is particularly important because of the known risks of losses to follow-up in many different disease groups after transfer to adult care [9]. A system to help patients coordinate all of their care is important. As on the pediatric side, it is recommended to have a mechanism to track patients who have been transferred to adult care [13]; it should continue throughout the high-risk period of emotional development, until the mid-20s. Attention to changes in financial or social circumstances and psychological well-being is also important. A navigator or coordinator can play an important role in all of these spheres and ideally continues to work with that patient after transfer to adult care.

Education and Training for Healthcare Professionals

There are educational gaps regarding transition challenges, barriers, and best practices in both pediatric and adult healthcare, and this pertains to physicians, nurses, and allied health professionals. It is essential for adult clinicians to learn about pediatric-onset diseases, as well as adolescent and young adult development. Pediatricians need to understand the adult model of care and the current resource limitations in the adult system. Emerging adults comprise a very small number of adult patients, in a system overburdened with an ever-expanding population of elderly patient with multiple comorbidities. Some specialty societies have developed healthcare transition training modules for residents, but more is needed, both during training and as part of continuing professional development. In nephrology, there should be bidirectional training opportunities for both adult and pediatric residents in pediatric, adolescent, and young adult nephrology. Pediatric nephrologists can also assist the education process by developing condition fact sheets for pediatric-onset kidney diseases, as mentioned in section "Open Bidirectional Communication Between the Pediatric and Adult Teams" above.

Financial Considerations

There are only a few published studies that have addressed the costs of transition. An evaluation of the financial impact requires assessment at several levels – cost to the individual clinic program, to the hospital, to the overall healthcare system, to the national economy, and to the individual patient's health. The Triple Aim, elaborated by the Institute for Health Improvement (IHI), is a framework to optimize health system performance in three dimensions: improvement of the individual experience of care (including quality and satisfaction), improvement of the health of populations, and reduction of the per capita costs associated with healthcare [72]. A recent systematic review used the Triple Aim Framework to evaluate transition interventions and found that better adherence (population health) was the most frequently reported benefit, with improvements also seen in the experience of care and health service use [73]. Effective transition interventions included disease-specific education, generic self-skills management, inclusion of a designated transition coordinator, explicit communication between pediatric and adult providers, a separate young adult clinic, a joint pediatric adult clinic, out of hours support, and enhanced follow-up. Individual transition programs that looked at the financial implications of transition interventions (costs of care) demonstrated either cost savings or cost neutrality, as well as improved

clinical outcomes [74–77]. This is an area for further research. The quality of transition also has an impact on the long-term health of adolescents and young adults with chronic conditions and fiscal issues. Since their health status has an effect on their ability to work and pay taxes, or become dependent on public social security agencies, the positive impact of effective transition of adolescents and young adults on the national economy needs to be included in cost evaluation.

Reimbursement of physicians for work related to transition of care also needs to be taken into account. In the USA, there are billing options that permit reimbursement for the extra time involved in the coordination of care of complex patients, including some specific aspects pertaining to transition of care [9, 78]. A roundtable report from transition experts makes explicit recommendations regarding payment for transition-specific activities, which are useful for the advocacy of policy change [79]. Healthcare providers in other countries can evaluate their available reimbursement possibilities using these recommendations as a guide.

Quality Improvement and Research

The Got Transition "Six Core Elements of Health Care Transition" provides adaptable templates for assessment of transition quality improvement initiatives at the individual clinic and institutional levels [71]. These facilitate progressive process improvement using a "Plan, Do, Study, Assess" (PDSA) approach.

There has been an exponential increase in publications related to transition over the past decade, but evidence-based research remains scarce. Most transition research has focused on the quality of interventions for transition preparation [80]. There is also a plethora of published descriptions of problems related to transition. Studies on the integration of adolescents and young adults into adult medicine and their long-term outcomes are largely lacking. There is a need to further define outcome measures and ensure that they include the patients' perspectives. High-quality research is required to develop and assess interventions and inform future evidence-based practices.

Public Policy

Appropriate transition to adult care is central to the health and well-being of adolescents and young adults with chronic health conditions and/or social complexity and needs to be integrated into social and healthcare policies. This includes recognition that the transition process continues after moving to adult care and that continuing support is needed for several years post-transfer (at least until the age of 25 years) [81]. Adolescents and young adults with chronic health conditions may also need support in the social system, e.g., those with educational or vocational challenges, mental health issues, and minimal family support or who are aging out of foster care. Youth with chronic kidney disease are particularly vulnerable.

Determined advocacy has led to recognition of the complex and ongoing needs of vulnerable young adults by the National Academies of Science in the USA and by the National Health Service (NHS) in Great Britain [12, 35, 82]. Although some progress has occurred, there is still much to achieve, in particular ongoing advocacy for policy change to improve transition to adult care and to take into account the special needs of emerging adults [81]. Within the healthcare system, examples include the provision of appropriate reimbursement of healthcare providers for the extra time involved in preparing and supporting youth in transition [79], the integration of knowledge and practice of transition to adult care into the required competencies of pediatric and adult healthcare training, and the incorporation of expectations of appropriate systems of transition to adult care into the standards of accreditation of healthcare institutions.

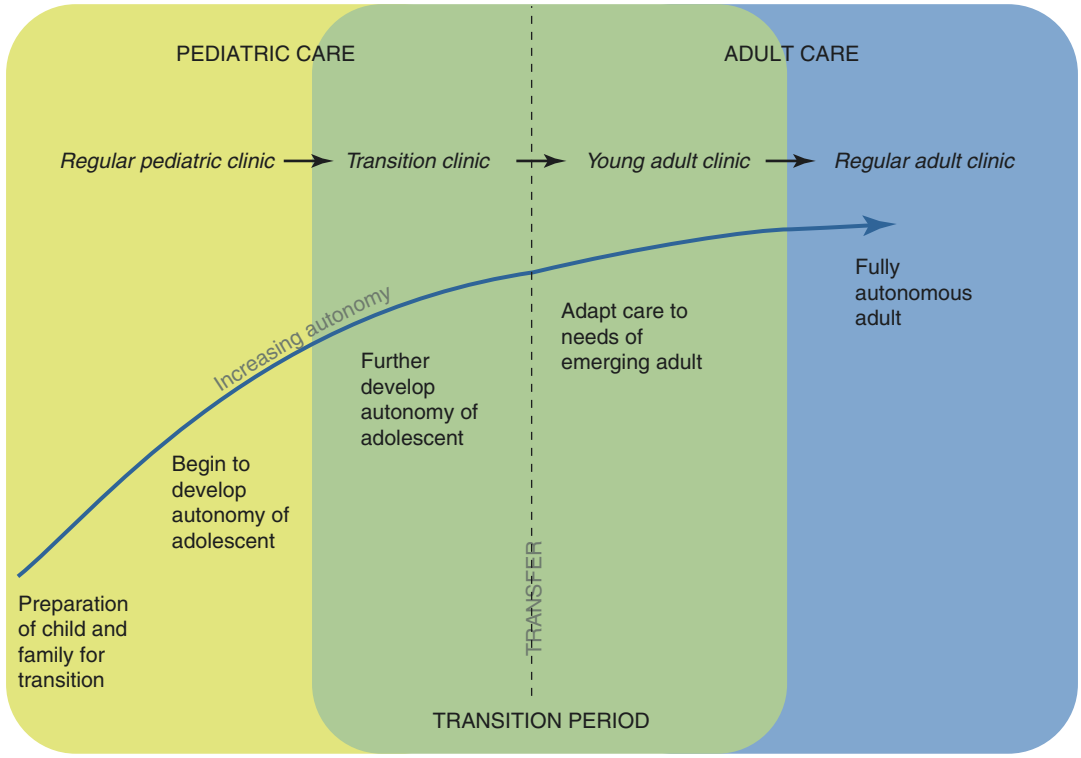

Fig. 41.4 The Transition Journey. (Image reproduced from Foster and Bell 2015, [63] with permission of Springer Nature)

Summary

Transition to adult care is a multifaceted, longitudinal process involving multiple stakeholders. It begins in childhood and ends in young adulthood and requires communication and collaboration among all the participants. Figure 41.4 summarizes the transition journey. Adolescents and young adults with chronic kidney disease are especially vulnerable because their lives depend on their adherence to treatment. Excellent general guidelines and tools exist to help improve the process, and implementation is facilitated by institutional resources and support. Advocacy, health, and social policy change and high-quality research are essential to further improve systems and outcomes.

References

1. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. Pediatrics. 2002;110(6 Pt 2):1304–6.
2. Tong A, Wong G, Hodson E, Walker RG, Tjaden L, Craig JC. Adolescent views on transition in diabetes and nephrology. Eur J Pediatr. 2013;172(3):293–304.
3. Gray WN, Schaefer MR, Resmini-Rawlinson A, Wagoner ST. Barriers to transition from pediatric to adult care: a systematic review. J Pediatr Psychol. 2018;43(5):488–502.
4. van Staa A, Sattoe JNT. Young Adults' experiences and satisfaction with the transfer of care. J Adolesc Health. 2014;55(6):796–803.
5. Okumura MJ, Kerr EA, Cabana MD, Davis MM, Demonner S, Heisler M. Physician views on barriers

to primary care for young adults with childhood-onset chronic disease. Pediatrics. 2010;125(4):e748–54.
6. van Staa AL, Jedeloo S, van Meeteren J, Latour JM. Crossing the transition chasm: experiences and recommendations for improving transitional care of young adults, parents and providers. Child Care Health Dev. 2011;37(6):821–32.
7. Canadian Association of Pediatric Health Centres (CAPHC), National Transitions Community of Practice. A guideline for transition from Paediatric to Adult Health Care for Youth with Special Health Care Needs: a national approach 2016; Available at https://ken.caphc.org/xwiki/bin/view/Transitioning+from+Paediatric+to+Adult+Care/A+Guideline+for+Transition+from+Paediatric+to+Adult+Care Accessed Mar 2, 2020.
8. Cooley WC, Sagerman PJ. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians, Transitions Clinical Report Authoring Group: supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics. 2011;128(1):182–200.
9. White PH, Cooley WC. Transitions Clinical Report Authoring Group, American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians.Supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics. 2018;142(5):e20182587.
10. Watson AR, Harden PN, Ferris M, Kerr PG, Mahan JD, Fouad RM. Transition from pediatric to adult renal services a consensus statement by the International Society of Nephrology (ISN) and the international pediatric nephrology association (IPNA). Pediatr Nephrol. 2011;26:1753–7.
11. Bell LE, Bartosh SM, Davis CL, Dobbels F, Al-Uzri A, Lotstein D, et al. Adolescent transition to adult care in solid organ transplantation: a consensus conference report. Am J Transplant. 2008;8(11):2230–42.
12. National Institute for Health and Clinical Excellence (NICE). Transition from children's to adults' services for young people using health or social care services (NICE guideline 43). 2017; Available at https://www.nice.org.uk/guidance/ng43/resources. Accessed Mar 2, 2020.
13. Got Transition 2014–2020; Available at http://www.gottransition.org/resources/index.cfm. Accessed Mar 2, 2020.
14. Ali-Faisal SF, Colella TJ, Medina-Jaudes N, Benz Scott L. The effectiveness of patient navigation to improve healthcare utilization outcomes: a meta-analysis of randomized controlled trials. Patient Educ Couns. 2017;100(3):436–48.
15. Allemang B, Allan K, Johnson C, Cheong M, Cheung P, Odame I, et al. Impact of a transition program with navigator on loss to follow-up, medication adherence, and appointment attendance in hemoglobinopathies. Pediatr Blood Cancer. 2019;66(8):e27781.
16. Annunziato RA, Baisley MC, Arrato N, Barton C, Henderling F, Arnon R, et al. Strangers headed to a strange land? A pilot study of using a transition coordinator to improve transfer from pediatric to adult services. J Pediatr. 2013;163(6):1628–33.
17. Freeman HP. The history, principles, and future of patient navigation: commentary. Semin Oncol Nurs. 2013;29(2):72–5.
18. Samuel S, Dimitropoulos G, Schraeder K, Klarenbach S, Nettel-Aguirre A, Guilcher G, et al. Pragmatic trial evaluating the effectiveness of a patient navigator to decrease emergency room utilisation in transition age youth with chronic conditions: the Transition Navigator Trial protocol. BMJ Open. 2019;9(12):e034309.
19. Van Walleghem N, MacDonald CA, Dean HJ. Evaluation of a systems navigator model for transition from pediatric to adult care for young adults with type 1 diabetes. Diabetes Care. 2008;31(8):1529–30.
20. Jolly SE, Navaneethan SD, Schold JD, Arrigain S, Konig V, Burrucker YK, et al. Development of a chronic kidney disease patient navigator program. BMC Nephrol. 2015;16:69.
21. van Zwieten A, Caldwell P, Howard K, Tong A, Craig JC, Alexander S, et al. NAV-KIDS(2) trial: protocol for a multi-centre, staggered randomised controlled trial of a patient navigator intervention in children with chronic kidney disease. BMC Nephrol. 2019;20(1):134.
22. Kubota W, Honda M, Okada H, Hattori M, Iwano M, Akioka Y, et al. A consensus statement on health-care transition of patients with childhood-onset chronic kidney diseases: providing adequate medical care in adolescence and young adulthood. Clin Exp Nephrol. 2018;22(4):743–51.
23. Cramm JM, Strating MMH, Roebroeck ME, Nieboer AP. The importance of general self-efficacy for the quality of life of adolescents with chronic conditions. Soc Indic Res. 2013;113(1):551–61.
24. Greenbaum LA, Warady BA, Furth SL. Current advances in chronic kidney disease in children: growth, cardiovascular, and neurocognitive risk factors. Semin Nephrol. 2009;29(4):425–34.
25. Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB, et al. Neurocognitive outcomes in children with chronic kidney disease: current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev. 2006;12(3):208–15.
26. Clavé S, Tsimaratos M, Boucekine M, Ranchin B, Salomon R, Dunand O, et al. Quality of life in adolescents with chronic kidney disease who initiate haemodialysis treatment. BMC Nephrol. 2019;20(1):163.
27. Tjaden LA, Grootenhuis MA, Noordzij M, Groothoff JW. Health-related quality of life in patients with pediatric onset of end-stage renal disease: state of the art and recommendations for clinical practice. Pediatr Nephrol. 2016;31(10):1579–91.
28. Splinter A, Tjaden LA, Haverman L, Adams B, Collard L, Cransberg K, et al. Children on dialysis as well as renal transplanted children report severely impaired health-related quality of life. Qual Life Res. 2018;27(6):1445–54.

29. Clementi MA, Zimmerman CT. Psychosocial considerations and recommendations for care of pediatric patients on dialysis. Pediatr Nephrol. 2019; https://doi.org/10.1007/s00467-019-04227-5. [Epub ahead of print]
30. Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann N Y Acad Sci. 2008;1124:111–26.
31. Olson A, Scherer DG, Cohen AL. Decision-making skills of emerging adults aging out of foster care. Child Youth Serv Rev. 2017;82:81–6.
32. Woodgate RL, Morakinyo O, Martin KM. Interventions for youth aging out of care: a scoping review. Child Youth Serv Rev. 2017;82:280–300.
33. Liabo K, McKenna C, Ingold A, Roberts H. Leaving foster or residential care: a participatory study of care leavers' experiences of health and social care transitions. Child Care Health Dev. 2017;43(2):182–91.
34. Collins JL. Integrative review: delivery of healthcare services to adolescents and young adults during and after Foster Care. J Pediatr Nurs. 2016;31(6):653–66.
35. Institute of Medicine; National Research Council of the National Academies. Bonnie RJ, Stroud C, Breiner H, editors. Investing in the Health and Well-Being of Young Adults. Washington, DC: The National Academies Press; 2015.
36. Bethe D, Reid C. History and Current State of Psychosocial Care in European Paediatric Nephrology. Paper presented at the 50th Anniversary meeting of the European Society for Paediatric Nephrology, 2017; Glasgow, Scotland. Available at http://www.ewopa-renalchild.com/presentations.html. Accessed March 3, 2020.
37. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. Am J Transplant. 2009;9(1):35–41.
38. Steinbeck K, Towns S, Bennett D. Adolescent and young adult medicine is a special and specific area of medical practice. J Paediatr Child Health. 2014;50(6):427–31.
39. Colver A, Longwell S. New understanding of adolescent brain development: relevance to transitional healthcare for young people with long term conditions. Arch Dis Child. 2013;98(11):902–7.
40. Foster BJ. Heightened graft failure risk during emerging adulthood and transition to adult care. Pediatr Nephrol. 2015;30:567–76.
41. Tong A, Lowe A, Sainsbury P, Craig JC. Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies. Pediatrics. 2008;121(2):349–60.
42. Wightman A, Zimmerman CT, Neul S, Lepere K, Cedars K, Opel D. Caregiver experience in pediatric dialysis. Pediatrics. 2019;143(2):e20182102.
43. Tsai TC, Liu SI, Tsai JD, Chou LH. Psychosocial effects on caregivers for children on chronic peritoneal dialysis. Kidney Int. 2006;70(11):1983–7.
44. Medway M, Tong A, Craig JC, Kim S, Mackie F, McTaggart S, et al. Parental perspectives on the financial impact of caring for a child with CKD. Am J Kidney Dis. 2015;65(3):384–93.
45. Kieckhefer GM, Trahms CM. Supporting development of children with chronic conditions: from compliance toward shared management. Pediatr Nurs. 2000;26(4):354–63.
46. Christin A, Akre C, Berchtold A, Suris JC. Parent-adolescent relationship in youths with a chronic condition. Child Care Health Dev. 2016;42(1):36–41.
47. Francis A, Johnson DW, Craig JC, Wong G. Moving on: transitioning young people with chronic kidney disease to adult care. Pediatr Nephrol. 2018;33(6):973–83.
48. Suris JC, Larbre JP, Hofer M, Hauschild M, Barrense-Dias Y, Berchtold A, Akre C. Transition from paediatric to adult care: what makes it easier for parents? Child Care Health Dev. 2017;43(1):152–5.
49. Got Transition: Validated Transition Tools. Available at https://www.gottransition.org/researchpolicy/index.cfm. Accessed Mar 2, 2020.
50. Bell LE, MacDonald D. Montreal Children's Hospital transition preparation checklists for adolescents and parents of adolescents. 2013.; available at https://www.thechildren.com/patients-families/information-parents/transitioning-adult-care-starting-early-and-finishing-strong. Accessed Mar 2, 2020.
51. Nagra A, McGinnity PM, Davis N, Salmon AP. Implementing transition: ready steady go. Arch Dis Childhood E. 2015;100(6):313–20.
52. Ready Steady Go and Hello to Adult Services. 2014; available at https://www.uhs.nhs.uk/OurServices/Childhealth/TransitiontoadultcareReadySteadyGo/Transitiontoadultcare.aspx. Accessed Mar 2, 2020.
53. American Society of Transplantation Pediatric Community of Practice. Pediatric Transition Portal 2015; available at https://www.myast.org/education/specialty-resources/peds-transition. Accessed January 28, 2020.
54. Got Transition -Six Core Elements of Health Care Transition 2.0. Sample Individual Transition Flow Sheet. 2014; available at https://www.gottransition.org/resourceGet.cfm?id=222. Accessed Mar 3, 2020.
55. Got Transition -Six Core Elements of Health Care Transition 2.0. Sample Transition Registry available at https://www.gottransition.org/resourceGet.cfm?id=223. Accessed Mar 3, 2020.
56. Prufe J, Dierks ML, Bethe D, Oldhafer M, Muther S, Thumfart J, et al. Transition structures and timing of transfer from paediatric to adult-based care after kidney transplantation in Germany: a qualitative study. BMJ Open. 2017;7(6):e015593.
57. Kreuzer M, Prufe J, Tonshoff B, Pape L. Survey on management of transition and transfer from pediatric- to adult-based care in pediatric kidney transplant recipients in Europe. Transplant Direct. 2018;4(7):e361.
58. Kreuzer M, Drube J, Prufe J, Schaefer F, Pape L. Current management of transition of young people affected by rare renal conditions in the ERKNet. Eur J Hum Genet. 2019;27(12):1783–90.
59. Rieger S, Bethe D, Bagorda A, Treiber D, Beimler J, Sommerer C, et al. A need-adapted transition program

after pediatric kidney transplantation. J Trans Med. 2019;1(1). https://doi.org/101515/jtm-2008-0004.
60. Javalkar K, Johnson M, Kshirsagar AV, Ocegueda S, Detwiler RK, Ferris M. Ecological factors predict transition readiness/self-management in youth with chronic conditions. J Adolesc Health. 2016;58(1):40–6.
61. Foster BJ, Dahhou M, Zhang X, Platt RW, Samuel SM, Hanley JA. Association between age and graft failure rates in young kidney transplant recipients. Transplantation. 2011;92(11):1237–43.
62. Foster BJ, Platt RW, Dahhou M, Zhang X, Bell LE, Hanley JA. The impact of age at transfer from pediatric to adult-oriented care on renal allograft survival. Pediatr Transplant. 2011;15(7):750–9.
63. Foster BJ, Bell L. Improving the transition to adult care for young people with chronic kidney disease. Curr Pediatr Rep. 2015;3:62–70.
64. Walter M, Kamphuis S, van Pelt P, de Vroed A, Hazes JMW. Successful implementation of a clinical transition pathway for adolescents with juvenile-onset rheumatic and musculoskeletal diseases. Pediatr Rheumatol. 2018;16(1):50.
65. Duguépéroux I, Tamalet A, Sermet-Gaudelus I, Le Bourgeois M, Gérardin M, Desmazes-Dufeu N, Hubert D. Clinical changes of patients with cystic fibrosis during transition from pediatric to adult care. J Adolesc Health. 2008;43(5):459–65.
66. Tucker L. The yard clinic in Vancouver: an original! CRAJ. 2008;18(2):18–9.
67. Wafa S, Nakhla M. Improving the transition from pediatric to adult diabetes healthcare: a literature review. Can J Diabetes. 2015;39(6):520–8.
68. Michaud V, Achille M, Chainey F, Phan V, Girardin C, Clermont MJ. Mixed-methods evaluation of a transition and young adult clinic for kidney transplant recipients. Pediatr Transplant. 2019;23(4):e13450.
69. Good 2 Go Transition Program – MyHealth Passport. 2012; available at https://www.sickkids.ca/myhealthpassport/. Accessed March 3, 2020.
70. Colver A, Rapley T, Parr JR, McConachie H, Dovey-Pearce G, Le Couteur A, et al. Facilitating the transition of young people with long-term conditions through health services from childhood to adulthood: the transition research programme. Prog Grants Appl Res. 2019;7(4):280.
71. Six Core Elements of Health Care Transition™. Health Care Providers tab. 2014. Available at https://www.gottransition.org/providers/index.cfm. Accessed Mar 3, 2020.
72. Berwick DM, Nolan TW, Whittington J. The triple aim: cares health, and cost. Health Aff. 2008;27(3):759–69.
73. Gabriel P, McManus M, Rogers K, White P. Outcome evidence for structured pediatric to adult health care transition interventions: a systematic review. J Pediatr. 2017;188:263–269.e215.
74. Burns K, Farrell K, Myszka R, Park K, Holmes-Walker DJ. Access to a youth-specific service for young adults with type 1 diabetes mellitus is associated with decreased hospital length of stay for diabetic ketoacidosis. Intern Med J. 2018;48(4):396–402.
75. Holmes-Walker DJ, Llewellyn AC, Farrell K. A transition care programme which improves diabetes control and reduces hospital admission rates in young adults with Type 1 diabetes aged 15-25 years. Diabetic Med. 2007;24(7):764–9.
76. Bent N, Tennant A, Swift T, Posnett J, Scuffham P, Chamberlain MA. Team approach versus ad hoc health services for young people with physical disabilities: a retrospective cohort study. Lancet. 2002;360(9342):1280–6.
77. Grimby G. Focused multidisciplinary services for young people with disabilities. Lancet. 2002;360(9342):1264.
78. McManus M, White P, Schmidt A, Kanter D, Salus T. Coding and reimbursement tip sheet for transition from pediatric to adult health care. Practice Resources. 2019; available at https://www.gottransition.org/resourceGet.cfm?id=353. Accessed Mar 3, 2020.
79. McManus M, White P, Schmidt A for the The National Alliance to Advance Adolescent Health. Recommendations for value-based transition payment for pediatric and adult health care systems: a leadership roundtable report. 2018; available at https://www.lpfch.org/sites/default/files/field/publications/value-based_payment_for_health_care_transition_report.pdf. Accessed Mar 3, 2020.
80. Hart LC, Patel-Nguyen SV, Merkley MG, Jonas DE. An evidence map for interventions addressing transition from pediatric to adult care: a systematic review of systematic reviews. J Pediatr Nurs. 2019;48:18–34.
81. Selectively moving to a '0–25 years' service will improve children's experience of care, outcomes and continuity of care. Available at https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/a--strong-start-in-life-for-children-and-young-people/redesigning-other-health-services-for-children-and-young-people/. Accessed March 3, 2020.
82. Making healthcare work for young people: a toolkit to support delivery of 'Developmentally Appropriate Healthcare' in the NHS. 2017; available at https://www.northumbria.nhs.uk/wp-content/uploads/2017/04/nhs-making-healthcare-work-web-02.pdf. Accessed March 3, 2020.
83. Heath G, Farre A, Shaw K. Parenting a child with chronic illness as they transition into adulthood: a systematic review and thematic synthesis of parents' experiences. Patient Educ Couns. 2017;100(1):76–92.
84. Bell LE. Transition to adult care. In: Pediatric dialysis case studies. Edited by Warady BA, Schaefer F, Alexander SR. Cham: Springer International Publishing AG 2017. p 239–248.

Ethical Decision-Making in Pediatric Dialysis

42

Aaron Wightman, Bruno Ranchin, and Aviva M. Goldberg

Introduction

Dialysis is a lifesaving intervention for children with end-stage kidney disease (ESKD) and in well-resourced countries serves as the default treatment for children until successful kidney transplantation. In some cases, it may be appropriate to withhold dialysis altogether or withdraw it once started. A decision to do so requires a thoughtful and multidisciplinary approach to a complex problem [1].

Withholding dialysis is defined as foregoing dialysis in a patient for whom dialysis has yet to be initiated (i.e., never starting). Withdrawal of dialysis means the discontinuation and forgoing of ongoing dialysis therapy (i.e., stopping after dialysis has been started or attempted). Both situations are similar in that life-sustaining treatments are possible but are not provided. While generally considered ethically equivalent, they are often treated differently by patients, families, and medical teams making clinical decisions.

Withdrawal of dialysis is common, especially for adults. In the United States, approximately one quarter of all deaths among adults who receive chronic dialysis occur after a decision has been made to withdraw dialysis, and withdrawal of dialysis is the second leading cause of death among adult chronic dialysis patients in the United States [2]. Less is known about withdrawal from pediatric dialysis, but an analysis of French-speaking pediatric nephrology centers from 1995 to 2001 found 50 cases where dialysis was withheld or withdrawn among 440 children with end-stage kidney disease (11.5%) [3]. The most common reasons for withdrawal included concerns of subsequent quality of life, severe neurological handicap, and consequences of the disease on the family [3]. This is consistent with other ill children, as withdrawal of life-sustaining treatments is a leading cause of death in both neonatal and pediatric intensive care units [4, 5]. This chapter will explore the ethics of withholding and withdrawing dialysis in children in general and for specific situations and populations.

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Ethical Considerations in Withholding and Withdrawing Dialysis Treatment

The History of Dialysis Provision and Ethical Implications

It is important to understand the history of ethics in dialysis, both to better understand how resource allocation fits into this decision-making and the context in which the medical community, government funders, and the larger public view dialysis coverage and choices. Many will be familiar with the infamous Seattle "God" committees of the 1960s as a turning point for both modern nephrology and modern bioethics [6, 7]. Revealed to the lay public in a *Life* magazine article by Shana Alexander, the committee was actually called the Admissions and Policy Committee of the Seattle Artificial Kidney Center at Swedish Hospital. This group of community members (a lawyer, a housewife, a labor leader, a clergy member, and others) was charged with deciding which ESKD patients would be able to access the extremely limited number of chronic hemodialysis chairs at Swedish Hospital. Demand far exceeded supply; the Scribner shunt had only recently been developed and its use was still experimental, and there were more people with ESKD than the program could accommodate [8]. At the time, patients under 18 years were not even considered as candidates, fearing the rigors of dialysis would be too traumatic for them [9].

One of the biggest criticisms of the "God" committee was that the members placed a heavy emphasis on the candidate's social worth. Characteristics like high prestige occupation, religious attendance, and breadwinning position within a family made candidates more attractive to the committee, resulting in white, employed, churchgoing men receiving disproportionate access [10]. When the public learned how the committee worked, there was a public outcry and a call for more dialysis chairs and better allocation decisions. A committee chaired by nephrologist Carl Gottschalk recommended federal funding for all patients with ESKD, and President Nixon signed this into law in 1972 [11, 12]. This relatively wide coverage continues today, where emergency and often chronic hemodialysis is covered for most residents in well-resourced countries, even in the United States where access to other types of healthcare is far from universal. One of the most persistent legacies of the "God" committees is the understanding that, at least for this particular therapy, the public supports the idea of providing it to all who need it, regardless of their presumed social worth or ability to pay [13].

Best Interest Standard and Harm Principle in Pediatric Decision-Making

The intricacies of the withholding and withdrawing of dialysis will be discussed in more detail later in the chapter, but it is first important to understand how high-stakes decisions are made in pediatrics in general. The best interest standard has long been held as an appropriate decision-making tool for pediatrics and other cases in which a person is incapable of expressing their own wishes. Described as "the option that maximizes the person's overall good and minimizes the person's overall risks of harm," this standard has been used in ethical decision-making, as a legal standard for decisions involving incapable minors, and by the United Nations, whose Convention on the Rights of the Child states "In all actions concerning children… the best interests of the child shall be a primary consideration" [14–16]. While there are invariably burdens associated with dialysis (discomfort, time away from home and school, complications such as infection, bleeding, etc.), dialysis is very often considered to be in the best interests of a child with ESKD by the medical team, family, and the child himself or herself compared with the alternative of comfort care only.

While the best interest standard is widely referenced in pediatric decision-making, it has a number of limitations. It is sometimes difficult to define the best interests of a child, especially when it comes to complex and burdensome chronic treatment. Dialysis may be well tolerated

by some children but can be much more difficult for others. It can be challenging to know what burdens and benefits are experienced, especially in children with no or limited verbal interaction (e.g., neonates, those with intellectual disabilities). Further, it can be difficult to accurately weigh the relative impact of both burdens and benefits, and disagreements about how much each matter can sometimes come down to a disagreement about values. For one family, length of life may be of utmost benefit, and they may then be willing to accept dialysis even when it is more burdensome, whereas other families may more highly value the quality of life and may be willing to give up longevity in order to minimize pain or time spent in hospital.

Another criticism is that the best interest standard places the interests of the child centrally. While this may make intuitive sense in most situations, the centrality of the patient does not necessarily take into account the effect that a decision will have on parents, other family members, or the larger society [17, 18]. Pediatric dialysis can have real and lasting negative effects on the mental health, economics, and marital stability of families [19–21]. Given the responsibilities placed upon families to provide dialysis, especially peritoneal dialysis (PD) or home hemodialysis, it would be unrealistic to discount the burden of the disease on the family. It is possible that a choice in the best interests of the child would not be in the best interests of other children in the family or the family as a whole. This impact is recognized by pediatric nephrologists as an important consideration in the withholding/withdrawing conversation, with 68% of respondents (21/31) in one survey recognizing that the impact of the dialysis on the family was an important consideration [3].

An additional criticism of the best interest standard is the absolutist nature of "best." Selecting the best treatment option requires weighing values such as survival, comorbidities, quality of life, and burden of care. It is possible that parents and the medical team may disagree on a treatment choice and both be making a decision consistent with their view of the child's best interests. Recognizing this limitation, others have proposed utilization of a "reasonable interest standard" or "not unreasonable standard" rather than best interest standard [22, 23]. With dialysis, it is clear that most "reasonable" parents would choose treatment in uncomplicated cases, but it is not clear what the "reasonable" parent would choose in more complicated situations, like the very young or very ill child. While the "reasonable interest" or "not unreasonable standard" might make sense when asking parents to choose among different types of renal replacement therapy (e.g., peritoneal dialysis vs. in-center hemodialysis vs. home hemodialysis), using these standards to decide whether or not to forgo dialysis does not seem to be the right fit.

A better framework for considering parental refusal of dialysis treatment may be the "harm principle" developed by Diekema [17]. The harm principle holds that parents should not be required to make the very "best" decision for their child in all situations but rather that they should not be permitted to make decisions that significantly increase the likelihood of serious harm as compared to other options. This principle allows for the differing values that parents may place on benefits and burdens of treatment options when compared to the opinions of medical professionals, but does not allow for parents to refuse a treatment in which serious, imminent harm is expected to occur and where there is a reasonable intervention that could avoid that harm. Such a standard might be reasonable to apply in situations where dialysis clearly provides more benefits than burdens. An example might be a 6-year-old with acute kidney failure from diarrhea-associated hemolytic uremic syndrome, clear indications for acute dialysis, a high likelihood of renal recovery, and no known comorbidities. If a parent refused medically recommended dialysis in this situation, it might be reasonable to apply the harm principle and explore whether the parent's choice can be respected or whether their authority should be abrogated. Such a decision would of course need due consideration and deliberation and likely the involvement of social work and other members of a multidisciplinary care team.

The Technological Imperative

Dialysis is a potentially lifesaving therapy, and the fact that it can be provided in pediatrics with excellent patient survival rates is something to be celebrated. As with other high-technology interventions, it is increasingly recognized that doing something simply because we can do it is not appropriate in all situations. First described by Fuchs, the technological imperative has been suggested as something which is imprinted on physicians during training: the drive to use the best, most modern, and most high-tech interventions because they are available [24]. It may be best understood at its core as "That which is possible to do has to be done" [25]. Pediatric nephrologists are well trained in the technical aspects of dialysis and can do amazing things with the technology: providing dialysis for children weighing as little as 1 kg, correcting severe electrolyte abnormalities, and managing and saving the lives of children with poisonings, overdoses, and inborn errors of metabolism. We are less well trained in holding back, declining to offer therapy when the burdens outweigh the benefits or when a patient or family does not want the treatment. Understanding the technological imperative that is a natural part of our specialty and preparing to manage the emotional reaction that we may have when a patient or family desires to forgo medically available therapy is a lifelong challenge but one that we should be prepared to confront. The technological imperative should not be allowed to stand in the way of shared decision-making as it sometimes is just as powerful to leave a tool unused.

Equivalence of Withholding and Withdrawing Dialysis

The Equivalence Thesis holds that there is no ethical distinction between withholding and withdrawing life-sustaining treatments. This means that if it is ethically permissible to withhold dialysis, it should also be permissible to withdraw the treatment, all other things being equal. While the ethical equivalence of withholding and withdrawing dialysis is widely accepted, there may be an emotional distinction for the patient, family, and medical team [26–28]. A series of surveys have demonstrated that physicians and the lay public do not feel that withholding and withdrawing life-sustaining treatments are the same, with most, though not all, preferring to withhold rather than withdraw life-sustaining treatments [29–34]. Providers may sense that withdrawing dialysis or other life-sustaining treatments feels more distressing than simply withholding the treatment. This may reflect a perception of greater moral agency, responsibility, and culpability on the part of the healthcare provider for a patient's death associated with withdrawal of treatment (commission) vs. never initiating life-sustaining treatment (omission). There is a tendency to describe a situation in which treatment has begun as "the train has left the station" and cannot be stopped [35].

Nephrologists' perceptions of a moral difference between withholding and withdrawing dialysis may result in negative consequences for patients. Implicit belief that withholding is preferable to withdrawing can result in both inappropriate undertreatment (reticence to begin therapy due to concerns that once begun it cannot be stopped) and overtreatment (failure to withdraw harmful treatment once started). Overtreatment may result in waste of limited medical and financial resources by insisting on a therapy that is no longer beneficial or desirable for the patient [28, 36, 37]. Others who feel withholding dialysis is more problematic than withdrawal may require all patients to undergo dialysis treatment, as withholding precludes a dying patient of a chance, even if extremely limited, of benefitting from dialysis treatment. While this approach offers the opportunity for unlikely patients to benefit, it would result in suffering for the majority who will not benefit and significant waste of resources by providing treatment unlikely to be beneficial [34, 38, 39].

The distinction between withdrawing and withholding dialysis is, in fact, morally and legally irrelevant. Both not initiating and stopping life-sustaining therapy can be justified,

depending on the circumstances [28, 40, 41]. Given the consequences that arise from implicit beliefs of moral differences between withholding and withdrawing, nephrologists would be better served to combine the concepts into a single term, *forgoing*. It is that term which we will use for the remainder of this chapter.

Considerations for Forgoing Dialysis

The 2010 Renal Physicians Association (RPA) Guidelines on Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis recommend forgoing dialysis if the initiation or continuation of dialysis is deemed to be harmful or of no benefit, and to strongly consider forgoing dialysis in a patient with a terminal illness whose long-term prognosis is poor [27]. Similarly, the European Paediatric Dialysis Working Group (EPDWG) clinical practice recommendations for the care of infants with stage 5 chronic kidney disease recommend forgoing dialysis if the expected short- or long-term prognosis is poor, there are significant concurrent medical care issues, or the predicted quality of life for the child and the family is likely to be poor [42]. It is important to recognize that a decision to forgo life-sustaining treatments is not the same as forgoing care [43]. An intensification of palliative treatments should occur in conjunction with any decision to forgo dialysis. This is especially important as palliative care may be underutilized for children with ESKD [44].

Process of Forgoing Dialysis

There is no universally accepted criterion in pediatrics for withholding or withdrawing of life-sustaining treatments such as dialysis. Decisions should be individualized and consistent with the interests of the child and with consideration of the benefits and burdens resulting from continued renal replacement therapy. Choices should reflect the patient and family's goals of care that are achievable and should be centered upon the patient's quality of life [27, 45, 46].

The RPA guidelines, along with the American Academy of Pediatrics, recommend that physicians develop a patient-physician relationship that promotes family-centered shared decision-making [27, 46]. Shared decision-making involves clinician-family collaboration and culminates in a decision arrived at through consensus of the involved groups [47]. Family-centered shared decision-making respects parental authority in medical decision-making for children and is supported by the ethical principles of beneficence, nonmaleficence, and respect for autonomy. If parents request to involve other family members, these requests should be respected. Although children generally do not have legal authority to make independent healthcare decisions, it is important to involve children in the decision-making process to the extent it is developmentally appropriate. In addition, other members of the medical team, potentially including the patient's pediatrician, intensivist, and any other relevant subspecialist, should be encouraged to participate in coordinating care related to treatment decisions made by the family. In the setting of a child with multiple medical comorbidities, decisions about dialysis should be made in the context of other life-sustaining treatments including ventilators, parenteral nutrition, and the provision of intensive care.

Parents should be provided with information regarding the risks, discomforts, side effects, and benefits of treatment alternatives including dialysis and comfort care only. As part of these discussions, the nephrologist should provide their recommendation of the best option for the child, citing reasons for their recommendation based on medical, experiential, and moral factors [48]. Importantly, changes in a patient's prognosis may change the nephrologist's recommendations. The family should be informed of this change without delay [45].

Care should be given to ensure that symptoms are minimized to the greatest degree possible and that patients experience a "good death" whenever possible, defined by patients and families as one which is "pain-free, brief, peaceful, occurring in the presence of loved ones, and at the place of one's choice" [49]. Some parents may request

that withdrawal of dialysis occur in the hospital setting, and in most circumstances this request should be respected. The goal of medical care is not limited to treatment and cure; medical teams also carry an obligation to ease a patient's pain and suffering associated with dying. In some circumstances, those obligations may best be met in the hospital setting.

Parents and providers should be prepared for the fact that death may not occur rapidly after forgoing dialysis. In an adult series, death after dialysis discontinuation occurred at a median of 8 days after stopping, but some patients lived over 3 years after reaching stage V CKD despite never starting dialysis [50].

Disagreement

Parents should be supported throughout the decision-making process, provided with the most accurate evidence on which to base their decisions, and not made to feel that they are alone in carrying the weight of this difficult choice [51]. In most situations, parents can be trusted to make a decision that is consistent with the medical information and well within the standard of care. In some situations, however, there may be fundamental differences of opinion within the family, within the medical team, or between the family and medical team as to the best course of action.

Instead of pursuing unilateral decisions, it is the duty of the medical team to continue to engage in respectful dialogue [52]. These discussions should include revisiting the family's goals of care for the child and education about the child's expected prognosis and treatment options. Discussions should also acknowledge the degree of uncertainty related to prognosis [27]. Palliative medicine, pastoral care, and cultural support can be extremely helpful in this communication and should be engaged early in this process [27, 45, 49, 53]. The RPA guideline recommends that medical teams explicitly describe comfort measures and other components of palliative care that are available [27]. The purpose of these discussions is to develop consensus (not unanimity) among the medical team and the family.

The RPA guideline also recommends the establishment of a systematic due process approach for conflict resolution if there is disagreement between parents and the medical team or within the medical team itself about what decision should be made [27]. Potential interventions could include consultation with colleagues not involved in the child's direct medical care or convening of multidisciplinary conferences to discuss different perspectives related to treatment. If consensus still cannot be reached or if the treating nephrologist believes that the parents are making decisions inconsistent with the best interests of the child, consultation with a hospital ethics committee is highly recommended [27]. Court involvement to order dialysis treatment over parental objections represents a serious challenge to parental authority and autonomy and may permanently alter a family's future interactions with medical providers. Further, a personal or cultural history of negative interactions with child protective services (e.g., the indigenous populations of Canada, Australia, and the United States) is the reality for many families and may further weaken trust in providers who involve protective services without exhausting attempts at reaching consensus. Pursuit of state intervention should be considered only as a last resort.

Futility

As part of discussions in the setting of disagreement regarding forgoing dialysis, nephrologists may be tempted to claim that dialysis treatment is futile. This is rarely, if ever, a sufficient basis to forgo dialysis. A claim of futility is supported by the standard that a doctor is under no moral obligation to do to a patient that which is of no benefit to the patient. Unfortunately, there is no single agreed-upon definition of futility, and the concept has different meanings to physicians, parents, and the press [26, 54]. Physiologic futility claims that an intervention cannot achieve the desired outcome [54]. An example of this would be dialysis in a child for whom it is impossible to obtain vascular or peritoneal access. Quantitative futility claims that while it is possible for an

intervention to achieve the desired goal, it is so unlikely that it should not be pursued [55]. An example may be providing dialysis to an exceptionally small newborn (i.e., one weighing less than <1000 g) who is too small for traditional forms of vascular or peritoneal access. While it may be possible to obtain access, it is very unlikely, but not impossible, to be successful. So long as access may be obtained, dialysis will almost always provide improved metabolic clearance and volume control and thus will not meet a standard of physiologic or quantitative futility. This is not to claim that in every instance dialysis should be pursued, but rather that futility is an inappropriate reason not to do so. The assessment of benefit in such cases goes beyond whether dialysis will provide renal clearance and ultrafiltration to more global questions focused on quality of life for the patient. These considerations are inherently value-based and should be determined by the child's parents except when there is reason to believe that the parents are not acting as appropriate decision-makers for the child [45, 54, 56].

Allocation of Resources

Some providers may be concerned over the allocation of resources to children with poor prognoses, or conversely they may be concerned about the "waste" of withholding or withdrawing dialysis therapy in a child in whom enormous resources have been invested. It is important to acknowledge that there are limited resources available for healthcare and that society should utilize these resources in the most efficient manner possible for the benefit of the greater good of the population. However, in a society with resources available to fund medical care, rationing decisions should not be left to doctors at the bedside; rather they should be considered at a societal level. In addition, studies of the neonatal and pediatric intensive care units suggest that few resources are "wasted" on those children with even the most futile diagnoses [57, 58]. Similarly, the degree of previous resource utilization or medical effort is irrelevant to this discussion of justification of ongoing treatments. A "sunk cost" does not justify continued treatment if that treatment is no longer in the child's interests [59].

Most discussions of resource allocation in dialysis presume that the child is living in a well-resourced country where there is access to dialysis for acute and chronic kidney disease. It must be acknowledged that much of the world does not experience such plenty and that resource decisions are very different in countries where poverty, politics, and/or war has limited what can be provided [60, 61]. Excellent outreach efforts by the pediatric community are attempting to bring acute dialysis to low-resource countries [62–64]. Increased and sustained efforts to make dialysis an option for children who would benefit from it in the developing world are an important part of our roles as advocates and global citizens.

Time-Limited Trials

In cases of uncertain prognosis or when consensus cannot be reached regarding initiating or forgoing dialysis, the RPA guidelines and others encourage nephrologists to consider a time-limited trial of dialysis [27, 52, 65]. A time-limited trial is an agreement between care providers and surrogate decision-makers to provide a medical therapy over a defined period of time to determine if the patient improves or deteriorates according to agreed-upon clinical outcomes [66]. A trial of dialysis therapy may allow for further information to be gathered about the benefits and burdens of dialysis therapy without committing the child to a lifetime of renal replacement therapy [27, 52, 65]. While intuitively appealing, time-limited trials have a number of important limitations that diminish their usefulness including the arbitrary use of time limits; difficulty in determining clear, meaningful endpoints; and differing interpretations of a trial of therapy between parents and providers [37]. As noted earlier, organ replacement therapies such as dialysis are almost always effective at improving metabolic and fluid balance which make these poor endpoints for a trial. Other potential endpoints such as peritonitis or catheter failure may reflect random, common, and

treatable complications. Other seemingly objective endpoints (e.g., ability to wean off a ventilator or outcome of neuroimaging) may instead reflect implicit value judgments by the treating team (e.g., the quality of a child's life on chronic mechanical ventilation or with significant intellectual disability) [37]. Finally, there may be differences in understanding what is meant by a "trial of therapy." In contrast to providers, many parents interpret a "trial of therapy" as continuing treatment indefinitely unless a complication arises and the burdens of continued treatment exceed the benefits [37]. This is the same as forgoing dialysis treatment that has been initiated. Pediatric nephrologists should be hesitant to consider time-limited trials and may be better served by limiting discussions with parents to the initiation, continuation, and forgoing of dialysis.

Special Populations

Suspected ESKD in the Antenatal Period

About 50% of infants who receive dialysis during the neonatal period are diagnosed antenatally, which makes antenatal counseling an important component of optimizing medical intervention after birth [67]. The process of shared decision-making can and does start in the antenatal period. This is accompanied by significant uncertainty as there are no absolute prognostic markers in the antenatal period that accurately predict the degree of renal impairment and postnatal survival and no universal consensus in the medical community on how these infants should be managed [68]. Nevertheless, difficult choices need to be made with incomplete information, which can be distressing and confusing to families.

This complexity is illustrated by the example of renal oligohydramnios (ROH), which serves as an important prognostic marker in the fetus with suspected renal anomalies [69, 70, 71]. In a 2018 study of 103 pregnancies with ROH, 38% of subjects opted for pregnancy termination after receiving prenatal counseling [69]. Importantly, prenatal evidence of severe renal disease did not predict a lethal diagnosis in those fetuses that were carried to term. Of infants in this study, 54% were born alive and 78% of these were managed with active care. Of those actively managed, chronic kidney disease was common (more than 50% at 3 years of follow-up), but survival was excellent, with 92% surviving until discharge and 84% after a median follow-up of 1.5 years. Although one third of surviving children needed dialysis during the first 6 weeks of life, 42% had some recovery of renal function. We now know that this is a serious but not necessarily fatal diagnosis, and the outcomes are somewhat based on what parents choose to treat and what medical professionals choose to offer. This underscores the importance of antenatal consultation with a nephrologist, as the majority of families in this study who opted for pregnancy termination never spoke with a nephrologist.

Loos and Kemper [70] advocate for the importance of a multidisciplinary approach of obstetrics, neonatology, urology, genetics, and nephrology in addition to psychological or social work support throughout the decision-making process. Through this consultation, all reasonable options can be discussed, including pregnancy termination and early dialysis, but also a wait-and-see approach that could provide palliative care at birth with the option for aggressive management if kidney function is better than expected [70].

Suspected ESKD in the Neonatal Period

When babies are born with ESKD, either because their parents decided to continue a pregnancy after antenatal consultation or if the diagnosis was not picked up in the antenatal period, they do face a potentially grim prognosis. Dialysis in newborns is more complicated than that of older children, with more comorbidities, complications, and hospitalizations and a lower survival rate [72, 73]. However, recent publications show that survival rates are improving, with survival of those put on dialysis at <1 month of age nearing the survival rates of older infants [74]. Parents who choose to pursue dialysis in the newborn

period need to be prepared for a long and potentially morbid course, but ESKD is survivable, and most children who survive will eventually be able to get a transplant with outcomes similar or better than older children [72].

Prognostic uncertainty and expected morbidity does impact on the physician's view of whether it is appropriate to forgo dialysis in the neonatal period. Two surveys by Geary and colleagues in 1998 and 2011 showed that pediatric nephrologists were much more comfortable in allowing parents of newborns to forgo dialysis when compared to older children [75, 76]. Among the factors most important to the nephrologists were the family's right to decide, the anticipated morbidity for the child, and the presence of comorbidities. Comorbidities are present in 73% of newborns who are RRT candidates, so it would be expected to play a larger role in neonatal decision-making [67, 77]. As the morbidity of dialysis decreased and survival of young infants increased between the two surveys, nephrologists' attitudes did change, but they continued to be much more willing to allow parents of newborns wider discretion than that for older children. This suggests a flexible approach that matured with emerging evidence, but also the possibility of a self-fulfilling prophecy – if we only rarely attempt dialysis in young babies, we will rarely have survivors. As with the lower limit of viability for preterm infants, the target is always moving, and what is now considered care that falls under parental discretion may well be the standard of care in the future [1, 78].

Communication strategy is of utmost importance in making important decisions in the NICU, which is universally a high-stress and high-stakes environment. Lantos proposes an approach to this communication which allows parents to be told the truth in the way that they need to hear it. This sometimes means "telling the truth slant" (sometimes through indirect communication) and seeking non-opposition to forgoing treatment instead of a too traumatic frank approval [79]. While designed for NICU cases, this compassionate communication technique may be useful in other cases of forgoing dialysis as well.

Developmentally Disabled Children and Those with Significant Comorbidities

Children with developmental disabilities (DD) or other significant comorbidities create special challenges when deciding whether to forgo dialysis. It is important to value the lives of these children as much as any other child and not to use their disability as a reason to give them less than we would provide to a child of average developmental ability. The limited data available suggests that many children with DD will have equivalent survival rates to children of average development, if dialysis is offered [80]. In some jurisdictions like the United States, it may be a violation of laws protecting the disabled to offer less treatment to a child based on their DD diagnosis [81]. However, it is important to recognize dialysis as a burdensome and potentially morbid intervention, and the burdens of this therapy may be different for children with different challenges. For example, a child with significant developmental disabilities may not be able to remain still for a dialysis session or may pull at intravascular or intraperitoneal catheters, raising a potential for serious bleeding or infection. Some of these concerns can be ameliorated with good multidisciplinary care (e.g., choosing the least intrusive method of dialysis, parent presence during the session, play or music therapy, use of anxiolytics, etc.), but there will be some children for whom the burdens of dialysis cannot be reduced enough to be outweighed by the benefits. Since these are important considerations for any child considering dialysis, they cannot be ignored in an assessment of the benefits and burdens for a child with DD [77]. Each case should be evaluated based on the specific medical aspects, quality of life factors, contextual features, and patient and parent preferences to arrive at a decision that meets the needs of that particular child, and DD should rarely, if ever, be considered an absolute contraindication for dialysis [52].

Children Who Are Not Transplant Candidates

Transplantation is usually considered as the best therapy for children with ESKD, enabling better survival, better cardiac health, and a better quality of life than those who remain on dialysis [68, 82, 83]. Contraindications to transplant are rare and generally limited to those diseases for which transplant will not be expected to benefit the child (e.g., children with life-limiting comorbidities like malignant cancer or children for whom quality of life is not expected to improve with transplant like those in a persistent vegetative state or those with an extremely high rate of disease recurrence in the graft, such as some types of nephrotic syndrome) [84–86]. While some of these children may become transplant candidates with future advances in medications or technology, some will never be transplant eligible.

In these children, dialysis needs to be reevaluated not as the bridge therapy it commonly is in pediatrics, but as a terminal therapy as is more common in adults with ESKD. Dialysis as a terminal therapy may still well be beneficial in these children, but again a careful weighing of benefits and burdens will be required [52].

Undocumented Immigrants/Refugees

As global conflicts continue to drive immigrants and refugees to better resourced countries in the Middle East, Europe, North America, and beyond, children will arrive with severe kidney disease or develop kidney disease while living with immigrant or refugee status. These children may present emergently with ESKD or have progressive disease which is expected to end in ESKD. Healthcare providers caring for these children may face ethical and legal difficulties in providing dialysis for these children when and if it becomes necessary.

In many countries, laws protect all patients (children and adults) who require emergency treatment including dialysis, but chronic therapy is much more variable. In a 2016 survey of nephrologists in the Middle East, Europe, and North Africa, dialysis for refugees was covered by government payors according to 40% of respondents, and a tiny minority reported that they had been forbidden from providing dialysis by either government or hospital authorities [87]. In Canada, dialysis is generally covered for refugee claimants by interim refugee health coverage [88]. In the United States, EMTALA protects those needing emergency dialysis, but chronic dialysis can be more variable and is often only provided in safety-net hospitals and federally qualified health centers, by specific state legislation or by philanthropy funds in hospitals [89]. In New Zealand, chronic dialysis is provided for "renal refugees" who cannot access it in their home countries [90]. There are reports that less well-resourced countries like Lebanon have much more difficulty in providing this ongoing care, both because of the large number of refugees that they are hosting and the financial limitations for healthcare that already limit access in those countries [91].

In the limited survey data available, most nephrologists recognize that the provision of dialysis to such patients, including children, is part of the physician's moral code [87]. Dialysis for those who need and want it is clearly beneficent for the patient, and denying it is stressful for healthcare providers as well [92]. While it might be reasonable to limit care available to those from far beyond our borders, immigrants and refugees are members of the communities to which they migrate. They contribute in countless social ways, but also economically with labor, taxes (sales, property, etc.), and contributions to social programs like social security [13]. Maintenance dialysis is also cheaper than emergency-only dialysis, because of the lower needs for inpatient stays and ER visits [93, 94]. Providing medical care to members of our community is an essential part of our obligations as physicians, and denying care based on immigration status violates the important commitments that we have made to beneficence and solidarity [95–97]. There is little defense to forgo dialysis because of a child's legal status in a country. Physicians faced with administrative or governmental barriers need to be strong advocates to get their patients the care

that they deserve. This may include advocating for patients to stay in a well-resourced country to get the care that they would not be able to receive in their home countries [90].

Adolescents Who Make a Request to Forgo Dialysis

While discontinuation of dialysis in adult units is relatively common, pediatric nephrologists will only rarely encounter an adolescent with ESKD who requests discontinuation of maintenance dialysis [98]. While it is important to respect the developing autonomy of an adolescent, nephrologists should also recognize their duty of beneficence toward the child [99]. Forgoing dialysis is rarely in such a patient's best interest, as defined by the healthcare team, but it is important to understand that the perception and grading of burdens and benefits may be very different for the patient him or herself [99, 100]. The adolescent's emerging autonomy and the complexity of the best interest analysis make these cases especially fraught. Wherever possible, nephrologists should work to address barriers to successful treatment including working to improve the doctor-patient relationship and therapeutic alliance; involvement of other specialists such as psychiatry, psychology, social work, palliative care, or pain medicine; and, if indicated, utilizing pain, anxiolytic, or psychotropic medications. If transplant is a feasible option, it should also be explored. If there is serious concern for child abuse or medical neglect, state custody should be sought, but it is important to explore how the provision of dialysis without consent will affect the teen and whether it can be logistically provided to someone who does not want to receive it. Dialysis treatment requires an ongoing commitment, and it would be practically difficult, if not impossible, to provide it to an adolescent who actively fought the treatment. If the adolescent required sedation or restraint to undergo each dialysis treatment against her wishes, the trauma and additional burdens placed on the adolescent and the dialysis team could likely exceed the benefits that continued dialysis provides [100]. Ultimately, if persuasion and additional resources cannot change the adolescent's views, the nephrologist may be forced to accept these views, discontinue dialysis, and transition the goals of care to palliative or comfort care only [100].

Conclusions

Dialysis is usually a lifesaving, life-improving, and welcomed technology for children with ESKD and their families. In some situations, a decision will be made to forgo the therapy because it is too burdensome or insufficiently beneficial. In others, resource limitations or external factors may limit what can and should be offered. These decisions are inherently complex and challenging and require the commitment of the medical team to support the patient and his or her family before, during, and after the decision-making process. In any of these cases, standard ethical decision-making frameworks can be applied in order to make the best decisions, but decision-makers should always be cognizant of how dialysis differs from other high-technology, chronic interventions.

References

1. Wightman AG, Freeman MA. Update on ethical issues in pediatric dialysis: has pediatric dialysis become morally obligatory? Clin J Am Soc Nephrol. 2016;11(8):1456–62.
2. System USRD. 2015 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda; 2015.
3. Fauriel I, Moutel G, Moutard ML, Montuclard L, Duchange N, Callies I, et al. Decisions concerning potentially life-sustaining treatments in paediatric nephrology: a multicentre study in French-speaking countries. Nephrol Dial Transplant. 2004;19(5):1252–7.
4. Vernon DD, Dean JM, Timmons OD, Banner W Jr, Allen-Webb EM. Modes of death in the pediatric intensive care unit: withdrawal and limitation of supportive care. Crit Care Med. 1993;21(11):1798–802.
5. Carter BS, Howenstein M, Gilmer MJ, Throop P, France D, Whitlock JA. Circumstances surrounding the deaths of hospitalized children:

opportunities for pediatric palliative care. Pediatrics. 2004;114(3):e361–6.
6. Jonsen AR. The god squad and the origins of transplantation ethics and policy. J Law Med Ethics. 2007;35(2):238–40.
7. Friedman EA. Book review. N Engl J Med. 1993;328(16):1204–5.
8. Alexander S. They decide who lives, who dies. Life. 1962:102–25.
9. Levine C. "The Seattle 'god committee': a cautionary tale," [Internet]. Health Affairs Blog. 2009.
10. Gordon EJ. Haunted by the "God Committee": reciprocity does no justice to eliminating social disparities. Am J Bioeth. 2004;4(4):23–5; discussion W35-7.
11. Rettig RA. Special treatment–the story of Medicare's ESRD entitlement. N Engl J Med. 2011;364(7):596–8.
12. Ross W. God panels and the history of hemodialysis in America: a cautionary tale. Virtual Mentor. 2012;14(11):890–6.
13. Goldberg AM, Simmerling M, Frader JE. Why nondocumented residents should have access to kidney transplantation: arguments for lifting the federal ban on reimbursement. Transplantation. 2007;83(1):17–20.
14. Kopelman LM. Using the best interests standard to generate actual duties. AJOB Prim Res. 2013;4(2):11–4.
15. A.C. v. Manitoba (Director of Child and Family Services). SCC; 2009.
16. Assembly UNG. Convention on the rights of the child 1989.
17. Diekema DS. Parental refusals of medical treatment: the harm principle as threshold for state intervention. Theor Med Bioeth. 2004;25(4):243–64.
18. Ross LF. Children, families and health care decisions. Oxford: Oxford University Press; 1998.
19. Tsai TC, Liu SI, Tsai JD, Chou LH. Psychosocial effects on caregivers for children on chronic peritoneal dialysis. Kidney Int. 2006;70(11):1983–7.
20. Laakkonen H, Taskinen S, Ronnholm K, Holmberg C, Sandberg S. Parent-child and spousal relationships in families with a young child with end-stage renal disease. Pediatr Nephrol. 2014;29(2):289–95.
21. Wightman A, Zimmerman CT, Neul S, Lepere K, Cedars K, Opel D. Caregiver experience in pediatric dialysis. Pediatrics. 2019;143(2):e20182102.
22. Veatch RM. Abandoning informed consent. Hast Cent Rep. 1995;25(2):5–12.
23. Rhodes R, Holzman IR. Is the best interest standard good for pediatrics? Pediatrics. 2014;134(Suppl 2):S121–9.
24. Fuchs VR. Who shall live? Health, economics and social choice. Singapore: World Scientific Publishing; 2011.
25. Hofmann B. Is there a technological imperative in health care? Int J Technol Assess Health Care. 2002;18(3):675–89.
26. Beauchamp TL, Childress JF. Principles of biomedical ethics. 8th ed. New York City: Oxford University Press; 2012. 480 p.
27. (RPA) RPA. Shared decision making in the appropriate initiation of and withdrawal from dialysis. 2nd ed. Rockville: RPA; 2010.
28. Wilkinson D, Savulescu J. A costly separation between withdrawing and withholding treatment in intensive care. Bioethics. 2014;28(3):127–37.
29. Solomon MZ, Sellers DE, Heller KS, Dokken DL, Levetown M, Rushton C, et al. New and lingering controversies in pediatric end-of-life care. Pediatrics. 2005;116(4):872–83.
30. Chung GS, Yoon JD, Rasinski KA, Curlin FA. US physicians' opinions about distinctions between withdrawing and withholding life-sustaining treatment. J Relig Health. 2016;55(5):1596–606.
31. Rebagliato M, Cuttini M, Broggin L, Berbik I, de Vonderweid U, Hansen G, et al. Neonatal end-of-life decision making: Physicians' attitudes and relationship with self-reported practices in 10 European countries. JAMA. 2000;284(19):2451–9.
32. Sprung CL, Paruk F, Kissoon N, Hartog CS, Lipman J, Du B, et al. The Durban world congress ethics round table conference report: I. Differences between withholding and withdrawing life-sustaining treatments. J Crit Care. 2014;29(6):890–5.
33. Feltman DM, Du H, Leuthner SR. Survey of neonatologists' attitudes toward limiting life-sustaining treatments in the neonatal intensive care unit. J Perinatol: official journal of the California Perinatal Association. 2012;32(11):886–92.
34. Ladin K, Pandya R, Kannam A, Loke R, Oskoui T, Perrone RD, et al. Discussing conservative management with older patients with CKD: an interview study of nephrologists. Am J Kidney Dis. 2018;71(5):627–35.
35. Fox RC, Swazey JP. The courage to fail : a social view of organ transplants and dialysis. Chicago: University of Chicago Press; 1974. p. xviii, 395 p.
36. Derse AR. Limitation of treatment at the end-of-life: withholding and withdrawal. Clin Geriatr Med. 2005;21(1):223–38. xi
37. Wightman A. Management dilemmas in pediatric nephrology: time-limited trials of dialysis therapy. Pediatr Nephrol. 2017;32(4):615–20.
38. Buchak L. Why high-risk, non-expected-utility-maximising gambles can be rational and beneficial: the case of HIV cure studies. J Med Ethics. 2017;43(2):90–5.
39. Orentlicher D. Matters of life and death : making moral theory work in medical ethics and the law. Princeton: Princeton University Press; 2001. p. viii, 234 p.
40. Levine DZ, Truog RD. Discontinuing immunosuppression in a child with a renal transplant: are there limits to withdrawing life support? Am J Kidney Dis. 2001;38(4):901–15.
41. Rachels J. Active and passive euthanasia. N Engl J Med. 1975;292(2):78–80.

42. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ, European Paediatric Dialysis Working Group. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). Pediatr Nephrol. 2013;28(9):1739–48.
43. Feudtner C, Mott AR. Expanding the envelope of care. Arch Pediatr Adolesc Med. 2012;166(8):772–3.
44. Thumfart J, Bethe D, Wagner S, Pommer W, Rheinlander C, Muller D. A survey demonstrates limited palliative care structures in paediatric nephrology from the perspective of a multidisciplinary healthcare team. Acta Paediatr. 2018;108(7):1350–6.
45. American Academy of Pediatrics Committee on Bioethics. Guidelines on foregoing life-sustaining medical treatment. Pediatrics. 1994;93(3):532–6.
46. Committee on Hospital Care and Institute for Patient- and Family-Centered Care. Patient- and family-centered care and the pediatrician's role. Pediatrics. 2012;129(2):394–404.
47. Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. Soc Sci Med. 1999;49(5):651–61.
48. Association AM. AMA Code of Medical Ethics Opinion 2.20 – withholding or withdrawing life-sustaining medical treatment 1996. Available from: http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion220.page?
49. Germain MJ, Cohen LM, Davison SN. Withholding and withdrawal from dialysis: what we know about how our patients die. Semin Dial. 2007;20(3):195–9.
50. Murtagh SN. Conservative management of end-stage renal disease. In: Chambers JE, Brown E, editors. Supportive care for the renal patient. Oxford: Oxford Press; 2004. p. 255–64.
51. Linder E, Burguet A, Nobili F, Vieux R. Neonatal renal replacement therapy: an ethical reflection for a crucial decision. Arch Pediatr. 2018;25(6):371–7.
52. Dionne JM, d'Agincourt-Canning L. Sustaining life or prolonging dying? Appropriate choice of conservative care for children in end-stage renal disease: an ethical framework. Pediatr Nephrol. 2015;30(10):1761–9.
53. Thumfart J, Reindl T, Rheinlaender C, Muller D. Supportive palliative care should be integrated into routine care for paediatric patients with life-limiting kidney disease. Acta Paediatr. 2018;107(3):403–7.
54. Helft PR, Siegler M, Lantos J. The rise and fall of the futility movement. N Engl J Med. 2000;343(4):293–6.
55. Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: its meaning and ethical implications. Ann Intern Med. 1990;112(12):949–54.
56. American Academy of Pediatrics Committee on Fetus and Newborn, Bell EF. The initiation or withdrawal of treatment for high-risk newborns. Pediatrics. 1995;96(2):362–3.
57. Sachdeva RC, Jefferson LS, Coss-Bu J, Brody BA. Resource consumption and the extent of futile care among patients in a pediatric intensive care unit setting. J Pediatr. 1996;128(6):742–7.
58. Lantos JD, Mokalla M, Meadow W. Resource allocation in neonatal and medical ICUs. Epidemiology and rationing at the extremes of life. Am J Respir Crit Care Med. 1997;156(1):185–9.
59. Kahneman D. Thinking, fast and slow. 1st ed. New York: Farrar, Straus and Giroux; 2011. p. 499.
60. Luyckx VA, Miljeteig I, Ejigu AM, Moosa MR. Ethical challenges in the provision of dialysis in resource-constrained environments. Semin Nephrol. 2017;37(3):273–86.
61. Olowu WA. Renal failure in Nigerian children: factors limiting access to dialysis. Pediatr Nephrol. 2003;18(12):1249–54.
62. Feehally J, Couser W, Dupuis S, Finkelstein F, Harden P, Harris D, et al. Nephrology in developing countries: the ISN's story. Lancet. 2014;383(9925):1271–2.
63. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258–70.
64. Smoyer WE, Finkelstein FO, McCulloch MI, Carter M, Brusselmans A, Feehally J. "Saving Young Lives" with acute kidney injury: the challenge of acute dialysis in low-resource settings. Kidney Int. 2016;89(2):254–6.
65. Scherer JS, Holley JL. The role of time-limited trials in dialysis decision making in critically ill patients. Clin J Am Soc Nephrol. 2016;11(2):344–53.
66. Quill TE, Holloway R. Time-limited trials near the end of life. JAMA. 2011;306(13):1483–4.
67. Rees L. Renal replacement therapies in neonates: issues and ethics. Semin Fetal Neonatal Med. 2017;22(2):104–8.
68. Lantos JD. Ethical problems in decision making in the neonatal ICU. N Engl J Med. 2018;379(19):1851–60.
69. Mehler K, Gottschalk I, Burgmaier K, Volland R, Buscher AK, Feldkotter M, et al. Prenatal parental decision-making and postnatal outcome in renal oligohydramnios. Pediatr Nephrol. 2018;33(4):651–9.
70. Loos S, Kemper MJ. Causes of renal oligohydramnios: impact on prenatal counseling and postnatal outcome. Pediatr Nephrol. 2018;33(4):541–5.
71. Hogan J, Dourthe ME, Blondiaux E, Jouannic JM, Garel C, Ulinski T. Renal outcome in children with antenatal diagnosis of severe CAKUT. Pediatr Nephrol. 2012;27(3):497–502.
72. Vidal E, Edefonti A, Murer L, Gianoglio B, Maringhini S, Pecoraro C, et al. Peritoneal dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. Nephrol Dial Transplant. 2012;27(1):388–95.
73. United States Renal Data System (USRDS) annual data report: end-stage renal disease in the United States. Bethesda 2018.
74. Sanderson KR, Yu Y, Dai H, Willig LK, Warady BA. Outcomes of infants receiving chronic peritoneal

dialysis: an analysis of the USRDS registry. Pediatr Nephrol. 2019;34(1):155–62.
75. Geary DF. Attitudes of pediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133(1):154–6.
76. Teh JC, Frieling ML, Sienna JL, Geary DF. Attitudes of caregivers to management of end-stage renal disease in infants. Perit Dial Int. 2011;31(4):459–65.
77. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). Pediatr Nephrol. 2013;28(9):1739–48.
78. Lantos JD, Warady BA. The evolving ethics of infant dialysis. Pediatr Nephrol. 2013;28(10):1943–7.
79. Lantos JD. Tell parents the truth, but tell it slant. Pediatrics. 2018;142(Suppl 3):S199–s204.
80. Aksu N, Yavascan O, Anil M, Kara OD, Bal A, Anil AB. Chronic peritoneal dialysis in children with special needs or social disadvantage or both: contraindications are not always contraindications. Perit Dial Int. 2012;32(4):424–30.
81. Wightman A, Kett J. Has neonatal dialysis become morally obligatory? Lessons from Baby Doe. Acta Paediatr. 2015;104(8):748–50.
82. Schmidt BMW, Sugianto RI, Thurn D, Azukaitis K, Bayazit AK, Canpolat N, et al. Early effects of renal replacement therapy on cardiovascular comorbidity in children with end-stage kidney disease: findings from the 4C-T study. Transplantation. 2018;102(3):484–92.
83. Wightman A, Bradford MC, Smith J. Health-related quality of life changes following renal transplantation in children. Pediatr Transplant. 2019;23(2):e13333.
84. Weber S, Tonshoff B. Recurrence of focal-segmental glomerulosclerosis in children after renal transplantation: clinical and genetic aspects. Transplantation. 2005;80(1 Suppl):S128–34.
85. Kamin DS, Freiberger D, Daly KP, Oliva M, Helfand L, Haynes K, et al. What is the role of developmental disability in patient selection for pediatric solid organ transplantation? Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2016;16(3):767–72.
86. Knoll G, Cockfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, et al. Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. CMAJ. 2005;173(10):1181–4.
87. Van Biesen W, Vanholder R, Vanderhaegen B, Lameire N, Wanner C, Wiecek A, et al. Renal replacement therapy for refugees with end-stage kidney disease: an international survey of the nephrological community. Kidney Int Suppl. 2016;6(2):35–41.
88. Canada Go. Interim Federal Health Program: Summary of coverage 2018 [updated 2018-10-12. Available from: https://www.canada.ca/en/immigration-refugees-citizenship/services/refugees/help-within-canada/health-care/interim-federal-health-program/coverage-summary.html
89. The Lancet Haematology. The undocumented struggle with emergency-only dialysis. Lancet Haematol. 2018;5(9):e378.
90. Sutherland L. Renal refugees. Am J Kidney Dis. 2018;72(4):A13–a4.
91. Mawad D. Dialysis for Syrian refugees at risk due to funds shortage UNHCR USA2018 [cited 2019 March 28]. Available from: https://www.unhcr.org/news/stories/2018/3/5abcfae24/dialysis-syrian-refugees-risk-due-funds-shortage.html
92. Cervantes L, Richardson S, Raghavan R, Hou N, Hasnain-Wynia R, Wynia MK, et al. Clinicians' perspectives on providing emergency-only hemodialysis to undocumented immigrants: a qualitative study perspectives on providing emergency hemodialysis to undocumented immigrants. Ann Intern Med. 2018;169(2):78–86.
93. Sheikh-Hamad D, Paiuk E, Wright AJ, Kleinmann C, Khosla U, Shandera WX. Care for immigrants with end-stage renal disease in Houston: a comparison of two practices. Tex Med. 2007;103(4):54–8.
94. Sher SJ, Aftab W, Moorthi RN, Moe SM, Weaver CS, Messina FC, et al. Healthcare outcomes in undocumented immigrants undergoing two emergency dialysis approaches. Clin Nephrol. 2017;88(10):181–92.
95. Anderson RJ. Why we should care for the undocumented. Virtual Mentor. 2008;10(4):245–8.
96. King LP. Why we can't turn our backs. Virtual Mentor. 2008;10(4):191–4.
97. Wightman A, Diekema D. Should an undocumented immigrant receive a heart transplant? AMA J Ethics. 2015;17(10):909–13.
98. Schowalter JE, Ferholt JB, Mann NM. The adolescent patient's decision to die. Pediatrics. 1973;51(1):97–103.
99. Ross LF. Against the tide: arguments against respecting a minor's refusal of efficacious life-saving treatment. Camb Q Healthc Ethics. 2009;18(3):302–15; discussion 15–22.
100. Tate T, Goldberg A, Wightman A, Warady BA, Lantos JD. Controversy about dialysis for an adolescent. Pediatrics. 2017;140(1):e20170327.

Part VIII

Special Indications, Techniques and Applications

43 Diagnosis and Treatment of Acute Kidney Injury in Children and Adolescents

Emma Heydari Ulrich, David Selewski, and Michael Zappitelli

Introduction

In the past 15 years, understanding of acute kidney injury (AKI) has replaced past perceptions of acute renal failure, reflecting a growing appreciation of AKI as a dynamic, graded pathologic process associated with significant morbidity and mortality. Significant effort is being made to increase knowledge of AKI pathophysiology and develop predictive models and biomarkers to advance treatments and improve outcomes. In parallel, renal support therapy (RST) has expanded from a "last resort" treatment to an important tool to prevent AKI complications and improve kidney outcomes. The last decade has also been marked by improved RST technology for small patients.

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Diagnosis of Acute Kidney Injury

Definition of AKI

Until recently, a major obstacle to understanding pediatric AKI epidemiology was the lack of a standardized definition. Since 2005, several definitions have been proposed, based on acute serum creatinine (SCr) rise and urine output (UO) decrease to grade AKI severity [1]. Development of these simple, categorical definitions led to a surge of AKI epidemiological studies, initially in adults and more recently in children [2–4]. The most recent and internationally accepted AKI definition is that of the Kidney Disease: Improving Global Outcomes (KDIGO) AKI work group (2012) [5] (Table 43.1). Initially developed for use in adults, the KDIGO definition incorporates pediatric-specific criteria. There is also a modified neonatal version (Chap. 44) [3, 6]. The KDIGO definition has been applied and shown to have strong associations with clinical outcomes, including mortality, in many pediatric populations, including the multinational Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study in critically ill children [2]. The AWARE study highlighted that both the SCr and UO components of the KDIGO definition are important and should be monitored closely in at-risk patients. A major limitation of these definitions remains the low sensitivity and specificity of SCr and UO measures [5]. SCr concentration is affected by muscle

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Table 43.1 KDIGO definition of acute kidney injury in children [5]

KDIGO		
Stage	Serum creatinine criteria	Urine output criteria
1	≥1.5–1.9× baseline rise within 7 days OR ≥26.5 μmol/L (≥0.3 mg/dL) rise within 48 h	<0.5 mL/kg/h for 6–12 h[a]
2	≥2.0–2.9× baseline	<0.5 mL/kg/h for ≥12 h[b]
3	≥3.0× baseline OR Serum creatinine ≥353.7 μmol/L (≥4.0 mg/dL) OR In patients <18 years, decrease eGFR to <35 mL/min/1.73 m^2 OR Initiation of RST for AKI	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

KDIGO Kidney Disease: Improving Global Outcomes, *RST* renal support therapy

[a]Pediatric literature consistently defines stage 1 AKI with decreased urine output for >8 h

[b]Pediatric literature consistently defines stage 2 AKI with decreased urine output >16 h

mass, fluid overload, and age, independent of glomerular filtration rate (GFR). Acute SCr rise is often delayed by up to 48–72 h and baseline SCr is often unknown. UO is affected by drugs, fluid status, and body habitus; measurement is affected by the presence/absence of a urinary catheter. The KDIGO definition does not provide information about AKI etiology or kidney structural/tissue injury but merely a delayed measure of *functional* abnormality (i.e., GFR).

The problem of late AKI diagnosis has severely delayed research on AKI treatments and likely contributed to many negative findings in AKI therapeutic trials. These problems have motivated research on new AKI diagnostic tests or *AKI biomarkers* to [1] enable earlier AKI diagnosis by reflecting kidney tissue damage before evidence of dysfunction; [2] isolate AKI to different renal compartments to identify AKI etiology; and [3] identify therapeutic targets. Studied AKI biomarkers may be broadly classified into functional markers (like SCr, filtered at the glomerulus, reflecting GFR), tubular damage biomarkers (mainly urinary proteins reabsorbed by the proximal tubular cells, such as beta-2 microglobulin or N-acetyl-beta-D-glucosaminidase), and biomarkers whose genes are induced or downregulated by AKI (e.g., neutrophil gelatinase-associated lipocalin; interleukin-18; kidney injury molecule-1).

An example of a functional AKI biomarker is serum cystatin C (CysC). CysC is filtered at the glomerulus and is a more accurate marker of GFR than SCr. In critically ill children and those undergoing cardiac surgery, CysC has been shown to rise before SCr does with AKI. Routine CysC measurement is available in many centers, but it is currently most commonly used to estimate GFR in the outpatient setting [7]. Tubular damage biomarkers have demonstrated modest success at best for AKI diagnosis prior to SCr rise. Biomarkers induced or downregulated with renal tubular injury have variably shown the highest promise for early AKI diagnosis. There is a need for ongoing validation of AKI biomarkers for use in clinical practice, including determining biomarker concentration positivity thresholds, determining age-specific (e.g., neonate) thresholds, and validation in different AKI etiologies. Although current AKI biomarker utility is still mainly used for research, future AKI definitions will likely incorporate markers of kidney tissue injury in addition to markers of kidney function (i.e., SCr and UO) [8].

Epidemiology and Outcomes of AKI

An extraordinary amount of multicenter research in pediatric intensive care unit (ICU) and cardiac surgery populations from developed nations has confirmed the high incidence and impact of AKI previously described in single-center studies. More recent studies have described other hospitalized populations (extracorporeal membrane oxygenation [ECMO], nephrotoxin-exposed, oncology, and neonatal ICU patients). Globally, AKI affects approximately 13 million people/year; most cases occur in low- and middle-income countries. In developing nations, AKI is often community-acquired, including dehydration and infection, and closely linked with socioeconomic factors. The

International Society of Nephrology launched its 0by25 initiative, aimed at eliminating preventable deaths due to AKI by 2025 by increasing global awareness of AKI and using a need-based approach to develop systems to achieve this goal [9].

Incidence and Short-Term Outcomes

The AWARE study was a multinational prospective study of 4683 children from 32 ICUs [2]; AKI incidence was 27%. This study showed that stage 2 or worse AKI was associated with increased risk of 28-day mortality and longer mechanical ventilation. The Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group studied 834 patients receiving ECMO at six centers over 5 years [10]. AKI incidence was 74%, occurred early in the course of ECMO (93% within 48 h of ECMO initiation), and was associated with increased mortality and ECMO duration. AKI in children undergoing cardiac surgery has been well studied and has shown highly variable AKI incidence (15–70%) across studies [4, 11]. The Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) study of 131 children from three centers over 2 years [12] found that AKI occurred in 40% of children within the first 3 days after surgery and was associated with increased length of ICU stay and mechanical ventilation. In 799 children from two centers in the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial, AKI developed in 36% of patients, with similar outcome associations [13]. However, AKI incidence differed significantly between institutions (U. Michigan, 66%, vs. Boston Children's Hospital, 15%), suggesting that institutional differences impact the AKI development. There is a relative paucity of AKI data in non-critically ill children, mostly from single-center studies. In one center, of 13,914 noncritical pediatric admissions, AKI incidence was ≥5% [14]. However, less than one-quarter of admissions had ≥2 SCr measures; when only patients with ≥2 SCr were considered, AKI incidence was 30%. This study suggests a need for protocol SCr monitoring. Other single-center work has identified other high-risk populations including nephrotic syndrome, sickle cell disease, and those exposed to nephrotoxic medications.

Risk Factors

Major non-modifiable risk factors for AKI in hospitalized children include underlying acute diseases (e.g., sepsis, circulatory disease, congenital cardiac anomalies) and acute illness severity (e.g., ventilation, shock, ECMO). These risks are important to appreciate to identify patients at highest AKI risk. Risk factors for AKI after cardiac surgery have included younger age, lower weight, higher surgical complexity, cardiopulmonary bypass time, intraoperative practices, delayed sternal closure, perioperative comorbidities, and release of inflammatory mediators during bypass. In recent years, there has been an increased focus on understanding AKI risk factors that may be potentially modifiable. Nephrotoxic medication exposures (Table 43.2) are a modifiable risk where interventions to reduce exposure have led to reduced AKI incidence. In a single-center study, the electronic health record was utilized to trigger healthcare providers to monitor kidney function in patients at high risk of nephrotoxic AKI (≥3 days of intravenous aminoglycoside or ≥3 simultaneous nephrotoxins) [15]. This multidisciplinary approach to AKI prevention was feasible, associated with a 42% decrease in patient AKI days, and was sustainable over a 4-year period with a reduction in AKI rate due to nephrotoxins by over 60% [16].

Long-Term Outcomes

Observational studies in adults have demonstrated a consistent and high increased risk for chronic kidney disease (CKD) and end-stage renal disease (ESRD) following AKI hospitalizations [17]. Pre-existing CKD and worse AKI severity significantly increases ESRD risk in adults. There is also extensive literature in adults showing a strong association between AKI and long-term cardiovascular events and death.

In children, studies of long-term AKI outcomes are limited. Single-center observational studies have shown a higher incidence of long-term CKD and hypertension in children with AKI, relative to the general pediatric population

Table 43.2 Non-exhaustive list of nephrotoxic medications administered to hospitalized children

Medication	Mechanism of drug-induced AKI	Medication	Mechanism of drug-induced AKI
Analgesics		*Chemotherapy (continued)*	
NSAIDs	AIN, CIN, altered intraglomerular hemodynamics	Gemcitabine	Altered intraglomerular hemodynamics, TMA
Selective COX-2 inhibitors	Altered intraglomerular hemodynamics	Ifosfamide	Tubular cell toxicity +/− Fanconi syndrome
Antiepileptics		Interferon	GN (MCD, FSGS), altered intraglomerular hemodynamics
Topiramate	Nephrolithiasis	Methotrexate	Crystal nephropathy
Antimicrobials		Mitomycin	Altered intraglomerular hemodynamics
Adefovir, cidofovir, tenofovir	Tubular cell toxicity	Pentostatin	Tubular cell toxicity
Aminoglycosides	Tubular cell toxicity	Vincristine	SIADH
Amphotericin B	Tubular cell toxicity. Lipid/liposomal formulations are less toxic	*Diuretics*	
Antivirals (acyclovir, ganciclovir)	AIN, crystal nephropathy	Loop diuretics, thiazides	AIN; reduced intravascular volume
Beta-lactams	AIN	*Drugs of abuse*	
Foscarnet	Crystal nephropathy	Cocaine, heroin, ketamine, methadone, methamphetamine	Rhabdomyolysis
Indinavir	AIN, crystal nephropathy	*Psychiatric medications*	
Pentamidine	Tubular cell toxicity	Amitriptyline, fluoxetine	Rhabdomyolysis
Polymyxin antimicrobials	Tubular cell toxicity	Benzodiazepines	Rhabdomyolysis
Quinolones	AIN, crystal nephropathy	Haloperidol	Rhabdomyolysis
Rifampin	AIN	Lithium	CIN, rhabdomyolysis
Sulfadiazine	Crystal nephropathy	*Proton pump inhibitors*	
Sulfonamides	AIN, crystal nephropathy	Lansoprazole, omeprazole, pantoprazole	AIN
Vancomycin	AIN, obstructive tubular cast formation	*Other*	
Calcineurin inhibitors		Allopurinol	AIN
Tacrolimus	Altered intraglomerular hemodynamics	Dextran, hydroxyethyl starch, sucrose	Osmotic nephropathy
Cardiovascular agents		Gold	GN
ACEi, ARBs	Altered intraglomerular hemodynamics	Pamidronate	GN (MCD, FSGS)
Clopidogrel	TMA	Quinine	TMA
Statins	Rhabdomyolysis	Ranitidine	AIN
Chemotherapy		SGL-2 inhibitors	Altered intraglomerular hemodynamics
Anti-VEGF	Microvascular injury, TMA	Sodium phosphate	Crystal nephropathy
Contrast dye	Tubular cell toxicity	Vitamin C	Crystal nephropathy
Cisplatin	CIN, tubular cell toxicity +/− Fanconi syndrome, TMA	Zoledronate	Tubular cell toxicity, GN (FSGS)

ACEi angiotensin-converting enzyme inhibitors, *AIN* acute interstitial nephritis, *ARBs* angiotensin II receptor blockers, *CIN* chronic interstitial nephritis, *FSGS* focal segmental glomerulosclerosis, *GN* glomerulonephritis, *MCD* minimal change disease, *SIADH* syndrome of inappropriate anti-diuretic hormone, *TMA* thrombotic microangiopathy, *VEGF* vascular endothelial growth factor [102–104]

[18]. A two-center study showed that ICU children with AKI have increased 5-year mortality and healthcare utilization [19, 20]. There is evidence of long-term kidney risk in the child oncology literature, due to a number of mechanisms, including nephrotoxin exposure. One study showed that 70% of hospitalized children exposed to nephrotoxins had evidence of CKD at 6-month follow-up [21]. Literature on long-term kidney outcomes of AKI after cardiac surgery is controversial. Two multicenter studies of children undergoing cardiac surgery showed that these patients have a high prevalence of hypertension and CKD 5 years after surgery (17% and 18%, respectively) but that post-operative AKI was not associated with 5–7-year kidney outcomes [12, 22]. This finding may be due to the phenomenon of renal reserve and hyperfiltration mechanisms which may initially lead to increased GFR after kidney damage. A large retrospective study conversely showed that 5-year post-cardiac surgery CKD incidence was 12% vs. 3% in patients with vs. without AKI [23]. Regardless of the uncertain results on the long-term impact of AKI, children having cardiac surgery are at high risk for long-term kidney disease and hypertension.

Long-term kidney outcomes are difficult to study in children for several reasons. AKI as a risk factor for poor clinical outcomes has only recently been appreciated; as a result, most children with AKI are not followed long term for kidney function monitoring, and little is known about their long-term health outcomes. One study found that <50% of ICU children with AKI had repeat SCr measurement prior to discharge [24]. Another challenge is the need for long-term studies to detect late-onset CKD which is resource exhaustive. Nonetheless, the high prevalence of kidney disease and hypertension after AKI found in studies to date and the long-term potential cardiovascular health effects underscore the need to better understand risk after AKI and develop guidelines for long-term follow-up. The KDIGO guidelines recommend that patients with AKI should be followed 3 months after the AKI episode to screen for new or worsening CKD and its complications and ensure AKI resolution. The optimal time for initial AKI follow-up in children remains unclear and will be elucidated by future research, but one approach is reviewed in the following reference [18].

Pathophysiology of AKI

A framework for AKI has been described [25]. Initially, there is a period of increased risk following an inciting event, with no evidence of overt organ damage. This point of injury is reversible if the injury source is removed; otherwise, tissue damage will occur. After some delay, there is evidence of reduced GFR with current biomarkers (SCr, UO). Without intervention, injury may progress, leading to complications and potentially death. Many diseases and nephrotoxins can trigger and injure the tight autoregulation of blood flow through the glomerulus [26] (Fig. 43.1). With hypovolemia, the kidney will maintain blood pressure and perfusion to other organs through multiple mechanisms that raise renal vascular resistance, including release of angiotensin II (via renin-angiotensin axis regulation) and norepinephrine (via sympathetic activation), leading to vasoconstriction and reduced GFR. Angiotensin II vasoconstricts the efferent more than the afferent arteriole, which preserves GFR by increasing hydrostatic pressure across the glomerulus. Other factors also mediate afferent arteriolar dilation, including prostaglandin-induced vasodilation; medications such as non-steroidal anti-inflammatory drugs (NSAIDs) interfere with this response and increase AKI risk in the context of hypovolemia. Sodium and water handling by tubular cells are also altered with AKI, leading to reduced fractional excretion of sodium and oliguria. Aldosterone promotes tubular sodium and water reabsorption to maintain blood pressure. Antidiuretic hormone (ADH) promotes water reabsorption at the collecting duct in the presence of hypovolemia and increased serum osmolality.

With sustained injury, renal blood flow is substantially reduced due to persistent vasoconstriction. Proximal tubular cells are very sensitive to injury [27] due to high metabolic demand and reduced capacity for anaerobic metabolism [28]. Tubular casts form from desquamated cells and leaked tubular protein, including Tamm-Horsfall protein, leading to tubular obstruction and further

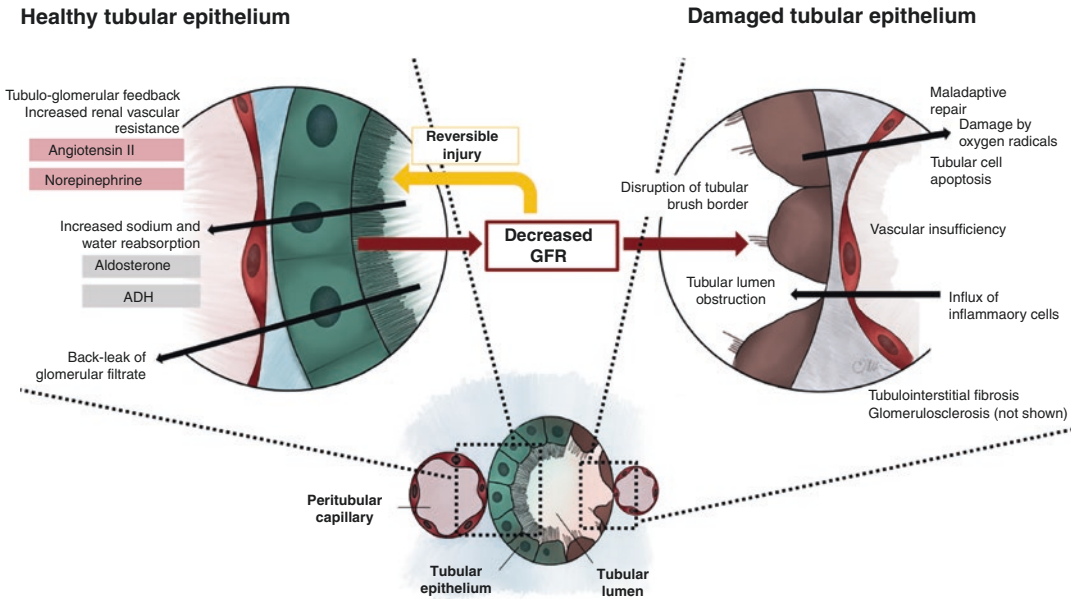

Fig. 43.1 Mechanisms leading to AKI are shown. Healthy tubular epithelium and physiologic responses are displayed on the left. Notably, there is a degree of reversibility of this damage, and therefore, decreased GFR can improve when the injury is not severe or reversed early enough in the process. These mechanisms include increased vascular resistance, mediated by angiotensin II and norepinephrine, resulting in vasoconstriction and reduced GFR. Also, tubuloglomerular feedback results in afferent arteriolar vasoconstriction, leading to reduced GFR. This is stimulated by detection of increased distal sodium delivery (due to proximal tubular leak) at the macula densa. Increased sodium and water reabsorption by healthy tubular cells, mediated by aldosterone and ADH, results in oliguria. Back-leak of glomerular filtrate also occurs. As renal injury progresses, the tubular epithelium is damaged in an irreversible manner. Tubular obstruction occurs by tubular cell casts and protein. Maladaptive cell repair and regeneration pathways persist long after the initial injury. Endothelial damage of tubulointerstitial cells results in microvascular dropout and further hypoxic-ischemic injury. The ensuing cellular dysfunction is further potentiated by glomerular hypertension, vascular insufficiency, and inflammation. Inflammatory cells trigger profibrotic signaling and lead to apoptosis and loss of normal cell cycle regulatory mechanisms. Over time, there is loss of the structural architecture of the renal tissue, including disruption of the tight junctions between tubular cells and denuding of the brush border. This results in tubular cell death and continued fibrosis. Glomerulosclerosis also occurs, resulting in hyperfiltration and further exacerbating damage of healthy tubular cells

injury. Tubuloglomerular feedback is mediated by increased distal tubular sodium delivery, leading to afferent arteriolar constriction and reduced GFR; this mechanism appears to be protective of injured tubular cells.

Over time, tubule atrophy and interstitial fibrosis following AKI result in chronic dysfunction. Loss of hemodynamic autoregulation mechanisms, glomerular hypertension, and glomerulosclerosis also contribute to further dysfunction and injury [29]. Much of our understanding of the pathophysiology of renal disease is derived from animal studies, which suggest several injury pathways, including maladaptive repair, disordered regeneration, or both (Fig. 43.1) [17]. Hyperfiltration occurs to compensate for nephron loss; over time, this causes further glomerular injury and sclerosis. With repeated insults, tubulointerstitial fibrosis and glomerulosclerosis lead to renal dysfunction and future progression to ESRD.

Clinical Evaluation of AKI

Classification and Etiology (Table 43.3)

The traditional approach to AKI involves classifying the potential etiology into three broad categories: "pre-renal," "intrinsic" renal, and

Table 43.3 A method for classifying etiology of AKI, with non-exhaustive list of causes

Pre-renal *Hypoxic-ischemic injury*	Renal *Involving the glomerular, tubular, interstitial, and/or vascular compartments*	Post-renal *Obstructive causes*
Hypotension or reduced intravascular volume Dehydration/hypovolemic shock due to GI, urinary, or other losses Hemorrhagic shock Sepsis *Reduced colloid pressure* Nephrotic syndrome Liver failure Malnutrition/hypoalbuminemia Sepsis/capillary leak Burns *Reduced cardiac output* Cardiogenic shock due to heart failure, tamponade, etc. *Vascular* Renal vein stenosis/thrombosis Renal artery stenosis/thrombosis Malignancy with secondary mass effects on vessels	*Glomerular* Glomerulonephritis *Tubular* Hypoxic-ischemic injury Hemolysis Rhabdomyolysis Tumor lysis syndrome Toxins *Interstitial* Pyelonephritis Acute interstitial nephritis *Vascular* Hemolytic uremic syndrome Thrombosis or stenosis of renal vessels (artery or vein) Malignant hypertension	*Renal obstruction with solitary kidney* Ureteral-pelvic junction Ureteral stenosis Ureteral-vesical junction Malignancy with secondary mass effects *Bilateral ureteral obstruction* Stones Malignancy *Urethral obstruction* Posterior urethral valves Catheter obstruction

"post-renal" causes (Table 43.3). While many episodes of AKI are multifactorial in nature, this systematic approach provides a framework for the diagnosis and clinical evaluation of AKI. In utilizing this conceptual framework, it is critical to appreciate that it does not speak to treatment (i.e., not all pre-renal states need fluid, such as congestive heart failure).

"Pre-renal" AKI causes include heterogeneous conditions causing reduced renal blood flow and hypoxic injury. Decreased renal blood flow may result from low intravascular volume, low cardiac output, loss of vascular tone, or increased renal perfusion resistance (Table 43.3). It is important to understand that low intravascular volume may result from an absolute decrease in volume (e.g., dehydration, hemorrhage) or fluid redistribution from the intravascular space (e.g., leaky vessels from inflammation). Understanding this is critical as these states will respond very differently to fluid resuscitation. Conditions like hypovolemia from diarrheal losses respond well to fluid resuscitation; conditions with reduced colloid pressure (e.g., nephrotic syndrome, cirrhosis) may benefit from albumin as opposed to isotonic fluids. Conditions like congestive heart failure or intra-abdominal hypertension may be worsened by fluid resuscitation.

"Intrinsic" AKI refers to damage to the renal parenchyma or tubular, glomerular, interstitial, and vascular tissue. The most common etiology for intrinsic AKI is severe hypoperfusion leading to tubular damage and acute tubular necrosis. Acute glomerular diseases are classically associated with a triad of AKI, hypertension, and hematuria. These disorders may be associated with systemic symptoms that provide insight into diagnosis (e.g., arthritis, pulmonary hemorrhage, rash, photosensitivity). The most common cause of interstitial disease is acute interstitial nephritis, which may or may not develop after exposure to an offending agent (e.g., antibiotics, proton pump inhibitors, NSAIDs, etc.). Vascular causes include large vessel disease (renal vein thrombosis, large vessel vasculitis) and microangiopathic processes (Table 43.3).

Nephrotoxic exposure represents an important cause of intrinsic AKI, which may impact all the previously mentioned anatomic locations depending on the medication (Table 43.2). As mentioned previously, the contribution of nephrotoxic medication exposures to AKI has

become clear. Drugs, such as NSAIDs and ACE inhibitors, can contribute to AKI by inhibiting renal vascular autoregulation. Common drugs implicated in AKI include aminoglycosides, amphotericin, chemotherapeutic agents (cisplatin, ifosfamide, methotrexate), and calcineurin inhibitors (cyclosporine, tacrolimus). Other non-medication nephrotoxins include radiocontrast agents, myoglobin, and hemoglobin.

"Post-renal" AKI is typically caused by obstruction, either functional (i.e., dysfunctional voiding) or structural (i.e., ureteropelvic junction obstruction) (Table 43.3).

History and Physical Examination

(Table 43.4)

Evaluation of AKI should include a thorough history, including medical/renal disease and recent medications and exposures. It is critical to evaluate the prior 48–72 h to capture potential exposures. Inquiries on systemic symptoms should be made to determine need to investigate systemic diseases further (e.g., vasculitis). A thorough family history for heritable causes of renal disease is important to elicit. Physical examination includes an assessment of volume status and for signs and symptoms of systemic disease (Table 43.4). Assessment of volume status includes evaluation of respiratory status and edema.

Table 43.4 History and physical examination for AKI

History	Physical examination
History of presenting illness, related to etiology	*Fluid status*
Urinary symptoms, including gross hematuria, foamy urine, dysuria, oliguria/polyuria, and other symptoms of bladder dysfunction	Blood pressure and vital signs
Pre-existing renal/medical disease	Fluid balance, weight, and fluid overload
Medications, including potential nephrotoxins	Urine output
NSAIDs	Edema
Aminoglycosides	Peripheral perfusion
Vancomycin	*Other systemic signs*
Piperacillin/tazobactam	Dermatologic exam
Angiotensin converting enzyme inhibitors	Musculoskeletal exam
Calcineurin inhibitors	Cardiac exam
Contrast	Respiratory; ear, nose, and throat; neurological exam (guided by underlying suspected etiology, aimed at identifying systemic diseases)
Review of symptoms, including systemic symptoms	
Headaches	
Hearing/vision problems	
Mouth sores	
Chest pain or hemoptysis	
Generalized edema (periorbital, scrotal, and peripheral)	
Rash (involving the face, palms, and/or extremities)	
Family history	

Fluid Overload Formal assessment of fluid overload (FO) is a critical vital sign for any patient with AKI. There are two common methods to calculate FO. Goldstein et al. first described the cumulative fluid balance method, which is the method most commonly utilized in the literature:

$$\text{Fluid overload}(\%) = \left[\text{fluid IN}(\text{liters}) - \text{fluid OUT}(\text{liters})\right] / \text{admit weight}(\text{kg}) \times 100$$

FO% may also be calculated using weight-based method:

$$\text{Fluid overload}(\%) = \left[\text{current weight}(\text{kg}) - \text{ICU admit weight}(\text{kg})\right] / \text{admit weight}(\text{kg}) \times 100$$

Significant FO represents the most common indication for intervention in children with AKI. The literature has consistently shown that increasing magnitude of FO is associated with adverse outcomes in a variety of populations, including children treated with continuous renal replacement therapy (CRRT) and other high-risk AKI populations (e.g., ECMO, bone marrow transplant) [30–32]. Literature supports that FO >10% should be considered a prognostic marker in ICU patients and a marker of need for intervention.

In recent years, it has also become clear that the development of FO may predate and delay the diagnosis of AKI. At the heart of this issue is the fact that SCr freely distributes between intracellular and extracellular spaces, resulting in inaccuracies due to fluid status. Several studies of ICU children show that failure to account for FO when interpreting AKI severity, as measured by SCr rise, leads to delays in diagnosis and staging of AKI and under-recognition of AKI incidence and association with mortality [33–35]. Recent studies have further cemented the concept that FO often occurs before meeting criteria for AKI [36–38]. The following formula is commonly utilized in the literature to correct SCr for FO:

$$\text{Corrected creatinine} = \text{serum creatinine}\left[1 + \left(\text{net fluid balance} / \text{TBW}\right)\right]$$

$$\text{where total body water}\left(\text{TBW}\right) = 0.6 \times \text{weight}\left(\text{kg}\right)$$

Diagnostic Laboratory Evaluation

(Table 43.5)

The initial laboratory workup of a patient with AKI seeks to identify the underlying etiology and potentially reversible causes of AKI (e.g., hypovolemia, nephrotoxins). The initial evaluation should minimally include electrolyte panel, SCr, urinalysis, urine sodium, urea and creatinine, and renal ultrasound.

Urinalysis and Urine Microscopy Urinalysis is a critical test to evaluate for hematuria, proteinuria (to rule out glomerular diseases), and/or signs of infection. Gross hematuria and severe proteinuria suggest glomerular disease. With sterile pyuria, acute interstitial nephritis must always be considered, and urinary eosinophil testing ordered. Urine microscopy aids in diagnosing intrinsic renal disease and may reveal muddy brown casts (acute tubular necrosis), red blood cell casts (glomerulonephritis), pyuria or crystals.

Fractional Excretion of Sodium and Urea With renal hypoperfusion, the kidney expands the intravascular volume by increasing sodium and urea retention, as described above [28]. This compensatory mechanism forms the basis of the fractional excretion of sodium (FeNa) and urea (FeUrea) calculations (Table 43.5). Both these calculations compare urine to serum concentrations of solute, corrected for GFR.

Renal Ultrasound Imaging plays a small role in diagnosing intrinsic renal disease. Ultrasound should be considered if there is concern for obstruction or performed with a Doppler to rule out large vessel disease (e.g., vessel thrombosis). Further information about the chronicity of a process may be obtained by evaluating renal size (e.g., small kidneys suggest CKD; larger kidneys may suggest an acute process).

Biopsy Renal biopsy is usually done to diagnose intrinsic AKI, findings of which are not reviewed here.

Table 43.5 A proposed list of investigations for AKI

Urine testing
Urinalysis and urine culture Dipstick testing for hematuria, proteinuria, signs of infection (leukocytes, nitrites) Urine culture should be collected by catheterization (non-toilet-trained children) or midstream sample (toilet-trained children)
Urine microscopy Muddy brown or granular casts are suggestive of acute tubular necrosis Predominant leukocytes are suggestive of acute interstitial nephritis Urinary eosinophils for suspected acute interstitial nephritis Red blood cell casts and/or white blood cell casts are suggestive of acute glomerulonephritis
Quantification of proteinuria Total (including glomerular and tubular) protein using protein/creatinine ratio Glomerular protein using albumin/creatinine ratio Tubular protein using ß2-microglobulin
Fractional excretion of sodium $\text{Fractional excretion of sodium}\left(\text{FeNa}\right)\left(\%\right)=\frac{\left(\text{urine Na / plasma Na}\right)}{\left(\text{urine creatinine / plasma creatinine}\right)}\times 100$ FeNa <1% (<2% for neonates[a]) suggests pre-renal AKI FeNa >2% (>2.5% for neonates[a]) suggests intrinsic AKI
Fractional excretion of urea[b] $\text{Fractional excretion of urea}\left(\text{FeUrea}\right)^{b}\left(\%\right)=\frac{\left(\text{urine urea / plasma urea}\right)}{\left(\text{urine creatinine / plasma creatinine}\right)}\times 100$ FeUrea <35% suggests pre-renal AKI FeUrea >50% suggests intrinsic AKI
Blood tests
Serum creatinine Indirect measure of GFR Limitations include: Delayed marker of reduction in GFR and tissue damage. Delay can be up to 72 h following renal insult Affected by a number of different factors, including age, sex, diet, muscle mass, and medications Serum creatinine varies with fluid status. Some investigators suggest correcting serum creatinine for fluid status: $\text{Corrected creatinine} = \text{serum creatinine}\left[1+\left(\frac{\text{net fluid balance}}{\text{total body water}}\right)\right]$
Further investigations for severity and etiology of AKI Complete blood count If concern of thrombotic microangiopathy (anemia and thrombocytopenia), send markers of hemolysis, including lactate dehydrogenase, bilirubin, haptoglobin, blood film. Further investigations if evidence of hemolysis is observed Sodium, potassium, chloride, bicarbonate, ionized and total calcium, magnesium, phosphate Albumin If concern of rhabdomyolysis, send serum creatine kinase, urine myoglobin
Tests, if abnormal, suggest acute on chronic kidney disease Iron studies, including ferritin, iron, transferrin, total iron binding capacity, and calculation of percent transferrin saturation (TSAT) Intact parathyroid hormone 25-[OH]-Vitamin D3
Other tests
Diagnostic imaging Includes renal ultrasound with Doppler Other investigations depend on etiology including VCUG, renal MAG3 scan, and DMSA renal scan
Renal biopsy
Renal biomarkers

[a]Neonates have reduced urine concentration and sodium retention due to relative tubular immaturity

[b]FeNa and FeUrea will be lowered with high urine flow rates. Diuretics reduce sodium reabsorption and thereby increase FeNa. FeUrea is less affected by diuretic therapy and may be helpful to distinguish pre-renal AKI from intrinsic AKI in patients treated with diuretics [105]

Management of Acute Kidney Injury

AKI Management Prior to Renal Support Therapy

Despite research advances described above, there remain no treatments for AKI. Many interventional trials aimed at treating established AKI have failed. Current management strategies are limited to preventing and treating AKI sequelae (FO, electrolyte abnormalities, etc.). There has been a recent paradigm shift from reactive AKI management to risk stratification and early identification. Targeted interventions in at-risk populations have shown some promising results for preventing AKI. This section focuses on risk stratification, potential interventions to prevent or treat AKI, and management of established AKI. In addition to close renal function monitoring, AKI management includes optimizing nutrition, avoiding hypotension and excessive FO, and limiting nephrotoxin exposure. Often, management decisions require a team-based collaborative approach to weigh AKI risks against benefits of individual interventions.

Investigational Strategies to Risk-Stratify AKI

Timely identification of patients at risk for developing severe AKI, before significant SCr rise or AKI sequelae development, is critical to allow early intervention. Recent examples of strategies developed to achieve early AKI identification include risk stratification (e.g., renal angina index, below), AKI biomarkers (discussed previously), and a functional assessment of kidney function (e.g., furosemide stress test, below).

Renal Angina Index The renal angina index is a scoring system developed and validated to predict AKI risk in ICU children by combining known AKI risk factors and functional evidence of injury (Fig. 43.2) [39]. Renal angina index derivation and validation studies showed that a score ≥8 predicted ≥ stage 2 AKI development on ICU day 3 [40, 41]. Combining the renal angina index score with AKI biomarker results (neutrophil gelatinase-associated lipocalin) in children at ICU admission led to almost perfect prediction of severe AKI on ICU admission day 3. This work demonstrates that achieving early/timely AKI and AKI risk identification likely requires both clinical and laboratory evidence of kidney tissue injury [42].

Furosemide Stress Test The furosemide stress test is a novel measure that evaluates UO response 6 h after furosemide administration, to predict severe AKI. In adults, patients with <200 mL of UO in the first 2 h of the test had the highest risk for severe AKI [43], and when the test was used in conjunction with biomarkers, severe AKI prediction improved further [44]. Emerging single-center studies evaluating the furosemide stress test in pediatric populations have shown similar promising results [45, 46].

Fluid Management

It is essential, but often challenging, to try to distinguish fluid responsive causes from fluid non-responsive causes of AKI (see Classification and Etiology of AKI). Patient weight should be measured daily and fluid balance should be monitored at least twice daily. After fluid resuscitation, fluid management should be critically assessed to avoid FO. With the exception of hypovolemia, a safe initial approach to fluid management is to replace insensible losses (~400 mL/m^2 of body surface area) and outputs (i.e., urine, gastrointestinal) to maintain euvolemia. Adult studies have not shown clear benefit of colloid vs. crystalloid (e.g., saline) solutions [47].

Diuretic use may be considered in oliguric AKI. KDIGO recommends not using diuretics for the prevention or treatment of AKI, except for the management of FO. Higher UO facilitates nutrition administration. Loop diuretics are typically used first (e.g., furosemide; in some centers, bumetanide) due to their rapid effectiveness, potency, and long history of use. When there is evidence that diuresis is effective and allows maintenance of desired fluid balance and nutrition, a second diuretic targeting different parts of the renal tubule (e.g., distal tubule-targeted diuretic, like thiazides or metolazone) may be

Risk	**Risk criteria**		**Score**
	ICU admission		**1**
	Solid organ or stem cell transplantation		**3**
	Mechanical ventilation or vasoactive support		**5**
Injury	**SCr/Baseline**	**% Fluid overload**	**Score**
	Decreased or no change	<5%	**1**
	>1×–1.49×	5–10%	**2**
	1.5×–1.99×	10–15%	**4**
	≥2×	>15%	**8**
			RAI index **Risk score × injury score (1–40)** **Renal angina = RAI index ≥8**

Fig. 43.2 Renal angina index [41]. Renal angina index (RAI) is used to prognosticate the risk of developing severe AKI (≥stage 2) 72 h later. RAI is calculated 12 h following admission to pediatric intensive care unit (ICU). Patient characteristics are assigned a score for "risk" (0, 1, 3, or 5). Elevation in SCr or fluid overload (%) is assigned a score for "injury." Baseline SCr is defined as the lowest SCr measured 3 months prior to ICU admission; baseline SCr was back-calculated when not available. The highest SCr between admission to ICU and 12 h after admission was used. When there was discrepancy between the score for SCr/Baseline or fluid overload, the worse score was used. The "risk" and "injury" scores are multiplied to achieve the "RAI Index," and RAI ≥8 defines renal angina. In addition to being an important prognostic marker, the finding of renal angina is strongly associated with worse outcomes

considered. However, with reduced GFR of AKI, most current diuretics are limited in their ability to reach tubules to exert their effect. Diuretics also have adverse effects, and many studies in adults have shown no benefit of diuretic use in AKI on time to AKI recovery or mortality. Thus, when using diuretics in AKI, frequent reassessment of benefit (negative balance, nutrition) vs. risk should be performed.

Electrolyte Management

Electrolyte management involves managing acute disturbances and anticipating potential problems. In oligoanuric AKI, the most common electrolyte disturbances are hyponatremia, hyperkalemia, hypocalcemia, and hyperphosphatemia. Hyponatremia occurs due to sodium and water retention, and this is most commonly managed by restricting fluid. Hyperkalemia is managed by reducing intake, correcting acidosis, and increasing elimination or intracellular shifts using diuretics, cation exchange resins (e.g., polystyrenes), beta-2 adrenergic receptor agonists (e.g., albuterol, salbutamol), or insulin with dextrose. When electrocardiogram changes are present or with severe hyperkalemia, cardioprotection with calcium gluconate is critical to preventing life-threatening arrhythmias. In refractory cases or those with a high potassium load (i.e., rhabdomyolysis), RST may be needed (see Timing and Modality of Renal Support Therapy). Hypocalcemia and hyperphosphatemia are treated with dietary adjustments and/or phosphate binders. It is important to appreciate that in severe hyperphosphatemia, together with severe hypocalcemia, RST may be the best treat-

ment option as infusing large amounts of IV calcium in patients with severe hyperphosphatemia may cause unwanted diffuse calcium-phosphate crystal formation. Also, when administering sodium bicarbonate therapy to correct acidosis or hyperkalemia, it is important to know the patient's calcium concentration, which will drop with bicarbonate infusions. Overall, it is crucial to be aware of all electrolyte abnormalities and anticipate the effects from treating one electrolyte abnormality on homeostasis of other electrolytes.

Pharmacological Therapy

Historically, vasodilators were felt to be renoprotective. Low-dose dopamine causes vasodilation of the renal vasculature and temporary increased natriuresis and GFR. However, many randomized controlled trials (RCTs) have shown that dopamine does not prevent or treat AKI, and some studies have shown that it can cause tachyarrhythmias and ischemia. Other vasodilators, including fenoldopam (dopamine receptor agonist) and natriuretic peptides, are not currently recommended for AKI prevention or treatment. Vasopressors, however, are recommended for patients with fluid-responsive hemodynamic compromise, to maintain renal perfusion.

There is emerging, tenuous evidence that adenosine receptor antagonists (e.g., theophylline, caffeine, aminophylline) may prevent or reduce severity of AKI in some children. These drugs have been studied mostly in neonates or children having cardiac surgery in RCTs and observational studies, with conflicting results [48–50]. The latest KDIGO guideline suggests that theophylline may reduce AKI or AKI severity in neonates with hypoxic-ischemic encephalopathy. However, there is no strong evidence supporting routine use of adenosine receptor antagonists in AKI. Dexmedetomidine, an alpha-2 adrenergic receptor agonist, may reduce post-cardiac surgery AKI rates, but more research is needed. Rasburicase, a urate oxidase commonly used to reduce urate levels in tumor lysis syndrome, may also benefit patients with severe hyperuricemia in specific AKI settings (e.g., rhabdomyolysis; hemolytic uremic syndrome) [51, 52].

Timing and Modality of Renal Support Therapy

Treating a patient with AKI with RST, even temporarily, is a decision carrying tremendous weight for the child, family, and healthcare team. There remains significant equipoise about the optimal timing of initiation of RST and the best modality to use in AKI.

Traditional indications for RST in AKI are well entrenched in the minds of nephrologists and intensivists, including severe electrolyte or metabolic disturbances (especially hyperkalemia, severe metabolic acidosis, or severe hyperphosphatemia with hypocalcemia), uremia (with uremic pericarditis or encephalopathy, more typically seen with severe CKD), symptomatic FO, and removal of a dialyzable toxin that is contributing to AKI. However, as our understanding of AKI moves beyond a binary model of "failure" or "not failure" to a graded level of injury and dysfunction, the optimal timing of initiation of RST becomes less clear. Several large RCTs have compared early vs. delayed RST initiation in ICU adults and produced conflicting results. In a single-center trial (Zarbock et al.) comparing RST initiation within 8 h of stage 2 AKI ("early") vs. within 12 h of stage 3 AKI ("late"), "early" RST was associated with higher 90-day survival (difference in hazard ratio of 15%, $p = 0.03$) [53]. The second trial was a multicenter study (Gaudry et al.) including only patients with stage 3 AKI; patients with "delayed" RST (requiring additional criteria, such as severe hyperkalemia, for >72 h to initiate RST) had no significantly different 60-day mortality vs. the earlier RST group [54]. Most recently, a multicenter RCT (Barbar et al.) including patients with septic shock and severe AKI compared "early" (within 12 h) vs. "late" RST initiation (>48 h) [55]. This trial was halted due to findings of futility of early RST. It thus remains unclear if earlier RST initiation improves patient outcomes. Notably, early RST was not found to be significantly associated with adverse events in these studies. A larger multicenter study is currently underway to compare accelerated vs. standard CRRT initiation in adults (ClinicalTrials.gov NCT02568722).

In children, there are no such trials. However, many observational studies have identified that higher FO at CRRT initiation is associated with poorer outcomes. In one multicenter study, the highest mortality (>65%) was seen with patients with ≥20% FO at CRRT initiation; this mortality is 8.5 times higher vs. patients with <20% FO [56]. Consensus opinion is that RST should be considered in patients with 10–20% FO. Despite the known risk of FO in ICU children, there remains equipoise on whether earlier intervention in children with severe FO improves outcomes.

Modality of RST

There are several RST modalities for AKI treatment commonly used in children, including peritoneal dialysis (PD), intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and also sustained low-efficiency daily dialysis (SLEDD). Many factors contribute to RST modality choice, including patient size, ease of access, comorbidities, and center experience and resources. Decisions regarding modality, particularly pertaining to FO, will be discussed here. SLEDD, which uses conventional HD machines to administer IHD over prolonged periods (e.g., 6–12 h), will not be discussed. The technical aspects of each modality in AKI will be discussed later in this section.

Peritoneal Dialysis Historically, PD was the preferred RST modality for AKI in children due to ease of use and availability (see Chap. 1). A major advantage of PD is the lack of need for vascular access, which can be very challenging in children. PD is well suited in children compared to adults because the peritoneal membrane surface area is larger relative to patient weight, enabling more efficient clearance. PD is less proinflammatory and promotes hemodynamic stability because it provides physiologic continuous RST [57]. Disadvantages of PD include inconsistency of fluid removal and solute clearance, slower solute clearance (vs. IHD or CRRT), and PD catheter site post-insertion leaks, especially in very edematous patients. Frequency of these complications is likely lower in centers primarily using PD to treat AKI. Recent data suggest a preferential shift toward use of CRRT. Today, PD is often preferred in small infants, where vascular access remains challenging [58]. PD is commonly used in children undergoing cardiac surgery for the additional benefit of abdominal decompression (to reduce venous pressure and improve renal perfusion) [5, 59]. Finally, for patients with some primary renal diseases (e.g., glomerular diseases, hemolytic uremic syndrome) that do not require a critical care setting, PD is preferred because it is well tolerated and allows vessel preservation [57].

A number of studies have evaluated PD in infants and small children undergoing cardiac surgery. Some centers place "prophylactic" PD catheters in high-risk patients at the time of cardiac surgery, and some observational studies have shown benefit with this approach [60], including earlier negative fluid balance and improved clinical outcomes. A single-center RCT showed superior fluid removal with PD compared to standard dose diuretics [61]. Several observational studies have shown benefit of earlier PD initiation following high-risk cardiac surgery. Prophylactic PD is generally defined as PD initiation in patients without FO or reduced UO; a single-center RCT did not show improved outcomes [62], while another study showed >40% reduced 30- and 90-day mortality in the prophylactic arm [63]. At this time, there is consensus that PD is the preferred modality for infants and small children following cardiac surgery. However, it is not known which patients should have prophylactic PD catheter insertion at the time of surgery. As well, there is equipoise regarding early PD initiation compared to standard use. In North America, other pediatric populations are predominantly treated with CRRT, unless limited by vascular access.

Intermittent Hemodialysis Although there has been significant shift away from PD toward CRRT, the use of intermittent hemodialysis (IHD) in AKI has remained relatively constant for the treatment of life-threatening hyperkalemia or acute poisoning (with or without AKI). However, several studies have shown that with

improvement in CRRT technology and high solute clearance, CRRT may also be used to rapidly decrease potassium and endogenous or exogenous toxins. The main reason for the limited use of IHD in AKI is the risk of hemodynamic compromise in ICU patients. IHD sessions tend to be performed over short periods, relative to CRRT, leading to hemodynamic instability when attempting to achieve fluid removal goals in a short time frame [64–66]. In some patients, rapid solute clearance in a short time frame may increase risk for dialysis disequilibrium syndrome. There is a need for nursing and nephrology expertise to perform IHD, access to a clean water source, and specialized equipment. For non-ICU hemodynamically stable patients with AKI (e.g., acute interstitial nephritis, rhabdomyolysis), IHD is a treatment of choice.

Continuous Renal Replacement Therapy Continuous renal replacement therapy (CRRT) provides more gradual and controlled ultrafiltration and solute clearance for hemodynamically unstable patients. CRRT allows for the precise control of fluid removal in real time while achieving a similar daily solute removal achieved by IHD. This enables liberalized fluid administration (for medications and nutrition) and moment-to-moment response to changes in clinical status. CRRT technique is also feasible to teach to large numbers of nurses; together with easily portable machines and solutions, CRRT is ideal for ease of use in the ICU setting. Data from the USA multicenter Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry showed that CRRT is used safely across a wide range of critically ill children [67], including neonates (weight as low as 1.3 kg) and hemodynamically unstable patients. Despite recent technological advancements in many countries, CRRT is performed utilizing machines designed for adults with large extracorporeal circuit volumes. This has stimulated development and currently ongoing research on neonatal-specific CRRT machines characterized by low extracorporeal volumes, increased fluid precision, and ability to use small vascular catheters [68–70]. CRRT has also been considered to treat specific pediatric populations, including those with sepsis or undergoing cardiac surgery. Convective clearance with CRRT may provide a theoretical benefit in sepsis-induced AKI by enabling middle molecule clearance and stabilizing the immune response [71]; however, RCTs and observational studies in adults and children have not demonstrated a clear benefit [72, 73]. There has been interest in using CRRT during cardiac surgery, specifically with respect to use of "modified ultrafiltration." The goal of this practice is to limit FO development and aid in removal of pro-inflammatory mediators. The use of intraoperative modified ultrafiltration in children undergoing cardiopulmonary bypass remains an area of extraordinary center-based practice variation and warrants further study [13].

CRRT with Extracorporeal Membrane Oxygenation (ECMO) Children treated with ECMO are at very high risk of AKI (see Epidemiology of AKI) [10]. Studies have shown that these patients are at risk of FO, which is associated with increased mortality risk and length of ECMO duration. About 20 years ago, Swaniker et al. reported that the ability to return to "dry weight" was associated with improved survival. There is consensus that CRRT aids with fluid removal during ECMO and nutritional status and is generally safe [74, 75]. In neonates, CRRT was associated with reduced duration of ECMO by 24 h [76]. In an international survey by the KIDMO group, treatment or prevention of FO was the CRRT indication in 59% of patients treated with ECMO [10]. The degree of FO at CRRT initiation for children on ECMO is associated with increased mortality [77]. Taken together, these data suggest that children on ECMO may benefit from the early initiation of RST on ECMO, and protocols describing this have been published [78]. Further studies are needed to understand optimal use of CRRT in this unique patient population. The technical aspects of CRRT during ECMO will not be covered in this chapter. However, briefly, two methods have been described. One is to add a hemofilter in line within the ECMO circuit and run dialysis fluid countercurrent to the blood flow using intravenous pumps. Alternatively, and likely the best method, is to add a CRRT machine in line to the ECMO

circuit, typically pre-ECMO pump at the venous end of the circuit. Additional anticoagulation is not needed because ECMO requires systemic heparinization [79].

Performing Acute Peritoneal Dialysis for AKI

The International Society for Peritoneal Dialysis (ISPD) released guidelines for the use of peritoneal dialysis in AKI in 2014 for adults and children [80].

Access

A peritoneal dialysis catheter can be relatively easy and safe to insert in the acute setting. PD catheters are most commonly inserted surgically using a Tenckhoff catheter; this method has the lowest risk for catheter-related complications and promotes higher-efficiency dialysis (ability to deliver higher dialysis flow rates, maximizing dwell times). Temporary catheters can also be inserted percutaneously at the bedside. The drawback of this approach is the increased risk of PD catheter site leakage, infection, and reduced efficacy given the requirement for low fill volumes. Expertise is highly recommended for successful temporary catheter insertion. Complications related to PD catheter insertion include bleeding and infection; rarely, perforation of the bowel or bladder can occur with insertion of rigid catheters. Perioperative antibiotics should be given for surgical prophylaxis; a single dose of cefazolin is the typical choice.

Acute Peritoneal Dialysis Prescription (Table 43.6)

For acute PD, patients typically require starting RST shortly after catheter insertion and catheter flushing with dialysis solution containing heparin (500 units/L) until fluid is clear. Commercial solutions are typically used containing sodium, chloride, calcium, magnesium, buffer, and variable amounts of dextrose. At our centers, "physiologic" (neutral pH with bicarbonate buffer) dextrose solutions are used. These solutions promote preservation of the peritoneal membrane in the long term and reduce abdominal pain with filling. Heparin is added to the dialysis solution for a minimum of 48–72 h in order to prevent catheter obstruction with fibrin clot; heparin may be kept in the dialysis solution bags for longer if there are concerns or there is evidence of fibrin (the goal being to reduce risk of catheter blockage).

Table 43.6 Sample acute PD prescription

Fill volume	10 mL/kg when catheter is inserted acutely	
Solution	Commercially available solution (e.g., Physioneal® 1.36% or Dianeal® 1.5%) + heparin 500 units/L	Depends on fluid requirements and other components of dialysis prescription (i.e., cycle length)
Cycle length	Hourly cycles: 5-min fill time, 45-min dwell time, and 10-min drain time	Cycle duration can be reduced to 30 min for several cycles to allow rapid fluid removal
Total dialysis duration	Typically, 24 h in infants and smaller children	Depends on metabolic and fluid requirements

With reduced time for wound healing, the risk of catheter leakage is high; therefore, low dextrose solutions (Table 43.6) are used with low fill volumes (10 mL/kg). Dextrose concentration is increased to achieve required ultrafiltration acutely; higher dextrose concentrations may be needed to achieve ultrafiltration needs when low fill volumes are used. Fill volumes are increased gradually; if tunneled catheter insertion was uncomplicated, fill volumes may be increased over several days to 20–35 mL/kg with close attention for catheter site leak. If there is leak, dialysis may be held, and fluid cell counts and cultures sent to rule out peritonitis (particularly with evidence of leak) with or without empiric antibiotic therapy.

With low fill volumes, manual intermittent PD (IPD) can be performed 24 h/day; automated PD (APD) with a cycler may be used with higher fill volumes, often in non-ICU settings. In general, with low fill volumes, dwell durations are short with approximately hourly cycles. If higher ultrafiltration or solute clearance is needed,

dialysis solution dextrose concentration may be increased, or cycle duration decreased (minimize fluid absorption via the peritoneal membrane; promote water and solute removal). Cycle durations as short as 30–45 min (dwell times ~15–20 min) may help achieve rapid fluid removal and solute clearance. Despite ISPD guideline recommendations, there is little data on ideal "dose" for acute PD [57].

Complications

There is increased risk for poor efficiency dialysis and ultrafiltration with acute PD due to use of low fill volumes. Severely ill children may have poor perfusion of the peritoneal membrane, which further reduces dialysis efficacy. As a result, patients with severe metabolic disturbances (e.g., hyperammonemia) or FO may need to be considered for alternative RST modalities (IHD or CRRT). Early PD catheter insertion in high-risk patients to reduce catheter-related complications is ideal, where possible. Of note, ultrafiltration may be unpredictable, resulting in less precise fluid removal that can result in dehydration and further renal injury [57], mandating frequent assessment of ultrafiltration and fluid balance after PD initiation.

Mechanical complications are similar to those of chronic PD (leaks around the catheter, in the subcutaneous tissue, or into pleural space; catheter kinking/malposition; catheter dysfunction due to constipation or obstruction by clot or omentum; hernias). These complications are lower with Tenckhoff catheters compared to rigid catheters. Tidal PD prescriptions are sometimes used in patients with significant fill and drain pain. As in chronic PD, vigilance for infection and use of aseptic technique when handling the catheter and performing dressing changes are crucial; this is important to impress upon ICU healthcare teams who may have limited experience with performing PD. Topical mupirocin ointment is applied to the PD catheter exit site at our center to reduce infection risk. Consideration for use of antifungal therapy (such as nystatin) should be made for patients receiving antimicrobials.

Other complications include the risk of hyperglycemia with high glucose concentration solutions. There is also risk for malnutrition due to PD-related protein loss and sodium disturbances associated with water and sodium losses. Hypothermia may occur if the dialysis fluid is not adequately warmed.

PD is fairly well tolerated from a hemodynamic perspective. Tidal PD prescriptions should be considered in pre-load-dependent patients that may not tolerate fill and drains. Patients with respiratory distress or infants with severe gastroesophageal reflux may not tolerate large fill volumes. Patients with prune belly syndrome and ventriculo-peritoneal shunts can receive peritoneal dialysis; however, a history of other abdominal surgeries may make PD quite challenging.

Acute Hemodialysis for AKI

Although there has been significant shift away from PD toward CRRT, the use of intermittent hemodialysis (IHD) in AKI has remained relatively constant for the treatment of life-threatening emergencies (e.g., severe hyperkalemia; ingestions; hyperammonemia) or non-critically ill patients with AKI. A limited discussion below will highlight unique aspects of IHD in AKI; more detail is provided in chronic hemodialysis chapters, and vascular access is discussed below in the CRRT section of this chapter.

Acute Hemodialysis Prescription

Acute IHD prescription is similar to initial prescription of chronic hemodialysis [81]. When IHD is performed outside the HD unit, access to water and use of a portable reverse osmosis device are needed. Dialysis fluid prescription is similar to that of chronic hemodialysis; prescribed potassium and phosphate concentration should be based on patient labs. Biocompatible dialyzers are used with a surface area close to the body surface area of the child. Blood priming of the circuit should be done if the extracorporeal volume is >10% of the total blood volume. Dialysis flow rate is typically set at a standard rate of 500 mL/min.

IHD for AKI is performed over a short period, and rapid urea reduction can cause disequilibrium syndrome (i.e., headache, cerebral edema, sei-

zures, and potentially death). Although patients with underlying CKD are at highest risk for disequilibrium syndrome, patients with AKI (especially if progression to RST need is over days to weeks), very high blood urea nitrogen levels (e.g., >30 mmol/L), and concomitant risks for cerebral edema (as often seen in ICU patients) may be at risk. Rapid urea reduction should be avoided in the first two to three IHD sessions. Some centers use slightly higher than usual dialysis fluid sodium concentration (i.e., 145 mmol/L), and most centers will administer intravenous mannitol (0.5–1 g/kg over the first 1–2 h of IHD) if there is concern for dialysis disequilibrium or blood urea nitrogen levels are very high. At our centers, two approaches are used to avoid rapid urea reduction and disequilibrium syndrome in AKI. The first is based on the fact that the primary determinant of solute clearance with IHD is blood flow. Thus, in the first IHD session for AKI, low blood flow rates (e.g., ~2 mL/kg/min) are used, and duration is short (2–2.5 h). In future sessions, blood flow and IHD duration are gradually increased as tolerated. Another approach is based on (a) initially aiming for urea reduction of 30%, which is relatively safe to avoid disequilibrium syndrome, (b) using the known logarithmic relationship between urea reduction and *Kt*/*V* (shown in Table 43.7) to determine duration of the first IHD session, and (c) slowly increasing urea reduction goals for future IHD sessions using data from previous IHD sessions (detailed in Table 43.7).

Fluid management when using IHD for AKI is challenging for oligoanuric patients as daily fluid

Table 43.7 Example approach to prescribing urea reduction for acute hemodialysis

Step 1. Determine urea reduction (UR) goal for first IHD session *and* Calculate first IHD session duration (minutes)	***Logarithmic relationship between UR and Kt/V is:*** − *ln* (post IHD urea concentration/pre - urea concentration) = *Kt*/*V* *t* = time (min) *V* = volume = total body water in *mL* (consider patient age when calculating − this parameter is estimated) *K* = urea reduction coefficient in mL/min (based on dialyzer, Q_B, Q_D). Often similar to blood flow, so if blood flow is 50 mL/min, K will often be 50 mL/min *First IHD treatment example*: UR goal is 30%: $-ln$(post IHD urea concentration/pre-urea concentration) = $-ln(0.7) = 0.36$ *Using formula above, solve for t (minutes) or duration of first IHD treatment:* $$t(\text{minutes of IHD}) = \frac{-ln(\text{post urea / pre - urea}) \times V(\text{mL})}{K(\text{mL / min})}$$ ***Ensure to order pre- and post-urea concentration testing for first 3–4 IHD treatments***
Step 2. Recalculate *V* (total body water in mL) based on previous IHD session data	***Solve for V using equation above and data from previous session:*** $$\text{New}V(\text{mL}) = \frac{t(\text{minutes of IHD of previous session}) \times K(\text{mL / min of previous IHD session})}{-ln(\text{post urea / pre - urea from the previous IHD session})}$$ $$= \text{recalculated}\, V(\text{mL})\, \text{to use for the current IHD session.}$$
Step 3. Calculate *t* (minutes) to achieve desired UR for future IHD sessions (e.g., second, third)	***Solve for t (minutes) of subsequent IHD treatments, using New (recalculated) V:*** $$t(\text{minutes of IHD}) = \frac{-ln(\text{post urea / pre - urea}) \times \text{New}V(\text{mL})}{K(\text{mL / min})}$$ *New V = V calculated in step 2, from data of previous IHD treatment.* ***Proposed UR goals for second and third IHD treatment:*** *Second IHD treatment* UR goal 50%: $-ln$(post urea/pre-urea) = $-ln(0.5) = 0.69$ *Third IHD treatment* UR goal 70%: $-ln$(post urea/pre-urea) = $-ln(0.3) = 1.2$

ln natural logarithm function, *IHD* intermittent hemodialysis, Q_B blood flow rate (mL/min), Q_D dialysis flow rate, (mL/min)

removal must be performed within a short session. Fluid restriction is often required. If IHD is tolerated and safe with regard to urea reduction, longer IHD sessions may help achieve fluid removal goals. In very hemodynamically stable patients, ultrafiltration rate as high as ~0.2 mL/kg/min (or 12 mL/kg/h) may be tolerated; however, in acutely ill patients, hypotension is common, limiting ability to achieve ultrafiltration >1–3 mL/kg/h. Some centers use blood volume monitoring software available with some dialysis machines to help guide fluid removal.

As in chronic IHD, heparin anticoagulation is used (10–20 units/kg bolus, followed by continuous infusion), and activated clotting time is monitored. However, in many acute illnesses, bleeding risk may be high, in which case IHD may be performed without anticoagulation. This often requires frequent flushing with normal saline to the circuit pre-filter to prevent clotting. Administering frequent fluid boluses to prevent clotting complicates fluid removal in infants, because this fluid must be removed, which may not be tolerated in small, sick children. For hemodynamically unstable patients, CRRT is thus a better option.

Continuous Renal Replacement Therapy for AKI

CRRT offers several advantages, most importantly the delivery of highly precise therapy [82]. Gradual fluid removal offers improved hemodynamic stability and enables nutrition. CRRT provides more efficient clearance than PD, allowing rapid correction of electrolyte and metabolic disturbances. The major limitation of CRRT has historically been requirement for technical expertise; however, this barrier has decreased, with simpler and safer machines adapted for use in children [83].

Vascular Access (Table 43.8)

Vascular access is challenging in children, especially infants. However, it is key to administering efficient CRRT, as access issues may lead to cessation of CRRT, circuit clotting, and, ultimately, time off therapy.

Table 43.8 Vascular access for CRRT

	Weight	Catheter[a]
Neck lines	<5 kg	8Fr Medcomp Hemo-Cath
	5 kg to <20 kg	10Fr Medcomp Split
	20 kg to <35 kg	12Fr Medcomp
	>35 kg	15.5Fr DuraMax Palindrome
Femoral lines	<5 kg	6.5Fr (10 cm) Gambro Gam Cath (may sometimes be used as a neck line in small children)
	5 to <20 kg	8Fr (12.5 cm) Gambro Gam Cath (5–15 kg) 10Fr (12 cm) Quinton Mahurkar (15–20 kg)
	20 to <40 kg	10Fr (15 cm) Quinton Mahurkar
	>40 kg	11.5Fr (13.5 cm or 16 cm) Quinton Mahurkar

[a]Catheters used at the Hospital for Sick Children, Toronto, Canada

Table 43.8 provides suggested catheter sizes based on patient weight. Access insertion expertise is highly recommended in order to successfully insert catheters of adequate caliber to enable adequate blood flow (lowest suggested catheter size in Table 43.8 is a non-tunneled 6.5 French catheter). Different centers have access to different catheters. It is important to be aware of available catheters and to have tunneled and un-tunneled catheter sizes appropriate for neonates, small, and larger children. Unsurprisingly, larger catheters have been shown to be associated with longer CRRT circuit survival, and use of very small catheters (double lumen 5 French) is associated with very low (<10 h) circuit survival [84]. In very small patients (<5 kg), use of two single-lumen catheters in two vessels has been described [85].

Access placement location will be influenced by patient factors and by expertise of the access inserter. Temporary or semi-permanent (tunneled) catheters may be used. Temporary catheters are often placed at the bedside. Neck vessels (internal jugular vein) are preferred over femoral veins, due to less recirculation (particularly in infants weighing <5 kg) and longer circuit survival associated with better blood flow

rates and potentially reduced infection rates. Femoral access should be considered a second choice for insertion site, especially in patients with high intra-abdominal pressure (may cause elevated venous return pressures), patients who are moving or combative, or patients who may need these vessels for future renal transplantation. Subclavian veins should be avoided due to the high risk of stenosis. Complications of vascular access insertion include bleeding, infection, and air emboli; these are less common in centers using ultrasound-guided access insertion. Longer-term complications include vessel thrombosis or stenosis.

CRRT Machine and Modality (Fig. 43.3)

The first children treated with CRRT used continuous arteriovenous hemofiltration (CAVH) in

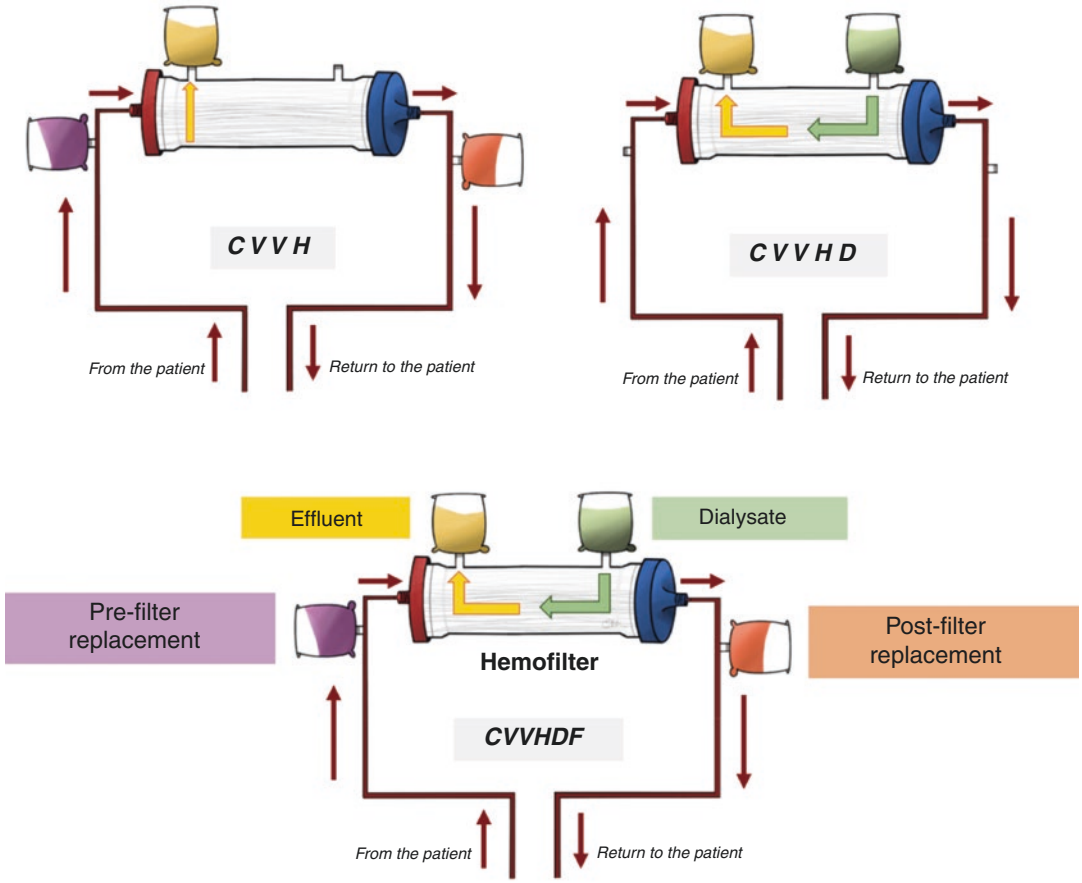

Fig. 43.3 Continuous renal replacement therapy extracorporeal circuit. Blood is pumped from the patient into the hemofilter and is returned to the patient via a central access, dual lumen dialysis line. With continuous venovenous hemofiltration (CVVH) (top left), blood flows through the hemofilter; solutes and water are forced across the semipermeable membrane by convection along a high-pressure hydrostatic gradient. Replacement fluid replenishes volume and electrolytes either pre-filter or post-filter. With continuous venovenous hemodialysis (CVVHD) (top right), blood flows through the hemofilter and dialysate fluid flows in the countercurrent direction. Solutes from the blood compartment move across the semipermeable membrane into the dialysate fluid compartment and are removed by diffusion. Water moves via ultrafiltration in the same direction. Cleared solutes and ultrafiltrate are drained into the effluent bag. With continuous venovenous hemodiafiltration (CVVHDF) (bottom), replacement and dialysate fluids are both used to remove solutes and water by a combination of diffusion, ultrafiltration, and convection. During citrate anticoagulation, citrate is infused using the pre-filter replacement circuit or via a separate intravenous pump to the pre-filter access port; calcium is infused to the patient via a separate access line

the 1980s; this system relied on the arteriovenous pressure gradient to drive circuit flow. The advent of continuous venovenous hemofiltration adapted for children in the 1990s, as well as improvements to filter and circuit design, allowed longer circuit survival and precise ultrafiltration. These advancements effectively replaced historical CAVH systems and ushered the way forward for the safe use of CRRT in children [85]. Several different commercially available machines may be used to deliver CRRT (not covered here).

Ultrafiltration (removal of fluid from the patient) is driven by hydrostatic pressure generated across the semipermeable membrane of the hemofilter. Clearance of solutes may be accomplished by convection (continuous venovenous hemofiltration, CVVH), diffusion (continuous venovenous hemodialysis, CVVHD), or both (continuous venovenous hemodiafiltration, CVVHDF) (Fig. 43.3) [72]. In *CVVHD*, as with IHD, solute clearance is achieved by diffusion, with dialysis fluid being run countercurrent to blood flow across the semipermeable membrane of the hemofilter. In *CVVH*, convective solute clearance is achieved by infusing high volumes of sterile replacement fluid solution into the circuit, in order to allow for simultaneous removal of large amounts of fluid across the hemofilter to drive convective clearance. With *CVVHDF*, both dialysis fluid and replacement fluid are used. It is theorized that CVVH or CVVHDF, which provides convective (middle molecule) clearance, may provide additional benefit over CVVHD due to clearance of inflammatory molecules (e.g., with sepsis). To date, there is little strong evidence to support this [86], and center practice variation dictates decisions on use of convective clearance in patients with severe inflammatory or infectious conditions.

Small solute clearance is achievable using *either* CVVHD *or* CVVH (or CVVHDF). CVVH and CVVHDF additionally provide middle molecule clearance (via convection). Replacement fluid in CVVH and CVVHDF can be delivered pre-filter (via a port located within the circuit, before the hemofilter) or post-filter. The advantage of *pre*-filter delivery of replacement fluid is a reduced risk of filter clotting (as the replacement fluid "dilutes" the blood entering the hemofilter) compared to post-filter replacement where the blood delivered to the filter is more viscous. The risk of circuit clotting with post-filter replacement in CVVH (as well as with CVVHD, where no replacement fluid is used) is increased when the filtration fraction rises above 25%. Filtration fraction is the ratio of ultrafiltration rate to plasma flow rate: filtration fraction = $Q_{UF}/[Q_b (1 - Hct) + Q_r]$, where Q_{UF} represents ultrafiltrate flow rate, Q_b represents blood flow rate, Hct represents hematocrit, and Q_r represents pre-dilution replacement flow rate (include where applicable). However, post-filter replacement provides higher solute clearance, as solute concentration in the blood pre-hemofilter is not affected by infused replacement fluid.

Hemofilter and Blood Prime

CRRT hemofilters contain hollow fibers that are permeable to non-protein-bound solutes with a molecular weight below approximately 40,000 Daltons. Filters are selected according to patient weight. Biocompatible filters are the standard for CRRT and include acrylonitrile (AN69)-based and polysulfone-based filters. AN69 membranes come with a risk of bradykinin release syndrome, which is worsened by the use of angiotensin-converting enzyme inhibitors and blood prime. The risk of this reaction is also pH dependent. In order to prevent this complication, the blood prime can be administered post-filter, and bicarbonate (infusion with bolus) is administered to maintain a neutral pH [87]. Another method utilized to minimize the bradykinin release syndrome with AN69 membranes and metabolic complications of performing blood prime is to perform a "pre-dialysis" procedure on the blood prime solution, whereby the blood is circulated through the CRRT machine against dialysis solution for 5–10 min (before connecting the patient to the circuit) to normalize pH, calcium, and potassium content of the blood prime solution [88]. Bradykinin release syndrome is not a complication of non-AN69 polysulfone membranes and is much less common and severe with newer protein-coated AN69 membranes. The size of the hemofilter

should be selected based on patient size, when possible, to avoid the need for a blood prime.

Children for whom the extracorporeal circuit volume exceeds ~10% of estimated blood volume will generally require a blood prime; most children <10–11 kg need a blood prime for CRRT initiation. Packed red blood cells (reconstituted to hematocrit ~30% to prevent circuit clotting and avoid excessive unwanted rise in patient hemoglobin) may be used to prime the CRRT circuit. In patients with borderline circuit extracorporeal volume and who are hemodynamically stable, 5% albumin solutions may be used for circuit priming.

Solutions (Table 43.9)

Typically, the same solution is used for dialysis fluid of CVVHD and replacement fluid of CVVH. Most centers use commercially prepared solutions with a bicarbonate buffer (and low concentrations of lactate) and a variable amount of sodium, potassium, calcium, phosphorus, magnesium, and glucose. Solutions bags are hung onto the CRRT machine for use (Fig. 43.3). Solutions used when performing citrate anticoagulation should be calcium-free. Table 43.9 outlines CRRT solutions commonly used at our centers. Sodium concentration of solutions may be modified (by adding water to reduce sodium concentration or adding sodium to increase sodium concentration) in patients with severe hyponatremia or hypernatremia to avoid rapid sodium shifts [89]. Potassium and phosphate concentrations of solutions are also commonly modified by addition of potassium chloride or sodium phosphate, due to the very common problem of severe hypokalemia and hypophosphatemia development during CRRT therapy. At some centers, modification of electrolyte concentrations of solutions is performed by pharmacy and in others, by the bedside CRRT nurses. Great care must be taken to attempt to remove any sources of errors when modifying CRRT solutions. In rare cases of specific conditions (e.g., Wilson's disease, to remove copper; certain protein-bound drug intoxications), 25% albumin may be added to the dialysis solution (to achieve ~5% albumin dialysis solution) to perform what is referred to as "single-pass albumin dialysis" and promote removal of protein-bound substances [90, 91].

CRRT Prescription: Blood Flow (Table 43.10)

Unlike IHD, the blood flow rate does not significantly impact solute clearance in CRRT but greatly impacts circuit survival. Blood flow rate is determined by patient size, hemofilter, and vascular access. Blood flow rates range from 2 to 10 mL/kg/min. At our centers, the minimum suggested blood flow rates are 50 mL/min for

Table 43.9 Commercially prepared CRRT solutions and citrate solutions (for anticoagulation)

	Dialysis/replacement solutions					Citrate solutions	
Analyte (mmol/L)	Prism0Cal®	Prism0Cal® B22	Prismasol® 0	Prismasol® 4	Phoxilium®[a]	ACD-A solution	Sodium citrate 4%
Sodium	140	140	140	140	140	224	408
Potassium	–	4	–	4	4	–	–
Chloride	106	120.5	109.5	113.5	116	–	–
Bicarbonate	32	22	32	32	30	–	–
Lactate	3	3	3	3	–	–	–
Calcium	–	–	1.75	1.75	1.25	–	–
Phosphate	–	–	–	–	1.2	–	–
Magnesium	0.5	0.75	0.5	0.5	0.6	–	–
Glucose	–	6.1	6.1	6.1	–	139	–
Trisodium citrate	–	–	–	–	–	74.8	136
Citric acid	–	–	–	–	–	38.1	Not specified

Table 43.10 Sample of some aspects of CRRT prescription

Vascular access	Table 43.7	
Hemofilter	Weight <10 kg	HF20 (polysulfone filter)
	10–30 kg	ST60 (AN69 filter)
	>30 kg	HF1000 (polysulfone filter)
Blood prime	<10 kg	Use blood prime; otherwise 0.9% NaCl solution
Modality	CVVH	
	CVVHD	
	CVVHDF	
Blood flow rate	HF20	50 mL/min (minimum 40 mL/min)
	ST60	~50–100 mL/min
	HF1000	100 mL/min (minimum 80 mL/min)
Dialysis flow rate	2 L/1.73 m^2/h	*Consider higher rate for neonates admitted with hyperammonemia*
Solution	Table 43.9	
Anticoagulation	Citrate	Use citrate if heparin-induced thrombocytopenia
	Heparin	

[a]CRRT prescription items taken from Hospital for Sick Children, Toronto, Canada

patients <11 kg (though blood flows as low as 30 mL/min have been used) and range from 50 to 150 mL/min (>11 kg) (Table 43.10). At our centers, we use the hemofilter (which is affected by patient size) to guide blood flow; at other centers, blood flow may be based specifically on patient size. Because of the need for minimum blood flows of 30–50 mL/min, neonates are subjected to high relative blood flow rates (per unit weight); this is especially relevant when using citrate anticoagulation because as described below, citrate prescription rate is based on blood flow. Reasons to change blood flow during CRRT may include access problems (e.g., blood flow reduced to address rising access pressures), rising hemofilter transmembrane pressures or clot formations (increasing blood flow may help reduce clot formation), or need to reduce citrate delivery (decreasing blood flow leads to lower citrate infusion requirements).

CRRT Prescription: Solute Clearance (Table 43.10)

With CRRT, solute clearance or "dialysis dose" is determined by the dialysis and/or replacement fluid flow rates, which affect the degree of diffusive and/or convective clearance of small solutes (i.e., urea). In adult studies and clinical practice, solute clearance rate (or delivered dialysis dose) is expressed in terms of dialysis and/or replacement fluid rate in mL/kg/h. A minimum dose of 20–25 mL/kg/h is generally recommended, and flow rates higher than this have not shown significant impacts on patient outcome [72, 92, 93].

In children, solute clearance dose is prescribed based on body surface area; a standard dose is 2–2.5 L/h/1.73 m^2. So if CVVHD is being performed in a patient with body surface area of 0.7 m^2, then the dialysis solution rate is run at ~2 L/1.73 m^2/h or ~800 mL/h. If CVVH is used for this patient, the replacement solution is run at ~800 mL/h. If CVVHDF is used, the combined rate of dialysis fluid and replacement fluid should total ~800 mL/h (e.g., 400 mL/h of dialysis fluid + 400 mL/h of replacement fluid). Some CRRT machines require a minimum post-filter replacement fluid rate to prevent clotting in the circuit; this replacement fluid should be included in the total solute clearance dose.

This level of solute clearance will be adequate for most patients treated with CRRT. However in some AKI patients, higher clearance may be desired. For example, in patients with hyperammonemia with AKI, much higher clearance rate (e.g., 4–8 L/1.73 m^2/h) may be desired to rapidly reduce ammonia levels; or patients with life-threatening serum potassium level may require higher than standard solute clearance to prevent arrhythmia and death. When prescribing high clearance rates, it is crucial to be mindful of

the effects. For example, if there is concern for dialysis disequilibrium syndrome and rapid urea reduction, administering intravenous mannitol may be helpful. Other solutes (e.g., potassium, phosphate), antibiotics, nutrition (especially amino acids), and citrate (for citrate anticoagulation) will also be cleared quickly, and infusion/medication adjustments should be made accordingly, ideally in conjunction with a pharmacist. Regarding high clearance CRRT during citrate anticoagulation, very close monitoring of circuit and patient ionized calcium levels is crucial (citrate will be cleared at a higher rate) as adjustments to citrate and calcium infusion rates will definitely be required to prevent low patient ionized calcium concentrations (citrate anticoagulation discussed below).

CRRT Prescription: Ultrafiltration

(Table 43.10)

Fluid removal is often a primary goal for initiating CRRT. In critically ill patients, a careful balance between achieving fluid removal goals and patient safety/tolerance may be challenging to achieve and must be reassessed frequently. Ultrafiltration rate (and desired daily and hourly negative patient balance) should be determined collaboratively between ICU and nephrology teams to meet safe targets for the patient. The prescribed ultrafiltration rate does not need to consider any fluids which are being administered by the machine (e.g., replacement fluid). In order to keep the patient in neutral hourly balance, the prescribed ultrafiltration rate (mL/h) should equal to the hourly rate of all fluids administered to the patient (e.g., medications, nutrition). Because ultrafiltration rate can be continuously increased to account for fluid intake, there is little reason to delay initiation of appropriate nutrition (parenteral or enteral) for patients receiving CRRT. If there is significant urine output or other outputs (e.g., high-output chest tube), these hourly volumes should be subtracted from the prescribed ultrafiltration rate. In order to achieve a negative hourly balance, the prescribed ultrafiltration rate is increased to achieve this negative balance.

Decisions on rate of negative balance (mL/h) in critically ill patients should consider hemodynamic stability (and likelihood of tolerating a negative balance) and urgency of need for fluid removal (e.g., severe pulmonary edema with reduced oxygenation). Overly aggressive negative fluid balance attainment can cause severe hemodynamic instability and be detrimental, especially in small patients, and potentially cause further kidney injury. Two rules of thumb on maximal negative balance in unstable patients receiving CRRT include avoiding daily negative balance >3–5% of body weight (e.g., 10 kg child, not exceeding >300–500 mL/day negative balance) and to aim for ≤1–2 mL/kg/h negative balance (e.g., 10 kg child, ≤20 mL/h negative balance). When achieving negative balance is urgent (e.g., need to stop ECMO as soon as possible), temporary slightly more aggressive negative balance goals may be carefully used. Increasing vasopressor support may be required for patients to tolerate fluid removal. It is not recommended to keep unstable patients in positive fluid balance by reducing the ultrafiltration; rather, additional fluid or inotropic support should be used to maintain blood pressure.

Anticoagulation

Although there are several options for anticoagulation, CRRT is generally performed using either regional citrate anticoagulation or systemic unfractionated heparin anticoagulation. CRRT may be successfully performed with *no* anticoagulation (with or without flushing of the circuit pre-filter with normal saline); however, circuit life will likely be much lower (high incidence of clotting).

As in IHD, systemic heparin anticoagulation is performed by infusing heparin pre-filter and monitoring partial thromboplastin time (PTT) and/or activated clotting time (ACT) for target PTT 1.5 times normal and/or ACT 180–220 s (with higher blood flows or bleeding risk concerns, target ACT may be lower). Patients with severe bleeding risk, active bleeding, or heparin-induced thrombocytopenia should not receive heparin. Increasingly, pediatric centers are using regional citrate anticoagulation for CRRT. Studies in adults and children support that though there is no difference in mortality, circuit life is likely to be longer when

using citrate anticoagulation, and bleeding events tend to be higher when using heparin anticoagulation [94, 95].

Regional citrate anticoagulation is achieved by infusing a commercially prepared citrate solution pre-filter (Table 43.9). Citrate chelates free ionized calcium, which is required for clotting. Citrate may be infused at the access port of the catheter (using an intravenous pump separate from the CRRT machine) or, for some machines, may be administered as a pre-filter replacement solution, incorporated within the machine. The goal is to target an ionized calcium concentration of ~0.3–0.4 mmol/L in the blood within the extracorporeal circuit ("circuit ionized calcium") to prevent clotting. Although calcium citrate complexes are cleared at the hemofilter, a substantial amount of citrate in the circuit blood will be returned to the patient, placing them at risk for hypocalcemia. Thus, patients must receive a continuous intravenous calcium infusion to prevent systemic hypocalcemia. Calcium is ideally infused through a separate central line; however, it may be infused at the end of the circuit, at the return port of the vascular access, or near to the patient's skin (acknowledging that there is a theoretical risk of access clotting; single-center data has not shown this to be the case) [96]. Systemic citrate is metabolized predominantly by the liver (and to a lesser extent by the skeletal muscle and kidney) with one molecule of citrate yielding three molecules of bicarbonate; calcium which is complexed to citrate is released when citrate is metabolized. Patient ionized calcium levels must be closely monitored and kept within normal range. Several delivery and monitoring protocols for regional citrate anticoagulation exist. Table 43.11 shows a sample citrate protocol. Typically, citrate is administered at a rate proportional to the blood flow (to ensure adequate anticoagulation). Circuit and serum ionized calcium levels are monitored serially (an hour after any citrate or calcium infusion change and every 4–6 h when stable) with citrate and calcium infusion adjustments accordingly. As mentioned, closer circuit and patient calcium monitoring is needed when using high clearance rates (e.g., when treating hyperammonemia, current citrate and calcium administration protocols were based on targeting a clearance rate of ~2 L/1.73 m/h or in patients with severe liver disease since systemic citrate may accumulate due to decreased liver metabolism). Some citrate protocols incorporate a priori modified (lower) citrate rates in patients with severe liver disease.

Common complications of citrate anticoagulation include hypocalcemia and metabolic alkalosis. Hypocalcemia occurs due to inadequate patient calcium delivery or excess systemic citrate binding free ionized calcium. Hypercalcemia may occur if the circuit clots and CRRT is stopped suddenly. In the setting of elevated systemic citrate, as citrate is metabolized to bicarbonate, previously complexed calcium is released into the bloodstream with limited means of excretion in a patient with severe renal dysfunction. Metabolic alkalosis is due to excess bicarbonate generation by citrate metabolism; metabolic alkalosis may also be contributed to by the high bicarbonate load in most commercially prepared solutions. Citrate use also contributes to hypomagnesemia, commonly seen in patients receiving CRRT, due to magnesium binding. Less commonly, hypernatremia (more commonly with sodium citrate solutions, Table 43.9), hyperglycemia, and metabolic acidosis can occur.

The occurrence of excess systemic citrate accumulation must be monitored, to avoid the situation commonly referred to in the literature as "citrate lock" or evidence of complications of citrate accumulation described above (i.e., hypocalcemia/increasing calcium infusion needs). To monitor for citrate accumulation, total patient calcium is measured at least every 12–24 h; with significant systemic citrate accumulation, total calcium rises (includes citrate complex and free calcium), and systemic ionized calcium will tend to be low. A ratio of total to ionized calcium >2.5–2.8 is a surrogate marker of significant systemic citrate accumulation (or a surrogate marker of high citrate concentration). Risk factors for significant citrate accumulation (or total/ionized calcium >2.5–2.8) include young age (due to the relatively high blood flows required and subsequently high citrate delivery), severe liver failure, and lactic acidosis. Citrate accumulation is

Table 43.11 Sample CRRT citrate anticoagulation protocol: key items

Vascular access	Hemodialysis central line, ideally second central line for calcium infusion		
Dialysis solution	Prism0Cal®	Table 43.9	
Citrate flow rate	1.5× blood flow rate (mL/h)	*For example, if blood flow 50 mL/min, citrate flow rate = 75 mL/h* *At Hospital for Sick Children, blood flow rate maximum of 100 mL/min to avoid excessive citrate delivery*	
Calcium flow rate	0.4× citrate flow rate (mL/h)	*For example, if citrate flow rate is 75 mL/h, calcium flow rate = 30 mL/h*	
Serum investigations	Initial	iCa[b], total calcium Electrolytes (sodium, potassium, chloride, bicarbonate, glucose, magnesium, phosphate) Lactate Creatinine, urea, albumin, ALT (assess for liver disease) Complete blood count, PTT, INR	
	Every 2 h	iCa	
	Every 4 h	Total calcium Electrolytes (sodium, potassium, chloride, bicarbonate, glucose, magnesium, phosphate)	
	Every 12 h	Lactate PTT, INR	
	Every 24 h	Creatinine, urea, albumin, ALT Complete blood count	
Target calcium concentration	**Circuit iCa**	**0.25–0.4 mmol/L** **Call MD if <0.2 or >0.4 mmol/L**	
	Patient iCa	**1.1–1.3 mmol/L** **Call MD if <1 or >1.5 mmol/L**	
Citrate anticoagulation management	Circuit iCa <0.25 mmol/L	<20 kg	Decrease citrate by 5 mL/h
		>20 kg	Decrease citrate by 10 mL/h
	Circuit iCa >0.4 mmol/L	<20 kg	Increase citrate by 5 mL/h
		>20 kg	Increase citrate by 10 mL/h
	Patient iCa <1 mmol/L	<20 kg	Increase calcium by 5 mL/h
		>20 kg	Increase calcium by 10 mL/h
	Patient iCa >1.3 mmo/L	<20 kg	Decrease calcium by 5 mL/h
		>20 kg	Decrease calcium by 10 mL/h
Circuit change	Every 72 h		

[a]Some items taken from CRRT citrate anticoagulation protocol used at the Hospital for Sick Children, Toronto, Canada
[b]Ionized calcium
ALT alanine aminotransferase, *INR* international normalized ratio, *PTT* partial thromboplastin time

treated by increasing citrate removal or reducing delivery. To increase removal, CRRT clearance may be increased (i.e., increasing dialysis fluid rate to increase removal of calcium citrate complexes; being mindful to adjust medication doses and monitor for effects of higher clearance), or blood flow decreased (to reduce citrate needs to maintain anticoagulation). To decrease citrate delivery, the citrate infusion may be decreased or temporarily stopped (e.g., 3–6 h). If the citrate infusion is held, it may be restarted at a lower rate (e.g., ~70%). When there is no evidence of citrate accumulation but there is clinically significant metabolic alkalosis, reducing citrate delivery

may help; another measure used by many centers is to run normal saline (which has an acidic pH) as a post-filter replacement solution (being careful to monitor electrolytes).

CRRT Complications

Being aware of potential CRRT complications is crucial to being able to avoid and prevent them and to act quickly when they occur. Catheter-related complications are highest in neonates and are often related to insertion (hemorrhage, infection). Pneumothorax and hemothorax after neck line insertions are rare but potential risks [97]. Vascular access risk is reduced using ultrasound-guided insertion. Hypothermia is very important to prevent and can occur very quickly in patients on CRRT. Measures to warm the blood in the extracorporeal circuit should be routinely used especially in the smallest patients. Hypotension is a major risk with CRRT, occurring in up to 30% of patients shortly after initiation [97]. Appropriate use of blood priming and avoiding excessive ultrafiltration are vital. Avoiding the use of AN69 membranes is the best way to avoid bradykinin release syndrome-associated hypotension. However, in centers using these membranes, measures described above (see *Hemofilters*), being wary of the risks and being ready to administer and/or adjust inotropic medications when initiating CRRT are important. A preventable but important complication of CRRT is electrolyte imbalance, which can be severe if not treated. During CRRT, patient serum electrolytes will ultimately equilibrate with the dialysis/replacement solution selected. If not monitored and addressed quickly, profound hypokalemia, hypophosphatemia, and hypomagnesemia can occur. Circuit clotting risk is higher in children, likely related to lower access size, blood flow, and hemofilter size used. Several measures/aspects of CRRT described above are aimed at reducing risk of circuit clotting. Incorrect or inadequate dosing of drugs and nutrition due to lack of accounting for clearance is another complication to be keenly aware of. In children receiving prolonged CRRT with immobilization, reduced bone mass and fractures may occur. This complication may be masked by the use of citrate (which may bind calcium released from bone resorption) [98].

Nutritional Management for AKI and RST-AKI

Critically ill children with AKI are at high risk for malnutrition due to many factors: increased energy requirements due to hypercatabolism, increased protein-energy wasting due to AKI, and inadequate nutrition supplementation due to severe fluid restriction. Malnourished children with AKI are also known to have worse outcomes. As a result, delivery of adequate nutrition is often an indication for starting RST [1]. Nutrition guidelines for critically ill children are summarized in Table 43.12. A goal for children with AKI should include adequate nutrition, rather than restriction. Choice of nutrition is similar to other patients in the ICU and children with CKD. Generally, children with oligoanuric AKI require low salt, low potassium, and low phosphate formulas. Children with tubular dysfunction (particularly in the recovery phase of AKI) or children receiving CRRT may have increased electrolyte losses, requiring supplementation.

In patients with AKI receiving RST, indirect calorimetry remains the gold standard and recommended measurement tool for caloric requirements, but it is not used routinely in the ICU. The Caldwell-Kennedy equation is recommended by KDIGO to approximate resting energy expenditure (bottom of Table 43.12). Some experts suggest 20–30% increased requirements as a ballpark measure. It is important to provide calories in the form of carbohydrates, proteins, and lipids. Consider including glucose and citrate in carbohydrate intake for patients on PD and CRRT, respectively.

Adequate protein intake is essential for hypercatabolic critically ill children. Protein intake >1.5 g/kg/day was associated with the greatest reduction in mortality for critically ill children in one large systematic review [99]. More studies are needed to identify the optimal intake for patients with AKI. For children receiving PD or CRRT, there is increased need for supplemental protein intake due to increased protein losses across the peritoneal membrane or through the hemofilter, respectively. For patients receiving CRRT, protein losses may be even greater with convective

Table 43.12 Nutritional guidelines[a] for critically ill children[b]

		Evidence[c]
1A	Malnutrition, including obesity, is associated with adverse clinical outcomes. Nutritional assessment should be performed weekly (at a minimum)	Strong
1B	On admission, weight, height/length, and (for patients <36 months) HC should be measured. BMI-for-age (weight-for-length <2 years) or weight-for-age (if height not available) z-scores should be plotted on WHO growth curves[d]	Strong
2A	Energy expenditure should be measured using IC	Weak
2B	If IC is not available, then energy expenditure should be measured using the Schofield equation[e]	Weak
2C	Target energy intake is two-thirds of the prescribed daily energy requirement 1 week after admission	Weak
3A	The minimum recommended protein intake is 1.5 g/kg/day. The optimal intake is that needed to attain a positive protein balance. Higher protein intake may be associated with lower 60-day mortality	Strong
3B	Protein should be administered early in the course of admission	Weak
3C	The optimal protein dose for improved clinical outcomes is not known. The RDA values should not be used	Strong
4A	EN is the preferred source of nutrition	Strong
4B	The optimal dose of EN is not known. Early initiation (within 24–48 h of admission) and administration of two-thirds of the prescribed daily energy requirement is associated with improved outcomes	Weak
5A	EN should be administered and advanced using a stepwise algorithm	Weak
5B	A nutrition support team, including a dietician, should be part of the ICU team	Weak
6A	The gastric route is preferred over the small bowel. The postpyloric or small bowel may be used in patients unable to tolerate gastric feeds or at high risk for aspiration	Weak
6B	Early EN (within 24–48 h of admission) should be delivered to all patients, unless contraindicated	Weak
7A	Early PN (with 24 h of admission) is not recommended[d]	Strong
7B	PN is not necessary to supplement EN for all patients tolerating EN and for whom nutritional delivery is being advanced as part of a stepwise algorithm. The timing of supplemental PN is not known PN should be delayed until 1 week after admission for patients with normal baseline nutritional status and low risk of deterioration[d]	Weak
8	The use of immunonutrition is not recommended	Strong
Caldwell-Kennedy equation[f] (resting energy expenditure): 22 + 31.05 × weight (kg) + 1.16 × age (years)		

BMI body mass index, *EN* enteral nutrition, *IC* indirect calorimetry, *ICU* intensive care unit, *HC* head circumference, *PN* parenteral nutrition, *RDA* recommended dietary allowance, *UN* United Nations, *WHO* World Health Organization
[a]Presented by the American Society of Parenteral and Enteral Nutrition and Society of Critical Care Medicine
[b]Children >1 month and <18 years admitted to the pediatric intensive care unit for >2–3 days
[c]GRADE recommendation
[d]Based on a single-center RCT [106]
[e]Joint report: World Health Organization; Food and Agriculture Organization of United Nations
[f]Energy expenditure is measured in kcal/kg/day

clearance. Therefore, for children with AKI, it is recommended to provide protein intake of 2 g/kg/day; for children with AKI receiving peritoneal dialysis or CRRT, it is recommended to increase protein intake by at least 30% increase or to 3–4 g/kg/day, especially in infants.

Improving our evaluation and management of nutrition will be essential to advancing our treatment of AKI. Furthermore, as we advance our modalities for RST, similarly must we advance our understanding of their impact on nutritional balance.

Table 43.13 Factors affecting drug clearance by continuous renal replacement therapy

Drug characteristics	Renal clearance	Drugs with primary renal clearance are most affected by renal failure and CRRT
	Molecular size	High-flux membranes clear non-protein-bound molecules easily, up to 30,000D
	Volume of distribution, Vd	Increased lipid solubility reflects higher Vd; vice versa for water solubility
		Drugs with Vd > 0.7 L/kg are less likely to be cleared by CRRT
	Protein binding	Higher protein binding reflects higher Vd
		Drugs with protein binding >80% are less likely to be cleared during CRRT
	Drug charge	Anionic proteins retained on the blood side of the filter reduce clearance of cationic molecules, called the Gibbs-Donnan effect
Dialysis filter characteristics	Filter composition	Polysulfone dialyzers are apolar and adsorb proteins
	Pore size	High-flux hemofilter allows free passage of non-protein-bound molecules
	Surface area	Increased surface area for body weight will increase clearance; particularly important in neonatal CRRT
	Circuit life	Clearance will gradually decrease with older filter (increased clotting, protein adsorption)
Other characteristics	Blood flow rate	Higher blood flow rate for weight will increase clearance, although to a lesser extent than with IHD
	Dialysis dose	Increased dialysate and replacement fluid flow rate will increase diffusive and convective clearance, respectively, by CRRT
	Ultrafiltration flow rate	Increased ultrafiltration will increase convective clearance ("solute drag")

CRRT continuous renal replacement therapy, *D* Daltons, *IHD* intermittent hemodialysis

Drugs in AKI

Drug dosing with RST for AKI will not be covered in any detail in this chapter. However, awareness of this issue is important. An essential function of the kidney is the excretion of drugs and their metabolites. When glomerular filtration rate falls below 50%, dosing of many drugs must be adjusted to avoid toxic accumulation and complications. On the other hand, for patients on CRRT, drug dosing may need to be increased to account for losses. Dosing adjustment is vital for life-sustaining medications, such as antimicrobials. When deciding whether or not a drug is cleared by RST, it is important to consider drug pharmacokinetics (Table 43.13) [100, 101]. If drug dosing is not available in references, then drug characteristics can be searched to make reasonable inferences about clearance on dialysis. Institutional pharmacists are thus invaluable team members of the AKI care team.

Conclusion

Development of a standardized, graded definition of AKI reflects a deeper understanding of the pathophysiology and reduced health outcomes for children with AKI. Medical and surgical advancements allow neonates and children to survive previously fatal illnesses. As a result, the incidence of AKI in critically ill children is very high. However, significant technological innovations have allowed us to perform RST in children with AKI safely and effectively. This progress in critical care reflects the growing importance of understanding AKI as it relates to short-term and long-term health outcomes, as well as the need for further advancement in the prediction, prevention, and treatment of AKI.

References

1. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. Pediatr Crit Care Med. 2017;18(7):675–715.
2. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med. 2017;376(1):11–20.
3. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184–94.
4. Li S, Krawczeski CD, Zappitelli M, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Crit Care Med. 2011;39(6):1493–9.
5. KDIGO Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.
6. Zappitelli M, Ambalavanan N, Askenazi DJ, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017;82(4):569–73.
7. Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445–53.
8. Malhotra R, Siew ED. Biomarkers for the early detection and prognosis of acute kidney injury. Clin J Am Soc Nephrol. 2017;12(1):149–73.
9. Mehta RL, Cerda J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385(9987):2616–43.
10. Fleming GM, Sahay R, Zappitelli M, et al. The incidence of acute kidney injury and its effect on neonatal and pediatric extracorporeal membrane oxygenation outcomes: a multicenter report from the kidney intervention during extracorporeal membrane oxygenation study group. Pediatr Crit Care Med. 2016;17(12):1157–69.
11. Ueno K, Seki S, Shiokawa N, et al. Validation of acute kidney injury according to the modified KDIGO criteria in infants after cardiac surgery for congenital heart disease. Nephrology (Carlton). 2019;24(3):294–300.
12. Greenberg JH, Zappitelli M, Devarajan P, et al. Kidney outcomes 5 years after pediatric cardiac surgery: the TRIBE-AKI Study. JAMA Pediatr. 2016;170(11):1071–8.
13. Blinder JJ, Asaro LA, Wypij D, et al. Acute kidney injury after pediatric cardiac surgery: a secondary analysis of the safe pediatric euglycemia after cardiac surgery trial. Pediatr Crit Care Med. 2017;18(7):638–46.
14. McGregor TL, Jones DP, Wang L, et al. Acute kidney injury incidence in noncritically ill hospitalized children, adolescents, and young adults: a retrospective observational study. Am J Kidney Dis. 2016;67(3):384–90.
15. Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. Pediatrics. 2013;132(3):e756–67.
16. Goldstein SL, Mottes T, Simpson K, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int. 2016;90(1):212–21.
17. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371(1):58–66.
18. Sigurjonsdottir VK, Chaturvedi S, Mammen C, Sutherland SM. Pediatric acute kidney injury and the subsequent risk for chronic kidney disease: is there cause for alarm? Pediatr Nephrol. 2018;33(11):2047–55.
19. Hessey E, Morissette G, Lacroix J, et al. Long-term mortality after acute kidney injury in the pediatric ICU. Hosp Pediatr. 2018;8(5):260–8.
20. Hessey E, Morissette G, Lacroix J, et al. Healthcare utilization after acute kidney injury in the pediatric intensive care unit. Clin J Am Soc Nephrol. 2018;13(5):685–92.
21. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. J Pediatr. 2014;165(3):522–527.e522.
22. Cooper DS, Claes D, Goldstein SL, et al. Follow-up renal assessment of injury long-term after acute kidney injury (FRAIL-AKI). Clin J Am Soc Nephrol. 2016;11(1):21–9.
23. Madsen NL, Goldstein SL, Froslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int. 2017;92(3):751–6.
24. Hessey E, Ali R, Dorais M, et al. Renal function follow-up and renal recovery after acute kidney injury in critically ill children. Pediatr Crit Care Med. 2017;18(8):733–40.
25. Murray PT, Devarajan P, Levey AS, et al. A framework and key research questions in AKI diagnosis and staging in different environments. Clin J Am Soc Nephrol. 2008;3(3):864–8.
26. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2(2):1303–53.
27. Kumar S. Cellular and molecular pathways of renal repair after acute kidney injury. Kidney Int. 2018;93(1):27–40.

28. Gorga SM, Murphy HJ, Selewski DT. An update on neonatal and pediatric acute kidney injury. Curr Pediatr Rep. 2018;6:278–90.
29. Venkatachalam MA, Weinberg JM, Kriz W, Bidani AK. Failed tubule recovery, AKI-CKD transition, and kidney disease progression. J Am Soc Nephrol. 2015;26(8):1765–76.
30. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001;107(6):1309–12.
31. Selewski DT, Cornell TT, Lombel RM, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. Intensive Care Med. 2011;37(7):1166–73.
32. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol. 2013;28(4):661–6.
33. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. Crit Care. 2010;14(3):R82.
34. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med. 2011;39(12):2665–71.
35. Basu RK, Andrews A, Krawczeski C, Manning P, Wheeler DS, Goldstein SL. Acute kidney injury based on corrected serum creatinine is associated with increased morbidity in children following the arterial switch operation. Pediatr Crit Care Med. 2013;14(5):e218–24.
36. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422–7.
37. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74.
38. Hassinger AB, Wald EL, Goodman DM. Early post-operative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. Pediatr Crit Care Med. 2014;15(2):131–8.
39. Basu RK, Chawla LS, Wheeler DS, Goldstein SL. Renal angina: an emerging paradigm to identify children at risk for acute kidney injury. Pediatr Nephrol. 2012;27(7):1067–78.
40. Basu RK, Zappitelli M, Brunner L, et al. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int. 2014;85(3):659–67.
41. Basu RK, Kaddourah A, Goldstein SL. Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study. Lancet Child Adolesc Health. 2018;2(2):112–20.
42. Menon S, Goldstein SL, Mottes T, et al. Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study. Nephrol Dial Transplant. 2016;31(4):586–94.
43. Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care. 2013;17(5):R207.
44. Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol. 2015;26(8):2023–31.
45. Borasino S, Wall KM, Crawford JH, et al. Furosemide response predicts acute kidney injury after cardiac surgery in infants and neonates. Pediatr Crit Care Med. 2018;19(4):310–7.
46. Kakajiwala A, Kim JY, Hughes JZ, et al. Lack of furosemide responsiveness predicts acute kidney injury in infants after cardiac surgery. Ann Thorac Surg. 2017;104(4):1388–94.
47. Basu RK, Wheeler DS. Approaches to the management of acute kidney injury in children. Recent Pat Biomark. 2011;1(1):49–59.
48. Raina A, Pandita A, Harish R, Yachha M, Jamwal A. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr. 2016;105(10):e448–51.
49. Harer MW, Askenazi DJ, Boohaker LJ, et al. Association between early caffeine citrate administration and risk of acute kidney injury in preterm neonates: results from the AWAKEN study. JAMA Pediatr. 2018;172(6):e180322.
50. Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ. A double-blinded, randomized, placebo-controlled clinical trial of aminophylline to prevent acute kidney injury in children following congenital heart surgery with cardiopulmonary bypass. Pediatr Crit Care Med. 2016;17(2):135–43.
51. Acosta AA, Hogg RJ. Rasburicase for hyperuricemia in hemolytic uremic syndrome. Pediatr Nephrol. 2012;27(2):325–9.
52. Hobbs DJ, Steinke JM, Chung JY, Barletta GM, Bunchman TE. Rasburicase improves hyperuricemia in infants with acute kidney injury. Pediatr Nephrol. 2010;25(2):305–9.
53. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315(20):2190–9.
54. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33.
55. Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of renal-replacement therapy in patients

with acute kidney injury and sepsis. N Engl J Med. 2018;379(15):1431–42.
56. Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010;55(2):316–25.
57. Vasudevan A, Phadke K, Yap HK. Peritoneal dialysis for the management of pediatric patients with acute kidney injury. Pediatr Nephrol. 2017;32(7):1145–56.
58. Warady BA, Bunchman T. Dialysis therapy for children with acute renal failure: survey results. Pediatr Nephrol. 2000;15(1–2):11–3.
59. Madenci AL, Thiagarajan RR, Stoffan AP, Emani SM, Rajagopal SK, Weldon CB. Characterizing peritoneal dialysis catheter use in pediatric patients after cardiac surgery. J Thorac Cardiovasc Surg. 2013;146(2):334–8.
60. Kwiatkowski DM, Menon S, Krawczeski CD, et al. Improved outcomes with peritoneal dialysis catheter placement after cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg. 2015;149(1):230–6.
61. Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP, Morales DL, Krawczeski CD. Peritoneal dialysis vs furosemide for prevention of fluid overload in infants after cardiac surgery: a randomized clinical trial. JAMA Pediatr. 2017;171(4):357–64.
62. Ryerson LM, Mackie AS, Atallah J, et al. Prophylactic peritoneal dialysis catheter does not decrease time to achieve a negative fluid balance after the Norwood procedure: a randomized controlled trial. J Thorac Cardiovasc Surg. 2015;149(1):222–8.
63. Bojan M, Gioanni S, Vouhe PR, Journois D, Pouard P. Early initiation of peritoneal dialysis in neonates and infants with acute kidney injury following cardiac surgery is associated with a significant decrease in mortality. Kidney Int. 2012;82(4):474–81.
64. Liang KV, Sileanu FE, Clermont G, et al. Modality of RRT and recovery of kidney function after AKI in patients surviving to hospital discharge. Clin J Am Soc Nephrol. 2016;11(1):30–8.
65. Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007;3:CD003773.
66. Truche AS, Darmon M, Bailly S, et al. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med. 2016;42(9):1408–17.
67. Symons JM, Chua AN, Somers MJ, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol. 2007;2(4):732–8.
68. Askenazi D, Ingram D, White S, et al. Smaller circuits for smaller patients: improving renal support therapy with Aquadex. Pediatr Nephrol. 2016;31(5):853–60.
69. Coulthard MG, Crosier J, Griffiths C, et al. Haemodialysing babies weighing <8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): comparison with peritoneal and conventional haemodialysis. Pediatr Nephrol. 2014;29(10):1873–81.
70. Ronco C, Garzotto F, Brendolan A, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM). Lancet. 2014;383(9931):1807–13.
71. Zhang J, Tian J, Sun H, et al. How does continuous renal replacement therapy affect septic acute kidney injury? Blood Purif. 2018;46(4):326–31.
72. Tolwani A. Continuous renal-replacement therapy for acute kidney injury. N Engl J Med. 2012;367(26):2505–14.
73. Romagnoli S, Ricci Z, Ronco C. CRRT for sepsis-induced acute kidney injury. Curr Opin Crit Care. 2018;24(6):483–92.
74. Hoover NG, Heard M, Reid C, et al. Enhanced fluid management with continuous venovenous hemofiltration in pediatric respiratory failure patients receiving extracorporeal membrane oxygenation support. Intensive Care Med. 2008;34(12):2241–7.
75. Murphy HJ, Cahill JB, Twombley KE, Kiger JR. Early continuous renal replacement therapy improves nutrition delivery in neonates during extracorporeal life support. J Ren Nutr. 2018;28(1):64–70.
76. Blijdorp K, Cransberg K, Wildschut ED, et al. Haemofiltration in newborns treated with extracorporeal membrane oxygenation: a case-comparison study. Crit Care. 2009;13(2):R48.
77. Selewski DT, Cornell TT, Blatt NB, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. Crit Care Med. 2012;40(9):2694–9.
78. Murphy HJ, Cahill JB, Twombley KE, Annibale DJ, Kiger JR. Implementing a practice change: early initiation of continuous renal replacement therapy during neonatal extracorporeal life support standardizes care and improves short-term outcomes. J Artif Organs. 2018;21(1):76–85.
79. Askenazi DJ, Selewski DT, Paden ML, et al. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. Clin J Am Soc Nephrol. 2012;7(8):1328–36.
80. Cullis B, Abdelraheem M, Abrahams G, et al. Peritoneal dialysis for acute kidney injury. Perit Dial Int. 2014;34(5):494–517.
81. Sethi SK, Bunchman T, Raina R, Kher V. Unique considerations in renal replacement therapy in children: core curriculum 2014. Am J Kidney Dis. 2014;63(2):329–45.
82. Macedo E, Mehta RL. Continuous dialysis therapies: core curriculum 2016. Am J Kidney Dis. 2016;68(4):645–57.
83. Walters S, Porter C, Brophy PD. Dialysis and pediatric acute kidney injury: choice of renal support modality. Pediatr Nephrol. 2009;24(1):37–48.

84. Hackbarth R, Bunchman TE, Chua AN, et al. The effect of vascular access location and size on circuit survival in pediatric continuous renal replacement therapy: a report from the PPCRRT registry. Int J Artif Organs. 2007;30(12):1116–21.
85. Garzotto F, Zanella M, Ronco C. The evolution of pediatric continuous renal replacement therapy. Nephron Clin Pract. 2014;127(1–4):172–5.
86. Flores FX, Brophy PD, Symons JM, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. Pediatr Nephrol. 2008;23(4):625–30.
87. Brophy PD, Mottes TA, Kudelka TL, et al. AN-69 membrane reactions are pH-dependent and preventable. Am J Kidney Dis. 2001;38(1):173–8.
88. Pasko DA, Mottes TA, Mueller BA. Pre dialysis of blood prime in continuous hemodialysis normalizes pH and electrolytes. Pediatr Nephrol. 2003;18(11):1177–83.
89. Yessayan L, Yee J, Frinak S, Szamosfalvi B. Treatment of severe hyponatremia in patients with kidney failure: role of continuous venovenous hemofiltration with low-sodium replacement fluid. Am J Kidney Dis. 2014;64(2):305–10.
90. Askenazi DJ, Goldstein SL, Chang IF, Elenberg E, Feig DI. Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. Pediatrics. 2004;113(2):406–9.
91. Collins KL, Roberts EA, Adeli K, Bohn D, Harvey EA. Single pass albumin dialysis (SPAD) in fulminant Wilsonian liver failure: a case report. Pediatr Nephrol. 2008;23(6):1013–6.
92. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7–20.
93. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361(17):1627–38.
94. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care. 2016;20(1):144.
95. Raymakers-Janssen P, Lilien M, van Kessel IA, Veldhoen ES, Wosten-van Asperen RM, van Gestel JPJ. Citrate versus heparin anticoagulation in continuous renal replacement therapy in small children. Pediatr Nephrol. 2017;32(10):1971–8.
96. Davenport A, Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. NDT Plus. 2009;2(6):439–47.
97. Santiago MJ, Lopez-Herce J, Urbano J, et al. Complications of continuous renal replacement therapy in critically ill children: a prospective observational evaluation study. Crit Care. 2009;13(6):R184.
98. Wang P-L, Meyer MM, Orloff SL, Anderson S. Bone resorption and "relative" immobilization hypercalcemia with prolonged continuous renal replacement therapy and citrate anticoagulation. Am J Kidney Dis. 2004;44(6):1110–4.
99. Hauschild DB, Ventura JC, Mehta NM, Moreno YMF. Impact of the structure and dose of protein intake on clinical and metabolic outcomes in critically ill children: a systematic review. Nutrition. 2017;41:97–106.
100. Zuppa AF. Understanding renal replacement therapy and dosing of drugs in pediatric patients with kidney disease. J Clin Pharmacol. 2012;52(1 Suppl):134s–40s.
101. Veltri MA, Neu AM, Fivush BA, Parekh RS, Furth SL. Drug dosing during intermittent hemodialysis and continuous renal replacement therapy: special considerations in pediatric patients. Paediatr Drugs. 2004;6(1):45–65.
102. Harris RC, Breyer MD. Update on cyclooxygenase-2 inhibitors. Clin J Am Soc Nephrol. 2006;1(2):236–45.
103. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol. 2012;7(10):1713–21.
104. Perazella MA. Pharmacology behind common drug nephrotoxicities. Clin J Am Soc Nephrol. 2018;13(12):1897–908.
105. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. Kidney Int. 2002;62(6):2223–9.
106. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med. 2016;374(12):1111–22.

Neonatal Acute Kidney Injury

44

Cherry Mammen and David Askenazi

Introduction

Critically ill neonates admitted to neonatal and cardiac intensive care units are at high risk for acute kidney injury (AKI). In theory, the potential benefits to providing renal replacement therapy (RRT) for neonates with severe AKI are similar to larger pediatric and adult populations. Performing peritoneal dialysis is possible even in the smallest of infants. The use of extracorporeal therapies to provide RRT has been limited as the devices that are commonly used are not designed for small infants and carry added risks to the patient. Fortunately, several novel machines with smaller extracorporeal volumes have been introduced into clinical practice in select centers around the world. In this chapter, we will describe a case of a critically ill neonate admitted to the neonatal intensive care unit to illustrate the diagnosis of neonatal AKI, delineate consequences and medical management of AKI, discuss indications for RRT, compare and contrast options for care, and provide specifics of RRT in neonates. Chapter contents directly relevant to the case are provided in *italics*. We conclude by reporting on the novel devices which promise to change the approach to the care of neonates who can benefit from RRT.

Case Presentation

A term male infant is born via *spontaneous vaginal delivery at 37 weeks gestational age to a 31-year-old G1P0 mother with history of maternal fever and prolonged rupture of membranes. The infant is assessed in the nursery on the first day of life (DOL) with poor latching, shallow respirations, and lethargy. With concerns of sepsis, he is transferred to the Neonatal Intensive Care Unit (NICU). Vital signs reveal elevated heart rate of 180 beats/minute, increased respiratory rate of 64 breaths/minute, increased temperature of 38.5 degrees Celsius, and low blood pressure (BP) of 42/20 mmHg (mean arterial pressure 30). Physical exam reveals poor peripheral pulses and prolonged capillary refill. Initial labs include neutropenia (1.0 × 10^9/L) and lactic acidosis (HCO_3 17 mmol/L, lactate 5.0 mmol/L). Chest X-ray shows normal heart size and lung fields. Umbilical venous and arterial catheters are placed. Boluses of 20 cc/kg of normal saline (NS) are administered with no improvement in blood pressure and no documented urine output. Broad-spectrum intravenous antibiotics are started (ampicillin 50 mg/kg/dose q8h and gentamycin 2.5 mg/kg/dose q12h). With ongoing hypotension,*

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dopamine is started at 5 mcg/kg/min, and 20 cc/kg of NS was administered again to optimize perfusion. Blood pressure stabilized at this point with a mean arterial pressure maintained above 40 mmHg. Over the next 12 hours, dopamine is stopped due to stable BP. Blood cultures are positive for Group B Streptococcus (GBS) at 36 hours. Infant is kept NPO, and standard total parenteral nutrition was commenced with an ongoing total fluid intake of 80 cc/kg/day and protein intake of 2.5 g/kg/day. Gentamycin trough level before the third dose is elevated at 5.0 mg/L, and antibiotics are switched to IV penicillin (sensitive to GBS). A Foley catheter is inserted due to ongoing oliguria. Renal ultrasound showed two normal-sized echogenic kidneys.

On the third DOL, severe body wall edema and ascites are noted, and the infant develops worsening respiratory distress requiring intubation and ventilation. Chest X-ray is consistent with pulmonary edema and a slightly large cardiac silhouette. Intravenous furosemide (1 mg/kg dose) is attempted with no increase in urine output. Chemistry on DOL #3 reveals sodium (Na^+) 127 mmol/L, potassium (K^+) 6.4 mmol/L, bicarbonate (HCO_3) 15 mmol/L (lactate normal), phosphate (PO_4) 9.1 mg/dL (2.94 mmol/L), ionized calcium (Ca^{++}) 1.0 mmol/L, uric acid 12 mg/dL (713 umol/L), and serum albumin of 1.8 g/dL. Pediatric nephrology is consulted for further management of acute kidney injury. Table 44.1 *provides trends of renal function (blood urea nitrogen, and serum creatinine), weight, and urine output from birth till DOL 3.*

Table 44.1 Renal function, weight, and urine output trends from case example

Day of life	0	1	2	3
BUN in mg/dL (urea in mmol/L)	N/A	22 (7.9)	42 (15)	70 (25)
SCr in mg/dL (umol/L)	N/A	0.7 (62)	1.1 (97)	2.1 (186)
Weight (kg)	3.4	3.7	4.0	4.3
Urine output (ml/kg/hour)	0	0.2	0.3	0.3

BUN blood urea nitrogen, *SCr* serum creatinine, *N/A* not available

Defining Neonatal AKI

Acute kidney injury (AKI) has replaced the previous term "acute renal failure" in order to represent the entire spectrum of injury severity ranging from mild increases in serum creatinine (SCr) to severe oligoanuria requiring renal replacement therapy (RRT). Consequently, there has been a steady evolution of severity graded AKI definitions based on changes in serum creatinine (SCr) and/or urine output including RIFLE (Risk, Injury, Failure, Loss, and End Stage Renal Disease), AKIN (Acute Kidney Injury Network), and most recently the KDIGO (Kidney Disease: Improving Global Outcomes) definition in 2013 [1–3]. These staged definitions were first validated for older pediatric and adult cohorts and more recently have been applied empirically to single- and multi-center neonatal studies.

Beyond the traditional challenges to using SCr to define AKI, there is added complexity in the first perinatal weeks due to the complex physiology surrounding adaptation and transition into the extrauterine environment. Neonatal SCr around birth represents maternal creatinine and achieves a steady-state value over several days as the innate renal function equilibrates. Preterm infants of approximately 30 weeks gestational age (GA) have a GFR <10 ml/min/1.73m^2 within the first 24–40 hours of birth, while glomerular filtration rate (GFR) in term infants is slightly higher, ranging from 10 to 40 ml/min/1.73m^2 [4, 5]. Consequently, a few days after birth once steady state is achieved, the SCr of premature infants is often higher compared to term infants. Then over the coming weeks, the trajectory of declining SCr is highly dependent on GA with a slower decline seen in lower GA patients [6, 7].

The neonatal modified KDIGO definition uses a SCr rise of ≥0.3 mg/dL (26 umol/L) or a ≥50% rise in SCr from baseline to define AKI (Table 44.2). Necessary modifications from the original KDIGO definition include (1) a reference SCr being defined as the lowest previous SCr value due to the ongoing decline of SCr in the first few weeks of life and (2) an absolute SCr cutoff of ≥2.5 mg/dL (221 umol/L) to define AKI stage 3 as this represents a GFR of <10 ml/

Table 44.2 Neonatal acute kidney injury modified KDIGO classification

Stage	SCr criteria	Urine output criteria
0	No change in SCr *or* rise <0.3 mg/dL	≥0.5 ml/kg/hour
1	SCr rise ≥0.3 mg/dl within 48 hours *or* SCr rise ≥1.5–1.9 × reference SCr[a] within 7 days	<0.5 ml/kg/hour for 6 to 12 hours
2	SCr rise ≥2 to 2.9 × reference SCr[a]	<0.5 ml/kg/hour for ≥12 hours
3	SCr rise ≥3 × reference SCr[a] *or* SCr ≥2.5 mg/dl *or* Receipt of dialysis	<0.3 ml/kg/hour for ≥24 hours *or* anuria for ≥12 hours

[a]Reference SCr defined as the lowest previous SCr value

min/1.73m^2 in a neonate (compared to ≥4 mg/dL or 354 umol/L in the original KDIGO definition). In 2013, an expert working group consisting of neonatologists and nephrologists at a National Institutes of Health (NIH)-sponsored neonatal AKI workshop agreed this empiric definition should be used across neonatal studies, highlighted the need to validate this definition using meaningful outcomes in larger multi-center cohorts, and urged adjustments to this definition based on sound evidence [8]. The suggested urine output (UOP) thresholds to define oliguria (<0.5 cc/kg/hour) for the modified neonatal KDIGO criteria (Table 44.2) are similar to prior definitions (RIFLE, AKIN, KDIGO), but have not been well studied in neonatal populations.

A multi-center study called AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) involving 24 participating neonatal intensive care unit (NICU) sites recently reported the incidence of AKI and validated that indeed, AKI using modified KDIGO definition is independently associated with mortality [9]. The AWAKEN study evaluated 2022 infants who were admitted in the NICU, did not need cardiac surgery in the first week of life, and were on intravenous fluids for at least 2 days. The incidence of AKI was similar to prior single-center studies using the modified KDIGO classification at 29.9%. The UOP criteria used in the AWAKEN study was slightly modified from the originally proposed criteria (Table 44.2) to include a average 24 hour urine output cutoffs for different stages of AKI for feasibility of the study, with a stage 1 threshold set at <1 ml/kg/hour averaged over 24 hours, excluding the first day of life. AKI incidence varied by gestational age groups (22–29 weeks = 49.7%, 29–36 weeks = 18.3%, >36 weeks = 36.7%). When classified according to highest AKI stage, 46.4%, 23.6%, and 29.9% of patients with AKI achieved stages 1, 2, and 3, respectively. Even after adjusting for multiple potential confounders, infants with AKI had a 4.6 higher odds of mortality (95% CI OR 6.1–11.5) and stayed in hospital 8.8 days longer (95% CI 6.1–11.5 days) compared to neonates without AKI. Data from this landmark study confirms the strong association of the neonatal KDIGO definition with poor outcomes observed in single-center studies and supports the notion that critically ill neonates die "from" AKI and not simply "with" AKI.

Using the SCr-based neonatal modified KDIGO criteria and trends from Table 44.1*, the patient in our case has achieved stage 3 AKI as the SCr rose to 2.1 mg/dL (185 umol/L) from the lowest previous value of 0.7 mg/dL (62 umol/L) representing a threefold rise in SCr. Using the UOP-based criteria, our case achieved stage 3 AKI based on a sustained urine output of 0.2–0.3 cc/kg/hour.*

Consequences and Medical Management of AKI

The first pivotal step in neonatal AKI management is to recognize AKI early using standardized and staged definitions such as the modified KDIGO classification with the importance of identifying renal "injury" at an early stage well before "failure" ensues. Next, a thorough evaluation of the underlying etiology and reversal of that process (if possible) is needed. Clues to the underlying etiology can be gained from the maternal, perinatal, and postnatal course, laboratory analysis, evaluation of serial weights, intake and output, and radiographic information. The clinician should look for signs of fluid excess or deficit and determine if there is a functional component of AKI that is

responsive to intravenous fluids (pre-renal AKI). This is important as what was previously labelled as "vasomotor nephropathy" is common and potentially reversible with easily disturbed renal hemodynamics in neonates favoring renal vasoconstriction from several triggers including hypovolemia, hypotension, and hypoxemia [10].

The evaluation and management of the consequences of AKI drive most of the interventions. AKI is characterized by an abrupt impairment in kidney function that can lead to significant retention of nitrogenous waste products and dysregulation of extracellular fluid volume, electrolytes, and acid-base homeostasis. *Our case of septic AKI highlights several common consequences of a severe AKI episode including fluid overload and electrolyte disturbances (hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and metabolic acidosis).*

Fluid Overload

The development of fluid overload in critically ill AKI patients is often multifactorial in nature with contributions from oliguria, generous fluid administration, systemic inflammation, capillary leak, and hypoalbuminemia. Initially introduced by Goldstein and colleagues from an analysis of children requiring continuous renal replacement therapy (CRRT) in 2001, the percent fluid overload (% FO) of a patient was defined by measuring the cumulative fluid balance from ICU admission as follows [11]:

$$\%\,\mathrm{FO} = \frac{\text{Sum of Daily Fluid In}\,(\text{litres}) - \text{Sum of Daily Fluid Out}\,(\text{litres})}{\text{Admission Weight}\,(\text{kg})} \times 100$$

A weight-based method has also been described to define %FO based on change in weight from a baseline weight, often at ICU admission, as follows [12]:

$$\%\,\mathrm{FO} = \frac{\text{Daily weight}\,(\text{kg}) - \text{Admission Weight}\,(\text{kg})}{\text{Admission Weight}\,(\text{kg})} \times 100$$

This weight-based determination of %FO may be more useful in neonatal populations where insensible losses may have more of an effect of fluid balance [13]. In addition, neonates often get daily weights measured during hospitalization, while urine output is difficult to accurately measure.

Even though there has been a growing body of neonatal AKI literature in the setting over the last decade, fluid overload in critically ill neonates has not been well studied. Fluid balance thresholds to predict poor outcomes in neonates may be different compared to older children, especially as neonates are expected to lose a relatively large percentage of their birth weight in the first week of life, up to 16% and 10% in premature and term infants, respectively. Furthermore, during a prolonged NICU stay, neonates increase their weight progressively for growth. Askenazi et al. found that in 58 term/near-term infants, %FO at day 3 of life was significantly higher in patients with AKI compared to patients without AKI (median FO% +8.2% vs. −4%) [14]. Even though mortality was significantly higher in AKI patients, the role of fluid overload in this mortality risk is unclear. In 34 unstable neonates who underwent

continuous renal replacement therapy (CRRT) including 15 premature infants, survival outcomes were worse in those with a FO ≥30% [15]. Fluid overload has also been found to impact on mortality in neonates with congenital heart disease undergoing cardiopulmonary bypass procedures and those on ECMO [16–18]. The impact of fluid overload on pulmonary outcomes was also recently studied in 645 term/near-term infants from the AWAKEN cohort [19]. Multivariable models showed that peak fluid balance (adjusted odds ratio (aOR) 1.12, 95% CI 1.08–1.17), lowest fluid balance in first postnatal week (aOR 1.14, 95%CI 1.07–1.22), fluid balance on postnatal day 7 (aOR 1.12, 95%CI 1.07–1.17), and negative fluid balance on postnatal day 7 (aOR 0.3, 95%CI 0.16–0.67) were independently associated with mechanical ventilation needs on postnatal day 7. Those with AKI had a higher peak fluid balance in the first week of life compared to those without AKI (+2.7% vs. +0.5%, $p < 0.0001$).

Fluid Management

In order to maximize renal perfusion, the clinician needs to assure that cardiac output is maximized. Maintenance of adequate stroke volume is imperative. Fluid-overloaded patients often have "third-space" losses due to capillary leak and/or hypoalbuminemia, which can result in a low effective circulating volume. In cases of hypoalbuminemia, critically ill patients can receive concentrated albumin infusions to ensure adequate albumin stores (>2.5 mg/dl) for adequate oncotic pressure. Often, "normal" blood pressure is not adequate enough to perfuse the kidneys. If there is evidence of low renal perfusion in a pre-renal state (e.g., (1) high BUN/Cr ratio, (2) low fractional excretion of sodium and/or urea), an attempt to keep blood pressure on the higher end of normal, or slightly above the 95th percentile for age, can be empirically attempted to see if maximizing perfusion can improve kidney function. Finally, the intra-abdominal pressure may need to be assessed. If the infant has intra-abdominal pathology (i.e., severe ascites or necrotizing enterocolitis) which causes a high intra-abdominal pressure and prevents adequate renal blood flow, placement of a drain to relieve abdominal pressure can sometimes improve renal perfusion.

There are several tools that the clinician can use to determine appropriate hemodynamics/pressures. The physical exam should confirm adequate tissue perfusion. An ultrasound can be performed to assess inferior vena cava volume as an estimate of stroke volume. An echocardiogram can evaluate cardiac output, with a normal reported neonatal ejection fraction of 52–75% [20]. A beta-natriuretic peptide can also be measured to estimate right atrial pressure. A bladder pressure measurement can be used to assess intra-abdominal compartment syndrome with values of >12 mmHg defining intra-abdominal hypertension and ≥20 mmHg suggestive of abdominal compartment syndrome [21]. Also, a fractional excretion of sodium (FENa) or fractional excretion of urea if a patient is on diuretics can be used to determine if the patient's rising creatinine and relative oliguria are due to poor renal perfusion in context of intact tubular function. In term infants, FENa <2% is indicative of functional or pre-renal AKI and usually >2.5% with tubular injury [22]. The FENa cutoff values in premature infants are higher compared to older children and adults due to tubular immaturity. Limited data suggests the following to differentiate intrinsic tubular injury from pre-renal AKI (FENa <2%): FENa >3% for >31 weeks gestational age (GA) and FENa >6% for 29–30 weeks GA [23, 24].

Even though diuretics remain a mainstay of fluid overload management, it is important to note that diuretics have never been proven to prevent AKI or improve outcomes in those with AKI [25–28]. However, a trial of intravenous diuretics would still be highly recommended in an attempt to increase urine output once volume depletion is ruled out. The most commonly used diuretic in neonates is furosemide, a highly protein-bound loop diuretic [29]. Traditionally, a bolus dose of 1 mg/kg is recommended in most drug formularies, but in neonates with AKI, the retained organic acids compete with furosemide for proximal tubu-

lar secretion, ultimately resulting in only 10–20% of the drug being secreted into the tubular lumen [30]. Therefore, higher doses (2–5 mg/kg/dose) should be considered in AKI [31]. However, the risk of ototoxicity increases with higher doses due to decreased clearance of the drug. If there is a positive response to furosemide, the drug can be continued either as repeat bolus dosing or continuous infusion. Even though a term infant can get be dosed every 6 hours, the half-life is prolonged in premature infants. Therefore, furosemide should only be administered every 12 hours in those ≥32 weeks gestational age (GA) and every 24 hours in those <32 weeks GA to avoid accumulation and ototoxicity [32]. Even though there have been no controlled studies showing superiority of bolus vs. continuous dosing, studies in neonatal cardiac surgery have shown that compared with bolus dosing of 1 mg/kg every 4 hours, a continuous infusion of 0.1 mg/kg/hour was associated with comparable urine output, lower cumulative doses of furosemide, and less fluctuation in urine output [33, 34]. Maximum furosemide infusion rate utilized in these neonatal studies was 0.4 mg/kg/hour, but doses up to 1 mg/kg/hour have been reported in infants. However, potential risks of toxicity and fluid/electrolyte imbalances exist with such high doses [35]. One of the other concerns for the use of furosemide is that it may delay the initiation of renal support therapy. If a large dose of diuretic does not allow for the fluid goals to be met, serious consideration should be placed on initiation of renal support therapy before fluid overload progresses even further [36].

Since hypoalbuminemia can limit diuretic effectiveness further, clinicians sometimes attempt to administer furosemide with or following a concentrated albumin infusion (e.g., 20% or 25%) in those with a significantly low serum albumin (<2.5 g/dL), which is common in sick neonates. However, this practice must be performed with caution given the risks of significant volume expansion and pulmonary edema in the face of oliguric AKI.

In our case of suspected early-onset neonatal sepsis, early and aggressive resuscitation with normal saline boluses and inotropes was appropriate to improve blood pressure and systemic perfusion in the face of evolving distributive shock. However, after the resuscitation stage, the total fluid intake was kept at 80 cc/kg/day, which exceeded the losses from the patient and contributed to progressive fluid overload requiring intubation and ventilation. Due to the significant cumulative weight-based fluid overload of 26% (birth weight 3.4 kg, max weight 4.3 kg) along with pulmonary edema in our case with ongoing oligoanuria, the pediatric nephrology team advised the neonatology team to decrease the total fluid intake (TFI) to 25 ml/kg/day, which represents insensible losses in a term infant. Since the 1 mg/kg/dose of furosemide administered to our patient may have been inadequate in the face of severe AKI, a higher intravenous dose of 2 mg/kg was trialed. Given the lack of response in urine output, the decision was made not to repeat any more doses of diuretics, recognizing that other measures would be needed to achieve a negative fluid balance.

Dysnatremias

Neonates with AKI may manifest either hyponatremia or hypernatremia depending on the underlying cause of AKI, their fluid balance status, sodium (Na^+) intake, and the ability of their kidneys to retain sodium appropriately. The sodium content of all intravenous (IV) and oral fluids including parenteral nutrition must be reviewed. In the face of hyponatremia where a net sodium loss is suspected, replacement of hypotonic IV fluids with isotonic fluids (0.9% NaCl) is recommended. If the problem is excess water accumulation, interventions are necessary to achieve a negative water balance including fluid restriction and/or diuretics. If the serum Na^+ is <120 mmol/L or the patient is symptomatic (e.g., seizures), sodium can be corrected to a safer level (e.g., 125 mmol/L). The amount of Na^+ needed to correct hyponatremia can be estimated from the formula: # of mmol of Na^+ = [desired Na^+(mmol/L) – actual Na^+(mmol/L)] × 0.8 × body weight (kg). The etiology of hypernatremia in the majority of patients is due to a free water deficit as opposed to Na^+ excess. Interventions to make the patient net fluid positive

by increasing the desired total fluid intake using enteral feeds or more hypotonic intravenous fluids are appropriate.

As in our case example, the hyponatremia (Na^+ 127 mmol/L) in the face of oliguric AKI is most likely related to hemodilution with no sodium deficit. Therefore, the management strategy includes strict fluid restriction and limiting additional free water intake as opposed to the common practice of increasing sodium intake to correct the hyponatremia.

Hyperkalemia

Hyperkalemia is one of the most dangerous complications of AKI that can lead to cardiac arrhythmias, cardiac arrest, and even death. Neonates, especially very low birth weight (VLBW) and extremely low birth weight (ELBW) infants, are more prone to hyperkalemia due to low GFR, concurrent acidosis, reduced Na^+/potassium (K^+) pump activity, and reduced tubular K^+ secretion from aldosterone insensitivity [37–40]. If significant hyperkalemia (>6.0 mmol/L) is confirmed, the first step is to discontinue any exogenous K^+ administration from IV fluids or parenteral nutrition. If any electrographic changes are observed, cardiac stabilization should begin with intravenous calcium gluconate (50–100 mg/kg/dose over 5–10 minutes) under electrocardiogram surveillance. IV dextrose and insulin (0.5 gram/kg glucose with 0.2 units of regular insulin per gram of glucose over 2 hours) can be used for moderate-severe hyperkalemia (6.5–7.5 mmol/L), but fluctuation in blood glucose is often problematic [41]. IV salbutamol is also an alternative in neonates. At 1 hour after salbutamol infusion (4 mcg/kg over 20 min), serum K^+ fell by 1.1 mmol/L (range 0.7–1.8 mmol/L) in seven hyperkalemic infants with AKI [42]. If concurrent metabolic acidosis is present, correction of acidosis using IV 4.2% sodium bicarbonate may also improve hyperkalemia via intracellular shifting.

Outside of promoting intracellular K^+ shifting, medical treatments including diuretics (e.g., furosemide) and cation exchange resins (e.g., sodium polystyrene sulfonate or SPS) can be used to promote K^+ removal via the urine and gut, respectively. SPS is a cation exchange resin that remains in the lumen of the gastrointestinal tract where it exchanges sodium for potassium and each gram of resin can potentially bind up to 0.5–1 mmol of K^+. SPS can be given by oral or rectal routes at a dose of 1 gram/kg/dose up to every 6 hours as needed. Potential SPS complications include hypernatremia and fluid retention from the high Na^+ content, constipation, bowel opacification, and irritation of the rectal mucosa. A calcium-based resin, calcium polystyrene sulfonate (CPS), is also available. The use of CPS and SPS in low birth weight infants has been questioned with reports of gastric bezoars after oral administration, intestinal perforation after SPS enemas, and necrotizing enterocolitis [43–46].

The K^+ content of all available nutritional options should be reviewed, and those with the lowest K^+ should be offered. Nutritional supplements such as human milk fortifier may increase K^+ content considerably. Breast milk is usually the best option with K^+ content of only 1.3–1.5 meq/100 mL. Other low K^+ neonatal formula options include Similac PM 60/40 (1.5 meq/100 mL), Gerber Good Start Gentle (1.9 meq/100 mL), and nephea Infant (1.5 meq/100 grams of powder). Due to the concerns of SPS side effects in young infants, several authors have described pre-treating formula or breast milk with SPS to decrease K^+ content further [47–49]. However, pre-treating formula with SPS may also increase sodium content and decrease calcium and magnesium content of the formula significantly [49].

Metabolic Acidosis

As the result of impairments in excretion of acid and regeneration of bicarbonate (HCO_3), AKI is commonly associated with metabolic acidosis. Acidosis can sometimes be worsened by the underlying AKI etiology (e.g., poor perfusion from sepsis, diarrhea, heart failure). Outside of AKI, both term and preterm infants normally have a lower serum bicarbonate (HCO_3) concentration compared to older populations, which can

be as low as 15 mmol/L in low birth weight newborns during the early postnatal period [50]. If the patient has significant metabolic acidosis, therapy with intravenous or oral Na^+HCO_3 is recommended. The amount of HCO_3 required for correction can be estimated by the following formula: mmol of Na^+HCO_3 = base deficit (mmol/L) × weight (kg) × 0.3. Cautious correction of acidosis during AKI is recommended as aggressive treatment with HCO_3 may result in Na^+ excess, worsening fluid overload, and significant hypocalcemia. If parenteral nutrition is being utilized, one can also consider substituting acetate for chloride.

Hyperphosphatemia and Hypocalcemia

Infants with AKI may develop hyperphosphatemia due to impaired phosphorus excretion and secondary hypocalcemia from increased binding of free calcium (Ca^{++}), putting the patient at a higher risk of seizures and tetany. Hypocalcemia can also exacerbate the adverse effects of hyperkalemia on cardiac conduction pathways. Compared to older children, neonates have significantly higher serum phosphate levels [51]. The management of AKI-associated hyperphosphatemia is particularly challenging in neonates. With parenteral nutrition, it is important to discontinue all phosphate (PO_4) supplementation immediately. If enterally fed, all nutritional options must be reviewed to minimize PO_4 content until AKI resolves. Concentrated preterm formulas and human milk fortifier are designed to contain high amounts of PO_4 and Ca^{++} content to assist in heightened bone development. Breast milk has the lowest PO_4 content of all nutritional options (13–14 mg/100 mL). Other low PO_4 formula options for young infants include Similac PM 60/40 (19 mg/100 mL), Gerber Good Start Gentle (26 mg/100 mL), and Similac Advance 20 (28 mg/100 mL). If the PO_4 content of a formula is too high, one option is to pre-treat the formula with calcium carbonate (PO_4 binder) or a non-calcium-based binder such as sevelamer [49, 52, 53]. Due to risks of an elevated PO_4/Ca^{++} product and extra-skeletal calcification, secondary hypocalcemia should not be treated unless severe and/or symptomatic.

Nutrition and Other Metabolic Alterations

Even though not well studied in neonates, important metabolic abnormalities are induced by AKI including activation of protein catabolism with excessive release of amino acids and sustained negative nitrogen balance, peripheral glucose intolerance/increased gluconeogenesis, and inhibition of lipolysis with altered fat clearance. These metabolic changes are determined not only by AKI, but also by the underlying process itself including sepsis and subsequent organ dysfunction. Caloric and protein needs of neonates tend to be quite high to support growth and development and should be maintained in catabolic states including AKI [54, 55]. In term infants, recommended caloric and protein intake is 108 kcal/kg/day and 2.2 grams/kg/day, respectively. The needs of premature infants are often higher at 110–150 kcal/kg/day and 3.4–4.4 grams/kg/day of protein.

Meeting nutritional goals can be a serious challenge in the face of neonatal AKI. When oliguria accompanies AKI, it can be difficult to provide enough nutrition without progression of fluid overload. Inability to remove waste products will lead to increases in blood urea nitrogen (BUN) and other uremic toxins. With the assistance of a dietician, the nutritional needs (provided parenteral or enteral) have to be balanced with the risk of further fluid and metabolic abnormalities. Concentrating the volume of parenteral nutrition is an option, but has osmolarity limits, and depends on the type of venous access (central vs. peripheral). In terms of enteral feeds, neonates may not tolerate highly concentrated formula feeds. Close surveillance of glucose and lipids needs to occur with the risk of developing hyperlipidemia and glucose intolerance during AKI. The inability to provide nutrition safely is one of the indications for renal replacement therapy (RRT).

In context of fluid overload and rising BUN levels, the medical team maximized the TPN concentration and decreased total protein intake to 1.5 g/kg/day from 2.5 g/kg/day temporarily. Even though this topic has not been studied in neonates and is controversial, the effects of inadequate early nutrition in critically ill children may not be as harmful as one might expect. In a recent multicenter randomized trial of 1440 children admitted to the pediatric intensive care unit (PICU), those who had parenteral nutrition held for the first week actually had improved outcomes in terms of infection risks, shorter ventilation, and earlier discharge, compared to those that had early initiation of parenteral nutrition during admission [56].

Limiting Nephrotoxin Exposure

In our case of suspected early-onset sepsis, the patient was placed on an aminoglycoside (gentamycin) as part of empiric coverage. Two US studies found that 57.5% of all neonates discharged from NICU and 86% of very low birth weight infants were exposed to gentamycin during their stay [57, 58]. With evolving AKI and the nephrotoxic potential of aminoglycosides, the treating team should discuss potential alternative antibiotic choices. If the aminoglycoside must continue, the appropriate dosage and interval must be discussed with the local pharmacist along with close surveillance on serum levels. Trough levels of gentamycin should be maintained between 0.5 and 2 mg/L, and elevated trough levels suggest reduced renal clearance of gentamycin, as was seen in our example (5.0 mg/L). A recent Cochrane review did not find any clinical difference between once daily and multiple daily doses of gentamycin in neonates, but recommends once daily frequency due to the improved pharmacokinetic profile achieved using this regimen. In theory, extended interval dosing of aminoglycosides may be safer for the kidney, but this has not been supported by any solid data in neonates [59]. While on gentamycin, exposure to any additional nephrotoxic agents including non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. *In our case, the gentamycin was appropriately switched to a less nephrotoxic choice (penicillin) as soon as blood culture results and antibiotic sensitivities were available and no further nephrotoxin agents were given.*

Other Medical Treatments of Neonatal AKI

Although there are currently no drugs approved for the treatment of AKI, some medications have been reported to ameliorate the effects of neonatal AKI. Four randomized clinical trials in asphyxiated infants found that a single prophylactic dose of intravenous theophylline, a methylxanthine with adenosine receptor antagonism properties, administered within 1 hour of birth, had a renoprotective effect [60–63]. Consequently, the KDIGO AKI guidelines for the management of AKI suggest that a single dose of theophylline should be considered in severely asphyxiated infants at high risk for AKI [48]. In an additional 2016 study published after the KDIGO recommendations, Raina et al. randomized 159 term infants to a single IV dose of 5 mg/kg theophylline vs. placebo [64]. Those randomized to theophylline had lower rates of AKI by KDIGO (15% vs. 49%), had lower mean SCr values on day 3 of life (0.83 ± 0.35 mg/dL vs. 1.47 ± 0.61 mg/dL), and displayed a lower incidence of oliguria (27% vs. 59%). No complications from theophylline were reported.

The effect of a more commonly used methylxanthine, caffeine, on AKI has been explored in several studies in premature infants [65–67]. Harer et al. explored 675 premature infants enrolled in the AWAKEN multi-center retrospective study [67]. Infants that received caffeine in the first 7 days after birth developed AKI less frequently than neonates who did not (11.2% vs. 31.6%). After multivariable adjustment, receipt of caffeine remained associated with a reduced odds for developing AKI (adjusted OR 0.20 (95% CI 0.11–0.34)), indicating that for every 4.3 neonates exposed to caffeine, 1 case of AKI was prevented.

Several case series have shown that rasburicase, a recombinant urate oxidase, may help infants with hyperuricemia and AKI [68–70]. In the largest series, Hobbs et al. reported on seven neonates who received a single IV dose of rasburicase (mean dose of 0.17 mg/kg) [70]. Within 24 hours, serum uric acid decreased from a mean of 13.6 to 0.9 mg/dl, SCr decreased from a mean of 3.2 to 2.0 mg/dl, and urine output increased from a mean of 2.4 to 5.9 ml/kg per hour (all $p < 0.05$). Prior to the use of rasburicase, glucose-6-phosphate dehydrogenase (G6PD) deficiency should be ruled out. Hemolytic anemia is likely to occur in G6PD-deficient patients due to their inability to break down hydrogen peroxide during the oxidation of uric acid to allantoin [71].

Indications for Renal Replacement Therapy (RRT)

The timing of renal replacement therapy (RRT) is one of the most controversial topics in acute care nephrology. Like any other intervention, the right time to start is when the potential benefits outweigh the potential risks. RRT should be considered when there is impending harm to the patient if the physiologic needs of the patient are not being met under maximal medical management. RRT should be considered if the patient is likely to be harmed from the impending consequences that occur when the kidney is not able to maintain one or more of its vital functions, namely, removal of waste products and/or maintenance of electrolyte/fluid/acid-base homeostasis. The potential benefits need to be weighed in context of the potential risks to the patient. There are no specific SCr or BUN cutpoints that signal the need to initiate RRT. Rather, an evaluation of the trajectory of consequences resulting from the inability of the kidneys to perform their physiologic functions drives the decision to initiate RRT.

In addition to the classic indications for RRT, neonates with hyperammonemia associated with inborn errors of metabolism often require RRT to reduce the risk of neurological sequelae of hyperammonemia [72, 73].

RRT is indicated when conservative management has failed to adequately control any of the following conditions [74, 75]:

1. Progressive hypervolemia affecting organ function
2. Hyperkalemia
3. Hyponatremia
4. Metabolic acidosis
5. Hyperphosphatemia
6. Inability to provide necessary blood products, drugs, and/or nutrition without progressive fluid overload
7. Toxicity of certain medication(s)
8. Hyperammonemia related to inborn errors of metabolism

Careful evaluation of the potential benefits and risk of initiation of RRT needs to be considered as part of the decision-making process to initiate RRT. The potential risks of neonatal RRT can be higher than the pediatric and adult populations. For all RRT across all ages, the risks can be mitigated on a programmatic level by developing a standardized approach to practice. Fortunately, more programs are developing expertise in neonatal RRT, and newer technologies are becoming more available, which will decrease the potential risk of RRT for neonates.

With persistence of oliguric AKI, significant fluid overload (26%) with negative respiratory effects, and the inability to maintain adequate nutrition in our case, the pediatric nephrology team discussed the risks and benefits of the available types of RRT including peritoneal dialysis (PD), intermittent hemodialysis (HD), and CRRT (continuous renal replacement therapy) with the neonatology team and the parents.

Renal Replacement Therapy Modalities

Renal replacement therapy is a broad term to describe the use of either the peritoneum or an extracorporeal circuit to provide renal support in patients whose kidneys are unable to maintain appropriate balance of fluids/electrolytes and/or

remove metabolic waste products. Once the decision to initiate RRT has been made, the type of therapy used will be driven by modality availability, patient condition, and clinician expertise. The use of RRT in the NICU is much lower than in other critical care units for multiple reasons. In the recent multi-center AWAKEN study [76], only 25/4273 (0.6%) of patients admitted during the 3-month study period (January–March 2014) received RRT. The types of therapy used were primarily peritoneal dialysis ($n = 9$) and CRRT in combination with extracorporeal membrane oxygenation (ECMO) ($n = 11$). In comparison, a similar multi-center study in pediatric ICU patients [77] found that 1.5% of children with AKI received RRT.

A recent survey of pediatric nephrologists from developed and developing nations showed that all centers who responded had access to PD, 85.1% had access to HD, and 54.1% had access to CRRT [78]. Centers in developed countries had twice the likelihood to have access to CRRT than those in developing countries (60% vs. 33.2% $p < 0.01$). The preferred modality for RRT in developed countries was HD or CRRT, while those in developed countries preferred PD.

Like all invasive procedures, RRT has potential risks. The risks of RRT are engrained in the vascular access (damage to vessel, clot, bleeding, infection), drop or rise in blood pressure in context of fluid removal, electrolyte abnormalities (although electrolytes will in general be much better balanced while on RRT), and infection. When using heparin for anticoagulation, there is risk for systemic bleeding. When using regional citrate anticoagulation, there is risk of metabolic alkalosis and citrate accumulation. Another important risk is that RRT can remove amino acids, minerals, and medications including antibiotics.

Peritoneal Dialysis

Overall, PD is easier to perform, requires less training, and is less expensive than HD or CRRT. In addition, PD can be utilized even in the smallest of infants. PD usually allows adequate clearance and removal of excess fluid. In addition, PD avoids the need for anticoagulation and maintenance of adequate vascular access, which are required for the other methods [79]. In neonates after cardiac bypass surgery, initiation of PD improves outcomes compared to passive fluid drainage and diuretics [80, 81].

PD has been successfully performed in very low birth weight (VLBW) infants. Yu et al. reported on the use of a 14 French arrow double-lumen vascular catheter to perform PD in 16 VLBW infants (smallest was 630 grams) [82]. Harshman et al. reported the use of a standard PD coiled catheter in an 830 gram VLBW infant with success [83]. Several important challenges were addressed by the authors including the need to tailor the access to the patient. For example, the surgeons placed a 8.5 French, 8 cm commercial temporary PD catheter (Pediatric Peritoneal Dialysis Set – Cook Medical) in the left upper abdominal quadrant, which allowed the distal coiled end to properly rest in the pelvis.

PD is contraindicated for any abdominal wall defects (omphalocele, gastroschisis), diaphragmatic or abdominal wall disruptions, perforated bowel due to necrotizing enterocolitis, or other reasons where the integrity of the peritoneum is disrupted (e.g., acute abdomen, recent surgery) [84]. In infants with imminent or current intracranial hemorrhage, PD may be preferred as this procedure does not require anticoagulation [85].

Although not a true contraindication, compared to HD or CRRT, PD does not provide adequate ammonia clearance for severe hyperammonemia. In the event that no HD or CRRT is available, starting PD while arranging transport to a medical center with HD and/or CRRT capabilities can be life-saving [85–87].

Depending on the expected duration and the acuity of the problem, neonates can get a surgically placed tunneled permanent catheter. If this is not available, PD can be performed with an angiocatheter, multipurpose drainage catheter (e.g., Cook Mac-Loc Multipurpose Drainage Catheter), or a temporary PD catheter that can be placed bedside with Seldinger technique [82, 84, 88]. Ideally, these temporary approaches should not be used for more than a few days. Surgically

inserted permanent catheters are associated with fewer acute complications [89]. Ideally, a surgical permanent catheter should have a few days (or preferably weeks) to heal before use, but immediate use is often necessary in patients with AKI. If one cannot wait, using small fill volumes should be used to reduce the risk of catheter leak and infection.

Since the use of automated peritoneal dialysis devices (cyclers) requires a significant amount of dead space for tubing and minimal fill volume for accurate functioning, their use in neonates is limited. Instead, manual continuous low-volume cycles at the bedside are usually employed. The manual PD setup involves a Buretrol device to measure volumes, to which the dialysate bag is attached to one end through spikes or a Luer lock, while the other end is connected to the PD catheter via a Y-set. The other limb of the Y-set is connected to the drainage line. An example of a commercially available neonatal/infant manual PD set is shown in Fig. 44.1 (Dialy-Nate system, Utah Medical Products, Midvale, Utah). This pre-assembled closed system with a total priming volume of 63 mL includes a 150 mL burette, a graduated dialysate meter for measuring outflow, and an inline helical infusate warmer. Warming the dialysate is extremely important for the neonate with their higher risk of temperature instability and hypothermia.

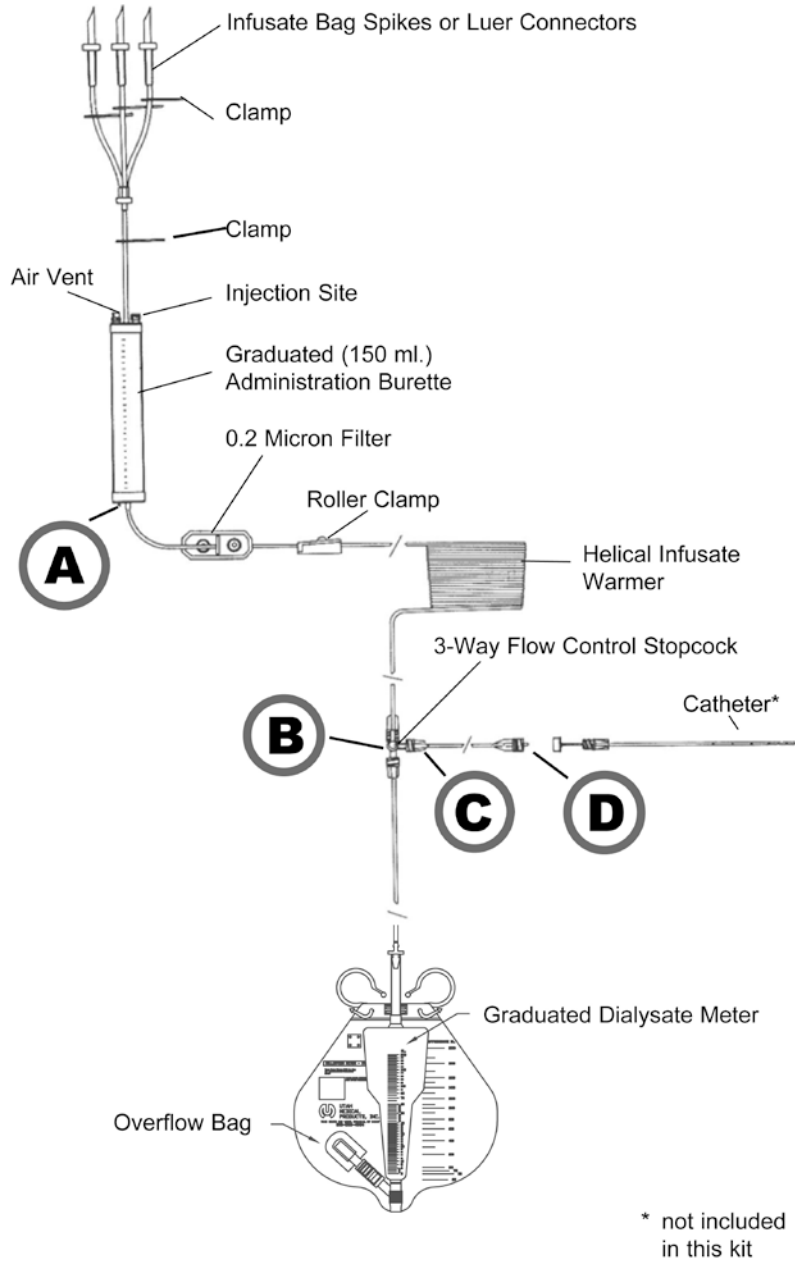
In the acute setting, the default PD cycle duration is 60 minutes. Approximately 10 ml/kg (or 200 ml/m^2) of dextrose-based dialysis fluid fills the abdomen, dwells, and then drains. The fill, dwell, and draining phases should be 5–10, 40–50, and 5–10 minutes in length, respectively. If more clearance of fluid or waste products is needed, then 32 cycles lasting 45 minutes can be performed in 24 hours. Another method to increase clearance is by increasing the dwell volume, but needs to be mitigated with higher chances of leaking from the catheter exit site. Increasing the dextrose concentration can increase ultrafiltration and may be necessary with low fill volumes. If commercially manufactured fluids are not available, they can be locally prepared [90]. Some programs add 500 units of heparin/L to prevent catheter obstruction from blood or fibrin. Potassium and phosphorous can also be added to the dialysate to prevent hypokalemia and hypophosphatemia, respectively, both of which can occur with prolonged frequent exchanges.

In discussions with the treating team, our patient was placed on PD, and the local surgeon placed a tunneled PD catheter in the OR with no complications. Manual PD was started using 30 ml fill volumes (10 ml/kg with 1.5% dextrose) with hourly cycles. The cycles consisted of 10-minute fill times, 40-minute dwell times, and 10-minute drain times. In the first 12 hours, total ultrafiltration was 100 mL, and hyperkalemia, acidosis, and hyperphosphatemia improved. Total protein intake was increased back to 2.5 g/kg/day to account for ongoing losses inherent to PD. At 24 hours after starting PD, a large leak developed around the catheter exit site, and PD could no longer be utilized effectively. Due to ongoing oliguric AKI, a decision was made to start extracorporeal therapy in the form of CRRT (continuous renal replacement therapy).

Extracorporeal Therapies

RRT using extracorporeal therapies has several advantages over PD. The first is that once vascular catheter access is established, the therapy can be started immediately. Second, higher clearances can be achieved, which can be critical in neonates, especially in those with severe hyperammonemia from inborn errors of metabolism [87, 91]. Third, the net ultrafiltration rate can be precisely titrated for the desired effect, and changes can be made in real time as necessary. This differs from fluid removal approaches in PD where the clinician prescribes a specific dextrose concentration, fill volume, and dwell time and then explores empirically what rates of fluid removal are achieved for several hours before the PD prescription is changed.

There are also several disadvantages to extracorporeal therapies. First, the cost of specialized equipment is higher. Second, the nursing expertise is significantly higher. Third, there are risks to anticoagulation. Fourth, there is risk for hemo-



Priming Volumes	
A to B	58 ml
C to D	5 ml
Total	63 ml

Fig. 44.1 Neonatal/infant manual peritoneal dialysis set. (Dialy-Nate system from Utah Medical Products, MidVale, UT)

dynamic instability during initiation. This risk can be mitigated to some degree by priming the circuit with blood in conjunction with steps to make the blood more physiologic before initiation. Finally, compared to older children, placement of a catheter is more challenging and has potentially more complications, especially in situations with significant fluid overload and high ventilation support.

Vascular Access

The ideal location for catheter placement depends on multiple factors including the size of the patient, estimated duration of therapy (cuffed catheters are preferred if the estimated duration of the CRRT will be for at least 2 weeks), urgency of the therapy, and local expertise. Access is achieved with either a double-lumen catheter or two single-lumen catheters (see Table 44.3 for sizes for neonates/infants). For those who will need renal support for more than a few weeks, the preferred location is a right internal jugular catheter (ideally tunneled with a cuff). Femoral and umbilical veins are usually smaller diameter than internal jugular veins, but can be used. With smaller circuits, smaller vascular access (5 or 6 French) can be used to provide adequate flows for these machines.

Fluid to Prime Machine

Whether one is using hemodialysis (HD) or continuous renal replacement therapy (CRRT), the clinician must determine which type of fluid is required to prime the machine as the relatively large extracorporeal volume places a young infant at a higher risk of cardiovascular instability upon initiation of RRT. The extracorporeal volume (ECV)/total blood volume (TBV) has been used as a gauge to determine the type of prime to use. The TBV of a neonate can be esti-

Table 44.3 Central venous catheter types and sizes for neonatal/infant extracorporeal therapies

Weight	Cuffed (tunneled)	Un-cuffed (un-tunneled)
<2.5 kg	[a]Bard 6Fr × 50 cm (Powerline) DLC Right IJ	2 × Single-lumen Cook 3 F or higher single-lumen catheter Cook 4Fr × 5 cm DL Right IJ [b]Cook 5Fr × 5 cm DLC Right IJ [b]Cook 6.5Fr × 12 cm DLC Femoral [a,b]Bard 6Fr × 50 cm (POWERHOHN) DLC Right IJ Femoral Umbilical [b]Gambro 6Fr × 15 cm DLC Femoral Umbilical Medcomp 7Fr × 7 cm DLC Right IJ
>2.5 kg	As Above Medcomp 8Fr × 18 cm DLC with cuff	As Above 2 × Single-lumen 4Fr or higher catheter Medcomp 7Fr × 10 cm DLC Femoral

Fr French, *DLC* double-lumen catheter

Note: The diameter of the catheter needs to be tailored to the size of the vessel by ultrasound. Above are catheters that have been suggested/reported for small infants

[a]PowerHohn and Powerline catheters are designed to cut the desired length

[b]These catheters have been reported in use with circuits with smaller extracorporeal volume (Aquadex, Carpediem, and Nidus)

mated as 80 ml/kg. In general, if the ECV/TBV is <10%, patients can generally tolerate initiation using a saline prime. Currently, for infants, most circuits available will be >10% of the ECV/TBV. An albumin prime can be used when the ECV is 10–15% of the TBV. A blood prime may be preferable when the ECV is >15% of the TBV or for any patients not stable enough for a saline or albumin prime.

Priming the circuit with packed red blood cells (pRBC) can reduce morbidity; however, it is important to recognize that compared to physiologic blood, pRBC are cold, very concentrated, acidic, hyperkalemic, and hypocalcemic. Most centers that perform neonatal CRRT have protocols in place to buffer the acidic environment, reverse hypocalcemia, and dilute the higher hematocrit of pRBCs. Even with these measures, blood primes are not without risk, as blood primes can cause hypothermia, acidosis, hypocalcemia, hyperkalemia, thrombocytopenia, hypotension, and coagulopathy. These risks increase exponentially with smaller-sized infants, those who are often hemodynamically unstable, along with the frequent need of repeated RRT initiation [92].

Continuous Versus Intermittent Duration

Hemodialysis

Intermittent hemodialysis (HD) using standard dialysis machines is the most efficient form of renal support clearance and is usually provided over a 3–4-hour period. However, the main challenge of HD is related to the machines requiring expert nursing care from dialysis-trained personnel. Intermittent hemodialysis can be used if the goals of the therapy can be achieved in a short amount of time. However, if the patient is hemodynamically unstable, it may be very difficult to accomplish the fluid removal goals during a short intermittent therapy.

The dialyzer size should be between 75% and 100% of the infant's total body surface area to minimize the ECV while maintaining effective solute removal. Dialyzers with smaller surface areas of $0.2m^2$ (e.g., Gambro Polyflux 2H, Fresenius FX Paed) and $0.4m^2$ (e.g., Fresenius F3) are available along with low priming volumes (17 mL and 28 mL, respectively). Blood lines designed for neonates with low volumes are also available (e.g., Gambro Phoenix BTS neonatal lines with 40 ml volume and Fresenius 2008K neonatal line options with 29ml and 52 ml). There are no published recommendations for blood flow rates in neonates. Initial blood flows should be prescribed to provide adequate clearance and flow to prevent clotting. Not more than 5% of the body weight should be removed per session with ultrafiltration to maintain hemodynamic stability. Most centers use systemic heparin for anticoagulation during HD. A report of HD in 33 infants <5 kg at a median of 10 days of age revealed that HD can be done safely and effectively in this age group [93]. Only 9/216 (4.2%) of HD treatments had to be stopped prematurely (3 from technical issues and 6 from intractable hypotension). During intermittent HD, the amount of dialysis is very high compared to when it is performed using CRRT; thus the limiting factors that drive clearance are the blood flow, dialyzer, and time.

CRRT

Continuous renal replacement therapy (CRRT) has become a popular modality for renal support in pediatric and adult cohorts. Use of CRRT should be limited to regional centers with the expertise to perform the therapy in neonates.

CRRT poses additional challenges and risks in neonates, even at experienced tertiary children's hospitals. When used, these larger machines necessitate that small children receive CRRT with proportionally larger filters, higher blood flows, massive clearance rates, and proportionally larger vascular catheters for their size, when compared to bigger children [94]. One of the main reasons for the difficulty comes from using CRRT filter sets that result in a very large ECV/TBV ratio. For example, the most commonly used CRRT machine in the United States has an ECV of about 93 ml (Prismaflex with M60 Filter). For this reason (and others), initiation of neonatal CRRT therapy has historically been

fraught with anxiety and hemodynamic compromise when initiating the therapy in small infants. The more critically ill the patient is, and the higher the ECV/TBV ratio, the more challenging the initiation of CRRT will be. For these reasons, many centers do not offer CRRT to any infant, especially very small infants and those who are considered too critically ill to tolerate CRRT initiation.

We chose to start CRRT using the smallest circuit available (Prismaflex M60: ECV = 93 ml). Our surgeons placed a 7 French, 7 cm catheter in the right internal jugular vein. Our infant has a weight of 3.4 kg, with a blood volume of 80 ml/kg = 272 ml. The ECV/TBV of the patient is 93/272 (34%), and a blood prime was indicated for circuit initiation. Blood flow was set at 40 ml/min. A clearance of 25 ml/kg/ hr = 90 ml/hr was prescribed. Because he had no specific risks for bleeding, we performed CRRT using heparin (20 units/kg/hr of heparin bolus followed by 20 units/kg/hr continuous infusion). Infusion rates were adjusted for a goal PTT of 50–70 seconds. Net ultrafiltration rate was prescribed to remove 10 ml/hr after accounting total intake and output.

Newer RRT Machines for Young Infants

In the United States, the most commonly used machine is Prismaflex. The smallest CRRT circuit volume has been 93 ml (Prismaflex M60) until the fall of 2020, when the US FDA issued an emergent use authorization for the use of 60 ml circuit (the HF20 circuit) in children > 8 kg. This filter has been available in Canada, Europe and other countries for several years with good experience. CRRT machines with even smaller ECV should reduce the risks associated with the therapy and improve outcomes. For these reasons, several groups have developed or adapted dialysis and convective clearance devices which use a smaller size circuit. The miniaturization of CRRT devices allows for adequate flows with much smaller diameter catheters. In addition, initiation of CRRT circuit with much lower ECV is for the most part uneventful, even in very small and very critically ill infants [95].

The Newcastle infant dialysis ultrafiltration system (Nidus) [96] has an ECV of around 10 ml and can provide continuous or intermittent dialysis with the use of a 4 French single-lumen catheter (Fig. 44.2a). The circuit uses automated syringe pumps to accomplish four separate steps: (a) remove a volume of blood from the patient, (b) send blood through a dialysis filter that has counter-current dialysis running, (c) return the blood back to the initial syringe pump, and (d) return that volume of blood (now cleaned) back to the patient.

The cardio-renal pediatric dialysis emergency machine (Carpediem™) has available circuits of 27, 34, and 45 ml [96, 97] for filters of 0.075m^2, 0.15m^2, and 0.25m^2, respectively (Fig. 44.2b). By using a smaller blood pump with a unique design, it reduces the peak pressure for a given blood volume, reducing the need for a very wide catheter. A 4.5 French double-lumen catheter can be used to accomplish the flow rates required for this machine. The circuit has to be exchanged daily. The blood flow rate can be titrated from 2 to 40 ml/minute, and it has very precise fluid scales available, minimizing any potential errors of ultrafiltration.

To mitigate concerns posed by CRRT machines with large ECV in relation to blood volume size, Askenazi et al. adapted the Aquadex™ machine (a machine initially designed for ultrafiltration in adults with heart failure) to provide convective clearance by using an independent IV pump to deliver the replacement fluid (Fig. 44.2c). The machine can ultrafilter up to 500 ml/hour. It has an integrated hematocrit detector that can help mitigate any abrupt changes in hematocrit. This system can provide clearance, electrolyte balance, and fluid ultrafiltration with minimal need for interventions during circuit initiation [95]. The biggest drawback to this system is that the replacement pump is not directly in communication with the blood flow pump. Several catheters have been used in the right internal jugular, femoral, and umbilical veins. More recently, use of a 6 French double-lumen catheter (Bard Powerline 6Fr x 50 cm tunneled, Tempe AZ, USA) that is cut to

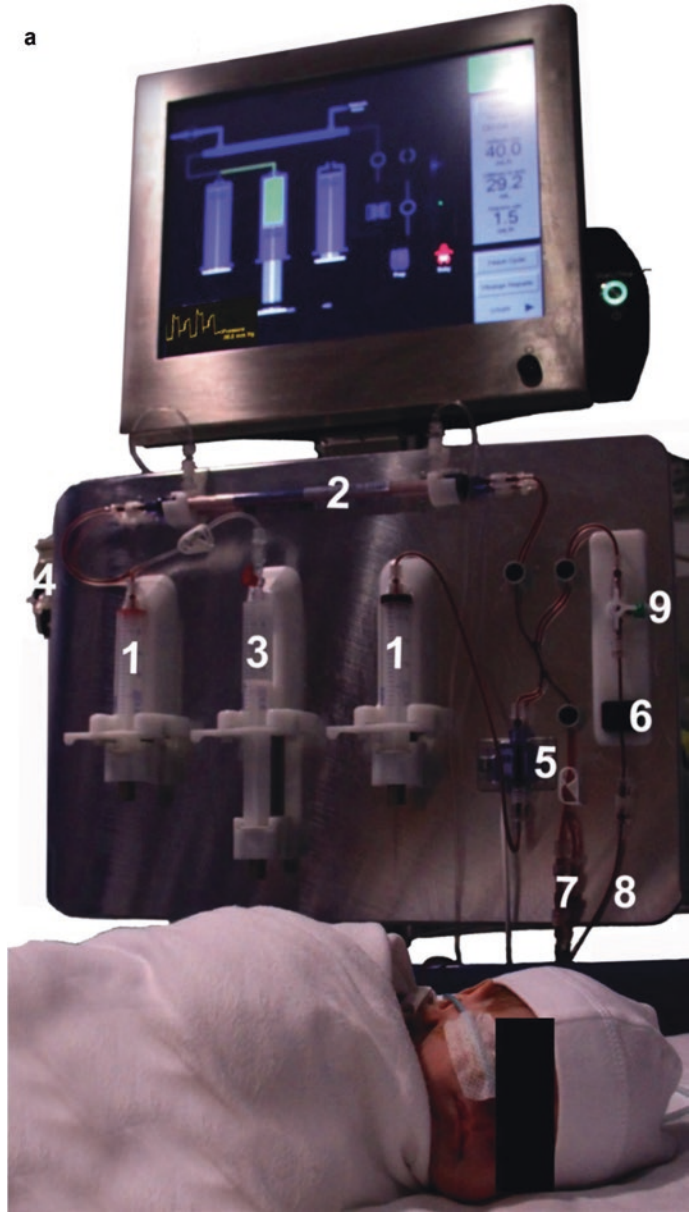
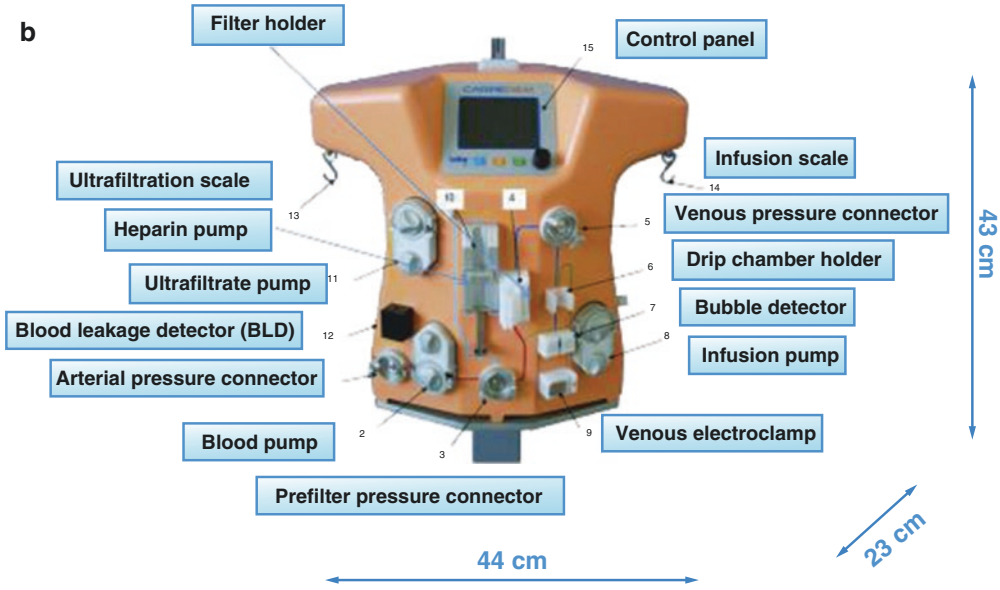


Fig. 44.2 Newer renal replacement therapy devices designed for neonates and young infants. (**a**) The Newcastle infant dialysis ultrafiltration system (Nidus). The circuit has two operating syringes (1), a high-flux polysulfone 0.045 m2 filter (2), a heparin syringe (3), pumped dialysate (4), a pressure transducer (5) and an air-detector (6), and self-primes with 4.3 ml of heparinized saline, giving a minimum operating volume of 9.3 ml. (**b**) The cardio-renal pediatric dialysis emergency machine (Carpediem™). (**c**) Continuous venovenous hemofiltration (CVVH) using the Aquadex™ machine. Heparin is infused through a y-connector attached to the withdraw (access) line of the patient's catheter. Using an in-line medication infusion machine, prereplacement fluid is infused via the proximal pigtail of the circuit. There are two pumps on the machine: the blood pump (which can pump blood to a maximum of 40 ml/min) and the ultrafiltration (UF) pump (which can perform UF to a maximum of 500 ml/h when the blood flow is 40 ml/min). Blood for anticoagulation monitoring is obtained through the distal pigtail of the circuit. A blood warmer is attached to the tubing on the infusion (return) line before the blood is returned to the patient. (Reprinted with permission from Coulthard et al. [56]. Reprinted with permission from Ronco C and Ricci Z. Evolution of the Management of AKI in Neonates. ASN Kidney News Volume. 2015. Reprinted with permission from Askenazi et al. [95])



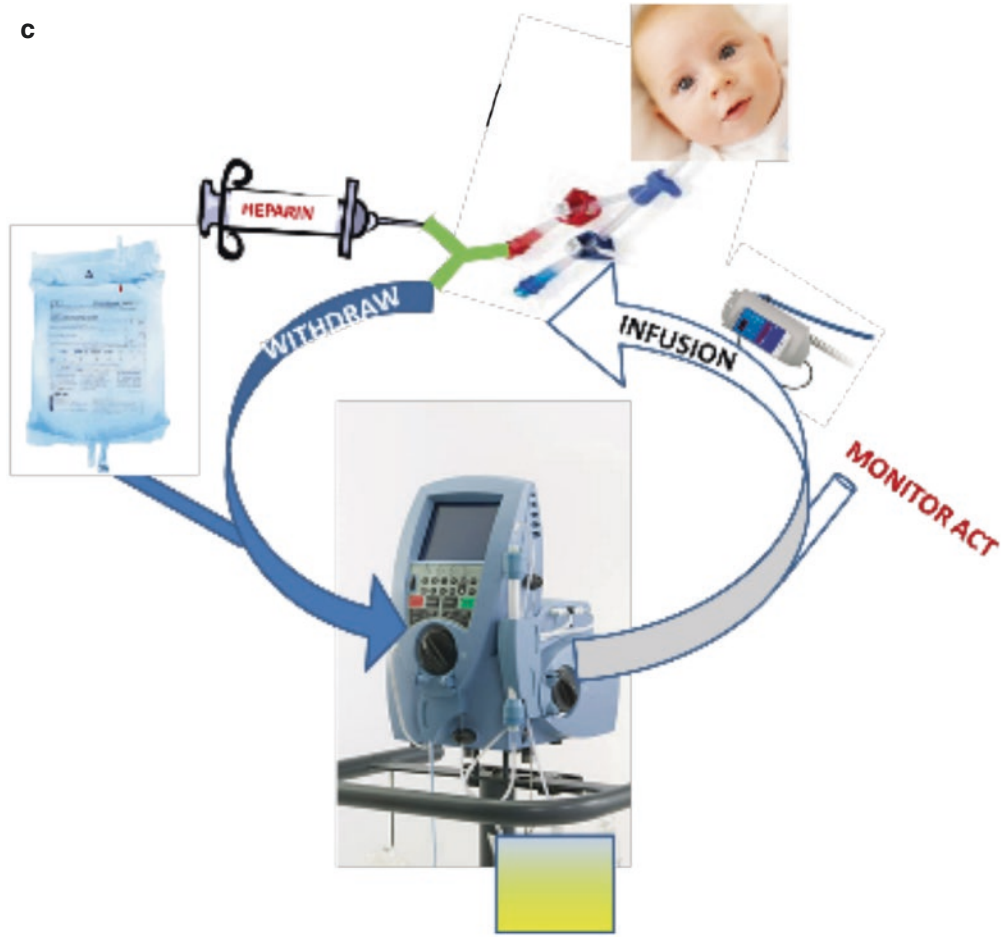


Fig. 44.2 (continued)

the desired length prior has led to fewer complications and longer duration of use compared to other hemodialysis catheters (author personal communication).

Clearly, as these devices become mainstream, there will be lower risks associated with performing extracorporeal forms of RRT in neonates. The risk/benefit ratio will allow for more judicious use and earlier intervention and will likely serve as a profound improvement in the care of critically ill neonates. With the development of smaller filters, it has already become possible to use CRRT in neonates when they require it. This area of investigation and clinical use is exciting, and we anticipate that CRRT for infants will be greatly enhanced with the use of these safer devices.

References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Workgroup ADQI. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.
2. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
3. Kellum JA, Lameire N, Work KAG. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care. 2013;17(1):204.
4. Veille JC, Hanson RA, Tatum K, Kelley K. Quantitative assessment of human fetal renal blood flow. Am J Obstet Gynecol. 1993;169(6):1399–402.
5. Chevalier RL. Developmental renal physiology of the low birth weight pre-term newborn. J Urol. 1996;156(2 pt 2):714–9.
6. Bueva A, Guignard JP. Renal function in preterm neonates. Pediatr Res. 1994;36(5):572–7.
7. Gallini F, Maggio L, Romagnoli C, Marrocco G, Tortorolo G. Progression of renal function in preterm neonates with gestational age < or = 32 weeks. Pediatr Nephrol. 2000;15(1–2):119–24.
8. Zappitelli M, Ambalavanan N, Askenazi DJ, Moxey-Mims MM, Kimmel PL, Star RA, et al. Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop. Pediatr Res. 2017;82(4):569–73.
9. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184–94.
10. Tóth-Heyn P, Drukker A, Guignard JP. The stressed neonatal kidney: from pathophysiology to clinical management of neonatal vasomotor nephropathy. Pediatr Nephrol. 2000;14(3):227–39.
11. Goldstein SL, Currier H, Cd G, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001;107(6):1309–12.
12. Selewski DT, Cornell TT, Lombel RM, Blatt NB, Han YY, Mottes T, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. Intensive Care Med. 2011;37(7):1166–73.
13. van Asperen Y, Brand PL, Bekhof J. Reliability of the fluid balance in neonates. Acta Paediatr. 2012;101(5):479–83.
14. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol. 2013;28(4):661–6.
15. Lee ST, Cho H. Fluid overload and outcomes in neonates receiving continuous renal replacement therapy. Pediatr Nephrol. 2016;31(11):2145–52.
16. Wilder NS, Yu S, Donohue JE, Goldberg CS, Blatt NB. Fluid overload is associated with late poor outcomes in neonates following cardiac surgery. Pediatr Crit Care Med. 2016;17(5):420–7.
17. Mah KE, Hao S, Sutherland SM, Kwiatkowski DM, Axelrod DM, Almond CS, et al. Fluid overload independent of acute kidney injury predicts poor outcomes in neonates following congenital heart surgery. Pediatr Nephrol. 2018;33(3):511–20.
18. Selewski DT, Askenazi DJ, Bridges BC, Cooper DS, Fleming GM, Paden ML, et al. The impact of fluid overload on outcomes in children treated with extracorporeal membrane oxygenation: a multicenter retrospective cohort study. Pediatr Crit Care Med. 2017;18(12):1126–35.
19. Selewski DT, Akcan-Arikan A, Bonachea EM, Gist KM, Goldstein SL, Hanna M, et al. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. Pediatr Res. 2018;
20. Lai WW, Mertens L, Cohen M, Geva T. Echocardiography in pediatric and congenital heart disease: from fetus to adult. 2nd ed. Chichester, West Sussex; Hoboken, NJ: Wiley; 2016. p. 785.
21. Carlotti AP, Carvalho WB. Abdominal compartment syndrome: a review. Pediatr Crit Care Med. 2009;10(1):115–20.
22. Mathew OP, Jones AS, James E, Bland H, Groshong T. Neonatal renal failure: usefulness of diagnostic indices. Pediatrics. 1980;65(1):57–60.
23. Gubhaju L, Sutherland MR, Horne RS, Medhurst A, Kent AL, Ramsden A, et al. Assessment of renal functional maturation and injury in preterm neonates

during the first month of life. Am J Physiol Renal Physiol. 2014;307(2):F149–58.
24. Ishizaki Y, Isozaki-Fukuda Y, Kojima T, Sasai M, Matsuzaki S, Kobayashi Y. Evaluation of diagnostic criteria of acute renal failure in premature infants. Acta Paediatr J. 1993;35(4):311–5.
25. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL, Group H-DFiARFS. High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Am J Kidney Dis. 2004;44(3):402–9.
26. van der Voort PH, Boerma EC, Koopmans M, Zandberg M, de Ruiter J, Gerritsen RT, et al. Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. Crit Care Med. 2009;37(2):533–8.
27. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, Fermanian J. Furosemide in acute oliguric renal failure. A controlled trial. Nephron. 1976;17(1):51–8.
28. Bagshaw SM, Bellomo R, Kellum JA. Oliguria, volume overload, and loop diuretics. Crit Care Med. 2008;36(4 Suppl):S172–8.
29. Laudignon N, Ciampi A, Coupal L, Chemtob S, Aranda JV. Furosemide and ethacrynic acid: risk factors for the occurrence of serum electrolyte abnormalities and metabolic alkalosis in newborns and infants. Acta Paediatr Scand. 1989;78(1):133–5.
30. Brater DC. The In vivo study of drug action: principles and applications of kinetic-dynamic modelling. In. In: van Boxtel CJ, Holford NH, Danhof M, editors. Diuretic pharmacokinetics and pharmacodynamics. Amsterdam: Elsevier Science; 1992. p. 253–75.
31. Prandota J. High doses of furosemide in children with acute renal failure. A preliminary retrospective study. Int Urol Nephrol. 1991;23(4):383–92.
32. Mirochnick MH, Miceli JJ, Kramer PA, Chapron DJ, Raye JR. Furosemide pharmacokinetics in very low birth weight infants. J Pediatr. 1988;112(4):653–7.
33. Singh NC, Kissoon N, al Mofada S, Bennett M, Bohn DJ. Comparison of continuous versus intermittent furosemide administration in postoperative pediatric cardiac patients. Crit Care Med. 1992;20(1):17–21.
34. Luciani GB, Nichani S, Chang AC, Wells WJ, Newth CJ, Starnes VA. Continuous versus intermittent furosemide infusion in critically ill infants after open heart operations. Ann Thorac Surg. 1997;64(4):1133–9.
35. Wilson NJ, Adderley RJ, McEniery JA. Supraventricular tachycardia associated with continuous furosemide infusion. Can J Anaesth. 1991;38(4 Pt 1):502–5.
36. Bagshaw SM, Darmon M, Ostermann M, Finkelstein FO, Wald R, Tolwani AJ, et al. Current state of the art for renal replacement therapy in critically ill patients with acute kidney injury. Intensive Care Med. 2017;43(6):841–54.
37. Delgado MM, Rohatgi R, Khan S, Holzman IR, Satlin LM. Sodium and potassium clearances by the maturing kidney: clinical-molecular correlates. Pediatr Nephrol. 2003;18(8):759–67.
38. Sulyok E, Németh M, Tényi I, Csaba IF, Varga F, György E, et al. Relationship between maturity, electrolyte balance and the function of the renin-angiotensin-aldosterone system in newborn infants. Biol Neonate. 1979;35(1–2):60–5.
39. Stefano JL, Norman ME, Morales MC, Goplerud JM, Mishra OP, Delivoria-Papadopoulos M. Decreased erythrocyte Na+,K(+)-ATPase activity associated with cellular potassium loss in extremely low birth weight infants with nonoliguric hyperkalemia. J Pediatr. 1993;122(2):276–84.
40. Sato K, Kondo T, Iwao H, Honda S, Ueda K. Internal potassium shift in premature infants: cause of nonoliguric hyperkalemia. J Pediatr. 1995;126(1):109–13.
41. Lui K, Thungappa U, Nair A, John E. Treatment with hypertonic dextrose and insulin in severe hyperkalaemia of immature infants. Acta Paediatr. 1992;81(3):213–6.
42. Greenough A, Emery EF, Brooker R, Gamsu HR. Salbutamol infusion to treat neonatal hyperkalaemia. J Perinat Med. 1992;20(6):437–41.
43. Ohlsson A, Hosking M. Complications following oral administration of exchange resins in extremely low-birth-weight infants. Eur J Pediatr. 1987;146(6):571–4.
44. Rugolotto S, Gruber M, Solano PD, Chini L, Gobbo S, Pecori S. Necrotizing enterocolitis in a 850 gram infant receiving sorbitol-free sodium polystyrene sulfonate (Kayexalate): clinical and histopathologic findings. J Perinatol. 2007;27(4):247–9.
45. Bennett LN, Myers TF, Lambert GH. Cecal perforation associated with sodium polystyrene sulfonate-sorbitol enemas in a 650 gram infant with hyperkalemia. Am J Perinatol. 1996;13(3):167–70.
46. Grammatikopoulos T, Greenough A, Pallidis C, Davenport M. Benefits and risks of calcium resonium therapy in hyperkalaemic preterm infants. Acta Paediatr. 2003;92(1):118–20.
47. Thompson K, Flynn J, Okamura D, Zhou L. Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate(®)) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. J Ren Nutr. 2013;23(5):333–9.
48. Cameron JC, Kennedy D, Feber J, Wong E, Geier P, Vaillancourt R. Pretreatment of infant formula with sodium polystyrene sulfonate: focus on optimal amount and contact time. Paediatr Drugs. 2013;15(1):43–8.
49. Taylor JM, Oladitan L, Carlson S, Hamilton-Reeves JM. Renal formulas pretreated with medications alters the nutrient profile. Pediatr Nephrol. 2015;30(10):1815–23.
50. Edelmann CM, Soriano JR, Boichis H, Gruskin AB, Acosta MI. Renal bicarbonate reabsorption and hydrogen ion excretion in normal infants. J Clin Invest. 1967;46(8):1309–17.

51. Brodehl J. Assessment and interpretation of the tubular threshold for phosphate in infants and children. Pediatr Nephrol. 1994;8(5):645.
52. Ferrara E, Lemire J, Reznik VM, Grimm PC. Dietary phosphorus reduction by pretreatment of human breast milk with sevelamer. Pediatr Nephrol. 2004;19(7):775–9.
53. Raaijmakers R, Houkes LM, Schroder CH, Willems JL, Monnens LA. Pre-treatment of dairy and breast milk with sevelamer hydrochloride and sevelamer carbonate to reduce phosphate. Perit Dial Int. 2013;33(5):565–72.
54. Spinozzi NS, Nelson P. Nutrition support in the newborn intensive care unit. J Ren Nutrition. 1996;6(4):188–97.
55. Nutrition of the preterm infant: Scientific basis and practical guidelines. 2 ed. Tsang RC, Uauy R, Koletzko B, Zlotkin S, editors. Cincinnati: Digital Education Publishing, Inc; 2005.
56. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med. 2016;374(12):1111–22.
57. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics. 2006;117(1):67–74.
58. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. J Matern Fetal Neonatal Med. 2014;27(14):1485–90.
59. Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2011;11:CD005091.
60. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis. 2009;3(4):222–6.
61. Cattarelli D, Spandrio M, Gasparoni A, Bottino R, Offer C, Chirico G. A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed. 2006;91(2):F80–4.
62. Bakr AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia–a study in a developing country. Pediatr Nephrol. 2005;20(9):1249–52.
63. Jenik AG, Ceriani Cernadas JM, Gorenstein A, Ramirez JA, Vain N, Armadans M, et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics. 2000;105(4):E45.
64. Raina A, Pandita A, Harish R, Yachha M, Jamwal A. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr. 2016;105(10):e448–51.
65. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. Clin J Am Soc Nephrol. 2014;9(12):2036–43.
66. Aviles-Otero N, Kumar R, Khalsa DD, Green G, Carmody JB. Caffeine exposure and acute kidney injury in premature infants with necrotizing enterocolitis and spontaneous intestinal perforation. Pediatr Nephrol. 2019;34(4):729–36.
67. Harer MW, Askenazi DJ, Boohaker LJ, Carmody JB, Griffin RL, Guillet R, et al. Association between early caffeine citrate administration and risk of acute kidney injury in preterm neonates: results from the AWAKEN study. JAMA Pediatr. 2018;172(6):e180322.
68. Sinha R, Dugar P. Rasburicase for acute kidney injury. Indian Pediatr. 2013;50(11):1051–2.
69. Canpolat FE, Cekmez F. Rasburicase for hyperuricemia in an extremely low birth weight infant. Indian Pediatr. 2011;48(7):573–4.
70. Hobbs DJ, Steinke JM, Chung JY, Barletta GM, Bunchman TE. Rasburicase improves hyperuricemia in infants with acute kidney injury. Pediatr Nephrol. 2010;25(2):305–9.
71. Nguyen AP, Ness GL. Hemolytic anemia following rasburicase administration: a review of published reports. J Pediatr Pharmacol Ther. 2014;19(4):310–6.
72. Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. J Pediatr. 1980;97(6):893–900.
73. Gortner L, Leupold D, Pohlandt F, Bartmann P. Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. Acta Paediatr Scand. 1989;78(5):706–11.
74. Selewski DT, Charlton JR, Jetton JG, Guillet R, Mhanna MJ, Askenazi DJ, et al. Neonatal acute kidney injury. Pediatrics. 2015;136(2):e463–73.
75. Moghal NE, Embleton ND. Management of acute renal failure in the newborn. Semin Fetal Neonatal Med. 2006;11(3):207–13.
76. Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Health. 2017;1(3):184–94.
77. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med. 2017;376(1):11–20.
78. Raina R, Chauvin AM, Bunchman T, Askenazi D, Deep A, Ensley MJ, et al. Treatment of AKI in developing and developed countries: an international survey of pediatric dialysis modalities. PLoS One. 2017;12(5):e0178233.
79. Chan KL, Ip P, Chiu CS, Cheung YF. Peritoneal dialysis after surgery for congenital heart disease in infants and young children. Ann Thorac Surg. 2003;76(5):1443–9.

80. Sasser WC, Dabal RJ, Askenazi DJ, Borasino S, Moellinger AB, Kirklin JK, et al. Prophylactic peritoneal dialysis following cardiopulmonary bypass in children is associated with decreased inflammation and improved clinical outcomes. Congenit Heart Dis. 2014;9(2):106–15.
81. Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP, Morales DL, Krawczeski CD. Peritoneal dialysis vs furosemide for prevention of fluid overload in infants after cardiac surgery: a randomized clinical trial. JAMA Pediatr. 2017;171(4):357–64.
82. Yu JE, Park MS, Pai KS. Acute peritoneal dialysis in very low birth weight neonates using a vascular catheter. Pediatr Nephrol. 2010;25(2):367–71.
83. Harshman LA, Muff-Luett M, Neuberger ML, Dagle JM, Shilyansky J, Nester CM, et al. Peritoneal dialysis in an extremely low-birth-weight infant with acute kidney injury. Clin Kidney J. 2014;7(6):582–5.
84. Cullis B, Abdelraheem M, Abrahams G, Balbi A, Cruz DN, Frishberg Y, et al. Peritoneal dialysis for acute kidney injury. Perit Dial Int. 2014;34(5):494–517.
85. Daschner M, Schaefer F. Emergency dialysis in neonatal metabolic crises. Adv Ren Replace Ther. 2002;9(1):63–9.
86. Arbeiter AK, Kranz B, Wingen AM, Bonzel KE, Dohna-Schwake C, Hanssler L, et al. Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. Nephrol Dial Transplant. 2010;25(4):1257–65.
87. Picca S, Dionisi-Vici C, Bartuli A, De Palo T, Papadia F, Montini G, et al. Short-term survival of hyperammonemic neonates treated with dialysis. Pediatr Nephrol. 2015;30(5):839–47.
88. Auron A, Warady BA, Simon S, Blowey DL, Srivastava T, Musharaf G, et al. Use of the multipurpose drainage catheter for the provision of acute peritoneal dialysis in infants and children. Am J Kidney Dis. 2007;49(5):650–5.
89. Bridges BC, Askenazi DJ, Smith J, Goldstein SL. Pediatric renal replacement therapy in the intensive care unit. Blood Purif. 2012;34(2):138–48.
90. Cullis B, Feehally J. Locally prepared solutions for treating AKI in low-resource environments. Perit Dial Int. 2018;38(4):240–1.
91. Rajpoot DK, Gargus JJ. Acute hemodialysis for hyperammonemia in small neonates. Pediatr Nephrol. 2004;19(4):390–5.
92. Fleming GM, Askenazi DJ, Bridges BC, Cooper DS, Paden ML, Selewski DT, et al. A multicenter international survey of renal supportive therapy during ECMO: the Kidney Intervention During Extracorporeal Membrane Oxygenation (KIDMO) group. ASAIO J. 2012;58(4):407–14.
93. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int. 1994;45(3):903–6.
94. Askenazi DJ, Goldstein SL, Koralkar R, Fortenberry J, Baum M, Hackbarth R, et al. Continuous renal replacement therapy for children ≤10 kg: a report from the prospective pediatric continuous renal replacement therapy registry. J Pediatr. 2013;162(3):587–92.
95. Askenazi D, Ingram D, White S, Cramer M, Borasino S, Coghill C, et al. Smaller circuits for smaller patients: improving renal support therapy with Aquadex. Pediatr Nephrol. 2016;31(5):853–60.
96. Coulthard MG, Crosier J, Griffiths C, Smith J, Drinnan M, Whitaker M, et al. Haemodialysing babies weighing <8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): comparison with peritoneal and conventional haemodialysis. Pediatr Nephrol. 2014;29(10):1873–81.
97. Ronco C, Garzotto F, Brendolan A, Zanella M, Bellettato M, Vedovato S, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM). Lancet. 2014;383(9931):1807–13.

Acute Kidney Injury in Less Well-Resourced Countries

45

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Introduction

Acute kidney injury (AKI) is a clinical syndrome characterized by rapid decline in renal function resulting in accumulation of nitrogenous waste and disturbed fluid and electrolyte homeostasis. A uniformly accepted definition of AKI based on blood level of creatinine and urine output has helped understand the burden of illness and its impact on outcome. The management of AKI requires knowledge of fluid-electrolyte homeostasis and understanding regarding renal replacement therapy. AKI is associated with short- and long-term complications, and an increased risk of mortality. The clinical syndrome of AKI is the same in less well-resourced countries as in high-income countries (HIC), but AKI etiology and presentation are often different, and management is made more challenging in many settings by the limited available resources. In this chapter, we review the current understanding of the syndrome of AKI in children and focus on the management strategies currently available in less well-resourced countries.

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Epidemiology and Etiology

The incidence of AKI in children is not precisely known. A systematic review involving primarily children cared for in high-income countries (HIC) that used a KDIGO-equivalent definition of AKI showed a pooled prevalence of 33.7% in hospitalized children and AKI-associated mortality of ~14% [1]. In a large multicenter epidemiologic study with a similar patient cohort (AWARE), 26% of critically ill children developed AKI, including 11.6% with severe AKI [2]. In another multicenter study in neonates (AWAKEN), the incidence of AKI was almost 30% [3]. Patients undergoing surgery for repair of congenital heart disease are at high risk of AKI, with an estimated incidence of 30–65% [4]. AKI is common in non-critically ill hospitalized patients with a reported incidence of 4–6%. Exposure to nephrotoxic drugs is another important risk factor.

AKI in the well-resourced world predominately occurs in hospital settings and is associated with multiple risk factors (e.g., sepsis, hypotension, following surgery) and use of nephrotoxic agents or radiocontrast agents. In low and low-middle-income countries (LLMIC), AKI is chiefly community-acquired and secondary to a single illness, e.g., gastroenteritis, hemolytic uremic syndrome (HUS), dengue, leptospirosis, or malaria. A recent global study confirmed that patients with community-acquired stage III AKI had high mortality in low-income countries,

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compared to high-income countries (HIC) [5]. Preventive measures are thus likely to be relatively more effective in low-income countries.

Since AKI is a heterogeneous syndrome, the primary mechanism resulting in renal injury is not the same for all causes. Prerenal causes include dehydration, wherein serum creatinine rises due to a functional adaptive drop in the glomerular filtration rate (GFR) and is fluid responsive. Differentiation between fluid responsive prerenal causes and other prerenal causes of acute tubular necrosis is important, since timely and appropriate fluid administration can help in reducing further renal injury.

The causes and presentation of AKI in LLMIC differ from that seen in HIC. The epidemiology is not well understood due to late presentation to hospitals, under-reporting, and reduced capacity to provide intensive care to severely ill patients. AKI complicates 1–5% of patients with malaria, 20–85% with leptospirosis, and ~2% of patients with dengue hemorrhagic fever and dengue shock syndrome. Hemorrhagic fever associated with hanta virus and AKI are common in parts of Asia and Latin America. Two reports from India suggest that the incidence of AKI was 5–9% in inpatient wards and 25–36% in intensive care units. The pattern of hospital-acquired AKI in tertiary hospitals in low-income countries is similar to that in high-income countries.

In rural or deprived areas with unsatisfactory health infrastructures, AKI is usually a community-acquired disease, affecting young and previously healthy individuals. The chief causes of AKI in the developing world are diarrhea, septicemia, and endemic infections such as malaria, leptospirosis, and rickettsial infections. HUS is an important cause of renal failure that often requires renal replacement therapy. Appropriate use of antibiotics for skin and throat infections has led to a decline in AKI due to post-infectious glomerulonephritis. Other causes include postsurgical complications, snake bites, and intake of traditional and nephrotoxic medicines. Patients with HIV/AIDS may develop AKI in association with infections, hypovolemia, and use of nephrotoxic antiretroviral drugs. Drug-induced hemolysis can occur with deficiency of glucose-6-phosphate dehydrogenase, frequently seen (15–20%) in north-west India, eastern Africa, and Nigeria.

Epidemics of AKI can occur after disasters, e.g., earthquakes or hurricanes, and are largely attributed to rhabdomyolysis resulting in crush syndrome. Venomous snake bites account for a proportion of patients with AKI in India, Burma, and Thailand. Exposure to industrial chemicals, including copper sulfate, might cause AKI in the tropics. Traditional remedies from plant toxins and indigenous delicacies, e.g., djenkol beans and mushrooms, may lead to AKI in Africa and Southeast Asia. Renal stones are an important cause of obstructive uropathy in northeast Africa and western Asia.

Shiga toxin-associated HUS, due to gastrointestinal infection with enterohemorrhagic *E. coli* (EHEC) or *Shigella dysenteriae*, is the predominant cause of AKI in the developed world and in many developing countries. Improved hygiene and appropriate use of antibiotics has resulted in a declining, and almost absent transmission of *S. dysenteriae* in India. Tertiary care centers in India therefore encounter more patients with atypical HUS than Shiga toxin-associated disease. Infection was the most common cause of pediatric AKI in a tertiary hospital in south India during 2010–11; non-communicable diseases and drug use were also notable.

In Nigeria, primary kidney disease (39%; mostly acute glomerulonephritis and nephrotic syndrome), sepsis (26%), and malaria (11%) were chief causes of AKI. Accidental contamination of medications can lead to epidemics of pediatric deaths from AKI, such as occurred with diethylene glycol contamination of agents prescribed for cough and fever in Haiti, Bangladesh, and India.

Diagnostic Evaluation (See Also Chaps. 43 and 44)

Clinical Evaluation

In patients with oliguria, the history should include questions on prerenal causes: vomiting, diarrhea, blood and volume loss, and fluid intake

in the last 24-hours. Acute tubular necrosis is the chief cause of AKI in hospitalized children and occurs in multiple settings: sepsis with capillary leak, burns, cardiac dysfunction, and inadequate fluid replacement. Attention is given to fluid balance; negative balance suggests dehydration, and progressive increase in weight indicates fluid accumulation.

History is obtained for features of the underlying cause: edema, hematuria, hypertension (glomerulonephritis); dysentery, pallor, thrombocytopenia (hemolytic uremic syndrome); sudden pallor, jaundice, cola-colored urine (intravascular hemolysis); rash, arthritis (SLE, vasculitis); abdominal colic, hematuria, dysuria (nephrolithiasis); and interrupted urinary stream, palpable urinary bladder (obstruction of lower urinary tract). Urine output is often preserved in patients with AKI secondary to nephrotoxic medications and radiocontrast agents. Anuria may be seen in patients with urinary tract obstruction, cortical necrosis, bilateral vascular occlusion, and severe glomerulonephritis. Polyuria is seen in patients with partial ureteral obstruction and AKI with pre-existing tubular disorders.

The diagnosis of AKI depends on serial monitoring of serum creatinine. Although efforts have been made to identify biomarkers that detect injury of renal tissue, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18, these so far have limited roles in the diagnosis of AKI.

Laboratory Evaluation

Investigations to confirm the etiology of AKI, assess severity, and detect complications are routinely performed. Prerenal conditions should be distinguished from intrinsic causes. In established acute tubular necrosis, diminished tubular function results in high urine sodium (>40 mEq/L) and dilute urine (<300 mOsm/kg). In the prerenal state, GFR is reduced but tubular reabsorption is normal; hence urine sodium is low (<20 mEq/L), fractional excretion of sodium is low (<1%), and there is an increased ratio of blood urea nitrogen to creatinine (>20). Peripheral smear is examined for features of hemolytic anemia and thrombocytopenia as typically seen in hemolytic uremic syndrome (HUS). Urinalysis helps in the evaluation of acute glomerulonephritis, indicated by proteinuria, hematuria, and red cell casts. Epithelial cells and muddy brown tubular casts suggest the diagnosis of ATN. Serum C3 and ASO/Anti-DNAse B titers are often helpful in the diagnosis of patients with post-infectious glomerulonephritis. An ultrasound kidney scan with Doppler is the most important radiological investigation for evaluating the etiology of AKI. Ultrasound scan allows delineation of kidney anatomy and identification of congenital anomalies of the kidney and urinary tract. Doppler ultrasonography can identify reduced renal blood flow and ischemic causes of AKI.

Patients with AKI should be screened for associated complications, including fluid overload, as will be discussed later in this chapter [6] Clinical evaluation should focus on detection of hypertension, signs of fluid overload, acidosis, and anemia. Laboratory investigations include blood levels of electrolytes, urea, creatinine, bicarbonate, and hemoglobin. An electrocardiogram is done for features of potassium excess and a chest x-ray for fluid overload. Most patients with AKI do not require renal biopsy. A biopsy is considered in patients where the histology is likely to modify therapy and enable recovery of renal function, as in patients with rapidly progressive glomerulonephritis, acute interstitial nephritis, and vasculitis. Renal biopsy should be considered if the etiology of AKI is unclear and with a prolonged course of AKI lasting more than 3–4 weeks.

Management

In a patient with suspected prerenal AKI, especially in the setting of oligo-anuria, assessment of intravascular volume is necessary. Correction of intravascular volume with IV fluids leads to better kidney perfusion and increased urine output. Suspected hypovolemia is initially corrected by administration of 20 ml/kg of an isotonic solution over 45–60 minutes. During fluid administration,

vital signs and central venous pressure should be monitored to determine adequacy of fluid replacement and avoid overhydration. If hypovolemia does not improve despite two 20 ml/kg fluid boluses, therapy with vasopressors should be considered. If despite fluid volume loading urine output is less than 1 ml/kg/h after 2-h and there are no signs of intravascular volume deficit, furosemide can be administered IV at a dose of 1–2 mg/kg. Failure of furosemide to increase urine output suggests an intrinsic cause of AKI. As noted above, all patients with AKI should undergo kidney ultrasonography to evaluate kidney size and exclude urinary tract obstruction.

Principles of management of established AKI include supportive care with attention to fluids and nutrition, treatment of complications, therapy of the underlying disorder, and renal replacement therapy if indicated.

Therapy of Complications

Patients with AKI and oligo-anuria should be screened for life-threatening complications including hyperkalemia, hypertension, pulmonary edema, and metabolic acidosis. Hyperkalemia is a serious complication that can result in arrhythmias and sudden death. Urgent treatment is instituted depending on serum potassium levels and ECG changes. Hyponatremia is related to hypotonic fluid administration and is managed by restricted fluid intake. Patients with sodium level >125 mEq/L are usually asymptomatic; those with symptomatic hyponatremia require therapy with 3% saline. Patients showing metabolic complications should be considered for early renal replacement therapy.

Specific therapy is possible in a small proportion of patients, including those with crescentic glomerulonephritis, lupus nephritis, interstitial nephritis, and atypical HUS. Patients with urinary tract obstruction often require bladder catheterization or urinary tract diversion through interventional radiology or urologic surgery.

Management of Fluid and Electrolytes

Fluid overload >10–15% is shown to be associated with an increased risk of mortality. Fluid management should be meticulous in order to mitigate this complication. Daily fluid intake should be restricted to insensible losses (400 ml/m^2 body surface area) and ongoing renal and gastrointestinal losses. Insensible losses are replaced intravenously with 10% dextrose, while urine and extrarenal losses are replaced with 0.45% saline in 5% dextrose. The oral route for fluid therapy is preferred, since it enables delivery of oral nutrition. In fluid overloaded patients, less than the total urine output should be replaced to promote negative balance. The daily fluid prescription should be guided by strict input and output monitoring, daily weight, physical examination, and serum sodium. Judicious fluid administration with appropriate fluid composition should allow 0.5–1% weight loss per day in fluid overloaded patients. Low serum sodium, hypertension, and failure to lose weight suggest excessive fluid intake, while weight loss and increasing sodium concentration suggest inadequate free water replacement. Patients with oligo-anuria are at risk of hyperkalemia; potassium-containing fluids should be avoided. Sodium intake should be restricted to 2–3 mEq/kg/day to avoid hypernatremia and fluid retention. In the setting of non-oliguric AKI, patients may lose excessive fluid and electrolytes and need potassium and sodium supplements. Patients with prolonged duration of AKI may develop hyperphosphatemia, which is managed with dietary phosphate restriction and oral phosphate binders.

Pharmacologic Therapy

There are limited data on the efficacy of pharmacologic agents for therapy of AKI. While dopamine in low doses improves renal blood flow and sodium excretion, this effect is short lasting and quite variable. There is no evidence that use of low-dose dopamine or fenoldopam prevents or improves renal recovery in AKI. Intravenous

furosemide may increase urine output in some patients, but there is no evidence that it improves renal recovery or long-term prognosis of patients with AKI. A single dose of theophylline (5–8 mg/kg/day) has been shown to reduce the incidence of severe AKI in term neonates with severe birth asphyxia [7].

Nutrition

Patients with AKI are critically ill, have increased metabolic requirements, and show protein catabolism. Adequate nutritional supplementation is a crucial component of AKI management. Protein intake should be 0.8–1.2 g/kg/day, which may be increased to 1.0–1.5 g/kg/day in patients on peritoneal or hemodialysis. Patients should receive 60–70 Cal/kg/day, which is 20–30% above the basal needs. Enteral feeding is preferred for patients with AKI. Patients on dialysis require supplementation of water-soluble vitamins and micronutrients [8, 9].

Fluid Administration

In LLMIC, the majority of cases of AKI are due to malaria, diarrhea, snake bites, and sepsis. Treatment includes the administration of intravenous fluids, which has become controversial. There is no clear consensus on the following questions:

- Which fluid?
- How much?
- Over what time period?
- Intravenous or oral?
- What percentage fluid overload is acceptable – 10% or 20%? [10]

Fluid Boluses

The role of fluid boluses in the management of acute AKI is controversial. One study which sparked this discussion was the FEAST trial [11] which was conducted in East Africa looking at bolus fluids in septic children. Poorer outcomes were seen in those receiving boluses. Subsequent publications have sought to explain this observation without coming to a clear conclusion [12], but the FEAST trial has raised awareness that too much intravenous fluid given too rapidly in sick children can be deleterious. As a result, the World Health Organization (WHO) and numerous international pediatric bodies (e.g., American Academy of Pediatrics) have advised caution when administering intravenous fluid rapidly or in large volumes without intermittent clinical assessment.

Sepsis and septic shock are frequently associated with AKI. Studies of early goal-directed therapies (EGDT) for septic shock in adults have not been as promising as originally thought; there have been no large trials of EGDT in pediatrics [13]. One meta-analysis confirmed that EGDT as a packaged protocol of care was not superior to usual care, with questions remaining regarding the most effective fluid and vasopressor regimens, the role of hemodynamic monitoring including central venous pressure measurement and appropriate targets in the resuscitation of patients with sepsis and septic shock. The future of sepsis therapy may lie with a more individualized approach with understanding of the complex interplay among host genetics, individual pathophysiological features, and the infective agent. Another hypothesis that AKI is due to renal microcirculatory alterations is currently being studied using the sublingual microcirculation as a surrogate for the renal microcirculation [14].

In children in LLMIC, many intensive care therapies such as central lines and vasopressors may not be easily available or even affordable and thus the emphasis remains on fluid therapy. The predominant use of 0.9% saline in the management of AKI has been questioned. This is a challenge in LLMIC as 0.9% saline is inexpensive and easily available. An alternative for intravenous fluid use, Ringer's lactate, is now being used in many centers with the lactated base being helpful in treating acidosis. Individuals may be concerned about the potassium content of 4 mmol/l in this fluid, but this does not usually result in adverse events.

Fluid Overload

Studies in well-resourced countries have shown that fluid overload in a pediatric intensive care setting has a higher incidence of renal replacement therapy requirement (in the form of continuous renal replacement therapy (CRRT)), as well as higher morbidity and mortality [10, 15].

The degree of fluid overload (%FO) at CRRT initiation can be calculated using the following formula [16]

%FO = (Fluid In - Fluid Out)/(PICU admission weight) × 100% Stuart Goldstein and colleagues' work with the Prospective Pediatric CRRT Registry [16] demonstrated that fluid overload of >20% over admission weight was associated with poorer outcomes and the need for CRRT. This is very relevant in LLMIC as this is a relatively easy measurement. The above formula requires only admission weights and calculations of "fluid in and out" without any sophisticated technology. Establishing this admission weight baseline with regular fluid monitoring has become accepted practice even in resource-poor settings, and will reduce the risk of excessive fluid resuscitation progressing to fluid overload requiring removal by dialysis/hemofiltration which may not be available (Fig. 45.1) [6].

Drugs to Remove Fluid

Managing a child who is passing at least some urine is easier than managing an anuric patient, especially in areas where dialysis is not available.

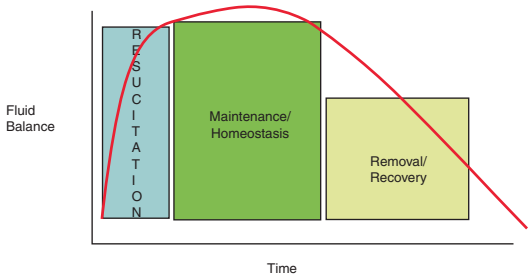

Fig. 45.1 The acute kidney injury fluid epidemiology paradigm and a proposed fluid accumulation 3-phase conceptual model for the patient with acute kidney injury. (Reprinted with permission from Goldstein [6]. SAGE Publications)

Furosemide is a controversial drug for use in the oliguric or anuric AKI patient raising concerns for the increased work of the kidney as well as the potential of ototoxicity. Furosemide, however, is an inexpensive drug that is easily available in most LLMIC where it is used either as 1 mg/kg/dose boluses 6–8-hourly or even as an infusion (0.1–1 mg/kg/h iv infusion).

Aminophylline has been used intermittently in the past, mainly in neonatology as a supplementary diuretic,[7], and there is some new work suggesting that the use of a combination of furosemide and aminophylline (1 mg/kg/dose 6 hourly iv infusion) works well to produce a diuresis. This could be trialed in a patient before switching to CRRT in resource-limited cases.

Drug Administration

Many drugs, both conventional and alternative preparations, have the potential to cause or contribute to AKI. Common and easily available drugs which are implicated in AKI include non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen for the treatment of fever or pain in children. This is often given in the face of poor feeding, malnutrition, and dehydration resulting in a second "hit" to kidneys which may already be vulnerable.

Aminoglycosides are also implicated in AKI and are both cheap and easily available, resulting in use as first-line therapy for sepsis. These drugs are often given without monitoring drug levels as drug levels may not be available on the whole or just too costly to do routinely.

Radiocontrast used in investigations such as CT scans or cardiac catheterization is also implicated in drug-related AKI and may in some cases be prevented by pre-hydration, which is achievable in less well-resourced areas.

In severely ill patients, inotropes may also be added. Recent studies have shown that the use of Dopamine in sepsis can be associated with an increase in mortality compared to Adrenaline (epinephrine) [17]. This is thought to be due to Dopamine impairment of the cellular immune function during sepsis. These drugs are often

used to support blood pressure in septic patients to improve renal perfusion which is decreased in AKI.

Adrenaline (epinephrine) is a cheap and easily available drug which can be used as a dilute peripheral infusion (in situations where ICU and central venous access are not available) and has value in sepsis where fluid boluses have failed to improve perfusion (starting Adrenaline infusion at 0.02 mcg/kg/min).

Traditional medications which come in many forms have also been responsible for AKI in many situations. These drugs are often produced with local substances, the identity of which may not be known, as well as the side effects thereof. Sclerosant agents can result in both poor feeding if given orally or severe diarrhea and bowel necrosis if given rectally. Family education should be given to prevent this and should be happening at the community level.

Clean water security is probably one of the most important ways of preventing AKI, and the use of chlorine tablets or boiling and filtering water is essential to teach even at school level.

New ideas such as the use of used dialyzers in a membrane filtration device have been implemented in Ghana – *Easy Water for Everyone* (https://www.easywaterforeveryone.org)

This simple strategy has the potential for preventing AKI from diarrheal disease in less well-resourced communities.

Snake and insect bites are also responsible for AKI in many regions. In Africa, malaria is responsible for much AKI morbidity and is one of the most frequent causes of mortality. This can be prevented to some extent by insecticide spraying and mosquito nets. Work on a malaria vaccine is at a fairly advanced stage and is eagerly awaited.

Renal Replacement Therapy (RRT): Table 45.1

In situations where conservative management of AKI has failed, early initiation of RRT may prevent complications and reduce mortality [18]. Advances in the use of RRT in pediatrics have led to a higher standard of care for young and critically ill patients. The type of RRT chosen for treatment of both AKI as well as end-stage kidney disease (ESKD) depends on the availability of RRT in that region. In HIC, decisions as to what kind of dialysis is used depend on patient size as well as clinicians' and parental choice. In LLMIC, this decision is severely restricted by availability of forms of RRT. This can range from no access at all to any form of dialysis for children; in some LLMIC settings. the only available option is chronic hemodialysis (HD) in an adult unit using adult-sized machines and consumables which is only possible for teenagers and larger children.

Peritoneal dialysis (PD), both acute and chronic, is accepted as most appropriate for most children and infants. An international dialysis survey showed PD to be available in almost all acute settings surveyed [19] (Table 45.2). Unfortunately, information from Africa, South America, and some parts of Asia was not available. Commercial PD fluid which is dextrose-based is available as a lactate-based buffer or a more biocompatible bicarbonate buffer which is more physiologic but comes at an increased cost. There is a growing trend of reduced use of PD in chronic dialysis with the increased growth of HD units across the world. International organizations such as the International Society of Nephrology (ISN) and International Society of Peritoneal Dialysis (ISPD) have tried to promote the concept of "PD First" to initiate chronic dialysis, with HD as a second choice. This has been hampered by the lack of commercial PD fluids, availability of PD catheters, and surgeons comfortable with inserting PD catheters, especially in pediatric patients.

In the treatment of AKI, acute PD was available in 100% of pediatric intensive care units surveyed [19]. The challenge in LLMIC is the availability of both fluids and catheters.

Saving Young Lives (SYL) is an organization which is a collaboration of the International Society of Nephrology (ISN), the International Pediatric Nephrology Association (IPNA), the International Society of Peritoneal Dialysis (ISPD), and EuroPD. This group has started as a

Table 45.1 Comparing different modalities of dialysis

Modality	Indications	Advantages	Disadvantages
Peritoneal dialysis (PD)	Most common form of dialysis in children	Can be used in LLMIC with limited equipment Not size-specific; used even in infants Staff does not need intensive training, specialized units	Abdominal sepsis or surgery relative contraindication
Manual PD	Infants <5 kg (automated PD not suitable)	Not reliant on electricity supply; minimal staff training required; can be used by neonatal units	Dedicated staff required to perform exchanges
Automated PD	Patients over 5 kg	Automated exchanges; done at home overnight allowing freedom to play and attend school	Cost: consumables, commercial dialysate Regular electricity supply Need to manage machines at home
Extracorporeal forms		Needs fluid priming in infants and small children with blood, plasma, or saline	
Slow low-efficiency dialysis (SLED)	Older children Blood flow rates 3–5 ml/kg/min	Prolonged hemodialysis (HD) available in non-intensive care setting; use in less stable patients	Need to stop therapy after 6–12 h
Continuous venovenous hemofiltration (CVVH)	Required for hemodynamically unstable patients	Slow sustained dialysis for unstable patients who would not tolerate HD	Requires trained staff; intensive care; venous access; expensive
Neonates	AKI common in young infants	PD more available and practical than HD/CVVH	Staff often not trained Venous access, dialysis equipment a challenge

pilot in Africa teaching bed-side acute PD catheter insertion – often with "improvised" catheters – as well as the use of locally made dialysis fluid solutions. PD catheters have ranged from any Seldinger device (Rigid stick catheters, "Peel away" Tenckhoff catheters, Cook® catheters, Chest drains, and nasogastric tubes) for short-term use in managing AKI [19]. Doctor and nurse teams are trained together in managing AKI.

Commercial PD fluid is surprisingly expensive due to the fact that there are no local manufacturing companies in many countries; for example, in Africa importation of PD dialysate from Europe is required. This has resulted in improvisations at the local hospital level where commonly available IV fluids such as Ringer's lactate with added dextrose are used to produce dialysis fluid for acute PD use. Studies from Cameroon have shown that there is no increased risk of peritonitis provided sterile technique is used in constituting the dialysis fluid [20]. To date 500 lives have been saved as a result of the *SYL* program, in addition to the improvement in the medical standard of care available to many other patients as a result of education about AKI (Brett Cullis – Chair of SYL Steering Committee, 2020, "personal communication").

Practical guidelines [21] for PD (Pediatric guidelines currently in revision) have provided a range of practical recommendations from referral to pediatric centers and surgical insertion of Tenckhoff catheters (the gold standard) to improvised techniques in remote regions for both dialysis catheters and dialysis fluids. In Table 45.1, a comparison is made between various forms of dialysis showing the advantages and disadvantages of each modality when used in LLMIC. Lack of knowledge and experience with various techniques and the vascular or peritoneal access required is supported by on-line resources such as https://www.pcrrt.com/ProtocolsAccess.html.

Anticoagulation in most less well-resourced centers consists of heparin with laboratory assessment of partial thromboplastin time (PTT). In a few centers, bedside activated clotting times (ACT) may be available which allows for more

Table 45.2 Summary of results for RRT in AKI

	Developing countries	Developed countries	p
Availability of pediatric nephrologist	35.4% (17/48)	100% (175/175)	0.000
Availability of dedicated pediatric dialysis unit	33.3% (16/48)	91% (159/175)	0.000
Institute's dialysis modality of choice in infants			
PD	68.5% (33/48)	5.7% (10/175)	0.000
HD	12.5% (6/48)	72% (126/175)	0.000
CRRT	10.4% (5/48)	24% (42/175)	0.041
SLED	8.3% (4/48)	1.1% (2/175)	0.006
Institute's dialysis modality of choice in older children (>12 years old)			
PD	29.1% (14/48)	22.2% (39/175)	0.319
HD	64.5% (31/48)	61.1% (107/175)	0.668
CRRT	2% (1/48)	14.8% (26/175)	0.016
SLED	2% (1/48)	2.2% (4/175)	0.933
Availability of RRT's			
PD	100% (48/48)	100% (175/175)	1
HD	54.1% (26/48)	85.1% (149/175)	0.000
CRRT	33.3% (16/48)	60% (105/175)	0.001
SLED	25% (12/48)	20% (35/175)	0.452
Indication for CRRT			
Fluid overload in critically ill child	12.5% (2/16)	40% (42/105)	0.033
Hyperkalemia	81.2% (13/16)	100% (105/105)	0.000
Persistent metabolic acidosis	31.2% (5/16)	61.9% (65/105)	0.021
Hyperammonemia secondary to inborn errors and liver failure	100% (16/16)	100% (105/105)	1
Preferred mode of CRRT			
CVVH	12.5% (2/16)	17.1% (18/105)	0.637
CVVHD	43.7% (7/16)	14.2% (15/105)	0.004
CVVHDF	12.5% (2/16)	31.4% (33/105)	0.120
Depends on the clinical situation	25% (4/16)	35.2% (37/105)	0.422
Change in dialysis modality choice in the past 10 years	41.6% (20/48)	70.2% (123/175)	0.000
Plans to add CRRT/HD services in the next 10 years	10.4% (5/48)	0% (0/175)	0.000
Access to newer dialysis machines (CARPEDIEM, Aquadex, NIDUS)	0% (0/48)	2.28% (4/175)	0.291

Open Access: Raina et al. [18]

rapid assessment of coagulation. Citrate anticoagulation is not widely available in less well-resourced countries due to its cost.

Outcomes

AKI in LLMIC remains a common yet treatable condition if diagnosed and managed early and appropriately. However, many cases present late and are unrecognized, resulting in poor outcomes. Epidemiological studies in pediatric AKI are needed at national levels in both in-patient and out-patient settings to determine the magnitude of the problem [22]. Electronic detection algorithms may be useful in the future [23].

Even basic forms of renal replacement therapy such as manual peritoneal dialysis may not be available due to absence of dialysis fluid and peritoneal dialysis catheters. This is a particular problem in infants and small children where appropriately sized equipment may not be available at all centers; in addition, governments often do not fund acute dialysis in children [24].

In bigger children and adolescents, adult hemodialysis units may provide short-term

hemodialysis, but often families must pay for the dialysis, both the catheters as well as the dialysis sessions. This is only possible in hemodynamically stable patients, as pediatric high care or intensive care facilities with cardiac monitors, inotropes, and continuous RRT are simply not available in many regions.

Ethical dilemmas are also related to the length of time for which children with AKI are dialyzed and what happens when this becomes chronic kidney failure with end-stage kidney disease (ESKD). Acute PD catheters inserted at the bedside would usually only be functional for 7–10 days before infection sets in, these devices become obstructed, or they become dislodged. The difficult decision then remains as to whether to convert to chronic dialysis – if even possible and available – usually in the form of chronic HD. This may not be possible for smaller children and infants and in some cases may only be performed 1–2 times per week due to cost and availability of dialysis slots in many LLMIC.

An alternative is continuous ambulatory PD (CAPD) which does not require sophisticated equipment or infrastructure and should be an ideal form of RRT for those living in remote areas. However, CAPD even in adults is scarcely available in many LLMICs due to high costs and unavailability of fluids, lack of expertise in catheter insertion, and management of complications combined with socio-economic complications [25].

A large review of adults and children with ESKD in Sub-Saharan Africa showed that the majority of children (95%) who could not access dialysis died (or were presumed to have died). Among those with ESKD for which children were dialyzed, 36% died and 28% were lost to follow-up. A large proportion (20%) of children left hospital against hospital advice [26]. When government funding is not available and families are required to cover the cost of dialysis, this can result in families selling their homes and compromising the rest of the family for short-term dialysis with no foreseeable outcome if adequate long-term dialysis and renal transplantation with availability of drugs and monitoring are not available [27].

Palliative or supportive care specifically in pediatric renal disease is an important component which has been unrecognized until recently both in well-resourced and possibly more importantly in LLMIC where failure of treatment or response to treatment of AKI frequently results in the demise of children and infants. This is particularly relevant when the AKI becomes ESKD for which treatment is not available. The priority is then to emphasize a good quality death rather than a lingering poor-quality life which results in death inevitably.

Most important is the role of advocacy by nephrologists and particularly pediatric nephrologists to urge authorities and governments to address preventative factors related to AKI – clean water, mosquito nets – as well as availability of treatment for AKI in children, with good training of both doctors and nurses at the local level [28].

References

1. Sutherland SM, Byrnes JJ, Kothari M, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol. 2015;10(4):554–61. https://doi.org/10.2215/CJN.01900214.
2. Basu RK, Kaddourah A, Terrell T, et al. Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE): study protocol for a prospective observational study. BMC Nephrol. 2015;16:24. Published 26 Feb 2015. https://doi.org/10.1186/s12882-015-0016-6.
3. Selewski DT, Gist KM, Nathan AT, et al. The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group. Pediatr Res. 2020;87(3):550–7. https://doi.org/10.1038/s41390-019-0579-1.
4. Madsen NL, et al. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int. 2017;92(3):751–6.
5. Aye KP, Thanachartwet V, Soe C, et al. Clinical and laboratory parameters associated with acute kidney injury in patients with snakebite envenomation: a prospective observational study from Myanmar. BMC Nephrol. 2017;18(1):92. Published 16 Mar 2017. https://doi.org/10.1186/s12882-017-0510-0.
6. Goldstein SL. Fluid management in acute kidney injury. J Intensive Care Med. 2014;29(4):183–9.
7. Bhatt GC, Gogia P, Bitzan M, Das RR. Theophylline and aminophylline for prevention of acute kidney

injury in neonates and children: a systematic review. Arch Dis Child. 2019;104(7):670–9.
8. Jankowska M, et al. Water soluble vitamins and peritoneal dialysis – state of the art. Clin Nutr. 2017;36(6):1483–9.
9. Harshman LA, Lee-Son K, Jetton JG. Vitamin and trace element deficiencies in the pediatric dialysis patient. Pediatr Nephrol. 2018;33(7):1133–43. https://doi.org/10.1007/s00467-017-3751-z.
10. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, Bunchman TE, Baker C, Mottes T, McAfee N, Barnett J, Morrison G, Rogers K, Fortenberry JD. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int. 2005;67(2):653–8.
11. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM, FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95.
12. Levin M, Cunnington AJ, Wilson C, Nadel S, Lang HJ, Ninis N, McCulloch M, Argent A, Buys H, Moxon CA, Best A, Nijma RG, Hoggart CJ. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. Lancet Respir Med. 2019;7(7):581–3.
13. PRISM Investigators, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, Canter RR, Coats TC, Delaney A, Gimbel E, Grieve RD, Harrison DA, Higgins AM, Howe B, Huang DT, Kellum JA, Mouncey PR, Music E, Peake SL, Pike F, Reade MC, Sadique MZ, Singer M, Yealy DM. Early goal-directed therapy for septic shock – a patient-level meta-analysis. N Engl J Med. 2017;376(23):2223–34.
14. Montomoli J, Donati A, Ince C. Acute kidney injury and fluid resuscitation in septic patients: are we protecting the kidney? Nephron Clin Pract. 2019;143(3):170–3.
15. Raina R, Sethi SK, Nikita W, Vemuganti M, Krishnappa V, Bansal SB. Fluid overload in critically ill children. Front Pediatr. 2018;6:2296–360.
16. Branco RG. Dopamine in sepsis-beginning of the end? Pediatr Crit Care Med. 2016;17(11):1099–100.
17. Sethi SK, Chakraborty R, Joshi H, Raina R. Renal replacement therapy in pediatric acute kidney injury. Indian J Pediatr. 2020. https://doi.org/10.1007/s12098-019-03150-9.
18. Raina R, Chauvin AM, Bunchman T, Askenazi D, Deep A, Ensley ME, Krishnappa V, Sethi SK. Treatment of AKI in developing and developed countries: an international survey of pediatric dialysis modalities. PLoS One. 2017;12(5):e0178233. https://doi.org/10.1371/journal.pone.0178233.t002.
19. Abdou N, Antwi S, Koffi LA, Lalya F, Adabayeri VM, Nyah N, Palmer D, Brusselmans A, Cullis B, Feehally J, McCulloch M, Smoyer W, Finkelstein FO. Peritoneal dialysis to treat patients with acute kidney injury-The saving young lives experience in West Africa: proceedings saving young lives session, international conference of dialysis in West Africa, Dakar, Senegal. Perit Dial Int. 2017;37(2):155–8.
20. Palmer D, Lawton WJ, Barrier C Jr, Fine BD Jr, Hemphill H, Nyah NN, Kinne V, Ringnwi NI, Yong G, Neufeldt AL, Mitterand Y, Finkelstein FO, Krahn TA. Peritoneal dialysis for AKI in Cameroon: commercial vs. locally-made solutions. Perit Dial Int. 2018;38(4):246–50.
21. Cullis B, Al-Hwiesh A, Kilonzo K, McCulloch M, Niang A, Nourse P, Parapiboon W, Ponce D, Finkelstein FO. ISPD guidelines for peritoneal dialysis in acute kidney injury: 2020 update (adults). Perit Dial Int. 2020 Dec 3:896860820970834. https://doi.org/10.1177/0896860820970834. Epub ahead of print. PMID: 33267747.
22. Selby NM, Lennon R. Be on alert for pediatric AKI. Kidney Int. 2017;92(2):286–8.
23. Holmes J, Roberts G, Geen J, Dodd A, Selby NM, Lewington A, Scholey G, Williams JD, Phillips AO, Welsh AKI Steering Group. Utility of electronic AKI alerts in intensive care: a national multicentre cohort study. J Crit Care. 2018;44:185–90.
24. Lalji R, Francis A, Johnson DW, McCulloch MI. Health disparities in access to kidney replacement therapy amongst children and adolescents with end stage kidney disease in low- and lower-middle income countries. Kidney Int. 2020;97(3):463–5.
25. Wearne N, Kilonzo K, Effa E, Davidson B, Nourse P, Ekrikpo U, Okpechi I. Continuous ambulatory peritoneal dialysis: perspectives on patient selection in low- to middle-income countries. Int J Nephrol Renovasc Dis. 2017;10:1–9.
26. Ashuntantang G, Osafo C, Olowu WA, Arogundade F, Niang A, Porter J, Naicker S, Luyckx VA. Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. Lancet Glob Health. 2017;5(4):e408–17.
27. Levy CS, Mudi A, Venter B, Geel J. Challenges facing children on chronic peritoneal dialysis in South Africa. Perit Dial Int. 2018;38(6):402–4.
28. McCulloch M, Luyckx VA, Cullis B, Davies SJ, Finkelstein FO, Yap HK, Feehally J, Smoyer WE. Challenges of access to kidney care for children in low-resource settings. Nat Rev Nephrol. 2021;17(1):33--45. https://doi.org/10.1038/s41581-020-00338-7. Epub 2020 Oct 1. PMID: 33005036.

46 Extracorporeal Liver Support Therapies for Children

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Introduction

Acute liver failure (ALF) and acute-on-chronic liver failure are rare but life-threatening disorders in children. Disease pathophysiology often depends on patient age. Metabolic disorders and viral hepatitis are more frequent in infants with ALF, drug intoxication, and autoimmune disease in older children, while the etiology of ALF remains unexplained in 40–50% of cases [1]. Age-specific algorithms may reduce the rate of unexplained causes [1]. In developing countries, infectious etiologies predominate,while in adults drug toxicity is the most common cause [2, 3].

The estimated frequency of ALF is unknown in children. Many children in the developing world are unaccounted for. Across all age groups in the United States, the estimated frequency is 17 per 100,000 population per year. While one-third of children recover with standard medical care [4], the other two-thirds require emergency liver transplantation. Common features of presentation for ALF include encephalopathy (present in more than 50% of children), seizures, and ascites [5]. Likewise, the majority of children with acute-on-chronic liver failure and those with progressive chronic liver disease require liver transplantation. Pediatric ALF accounts for approximately 10% of liver transplants performed in the United States annually. Since organ availability is limited and considerable bridging time may be required, extracorporeal liver support therapies (ELS) are increasingly applied.

Therapies for ALF are targeted to two paradigms of outcome. The primary goal of therapy is for the liver to recover back to normal health. For the most part, supportive care of other vital organs is required while liver function is supported through supplemental restoration of synthetic function products such as coagulation products (Factor VII) and albumin. Meanwhile, supportive care for the remainder of organs targets a return to primary health if the offending agent for the ALF abates. In contrast, for patients with acute-on-chronic liver failure, the primary goal is to return to the pre-ALF morbidity level.

The goal of ELS therapy is to bridge the patient until transplantation or recovery of liver function (Fig. 46.1). ELS options include both non-biological and biological systems. The ideal system would be able to remove water, lipid, and protein-bound metabolites, correct coagulopathy, and address ongoing immunologic deficits and perturbations. The primary goal of ELS therapy is to prevent or limit the severity of hepatic encephalopathy – along with important clinical management adjuncts to limit other preventable causes

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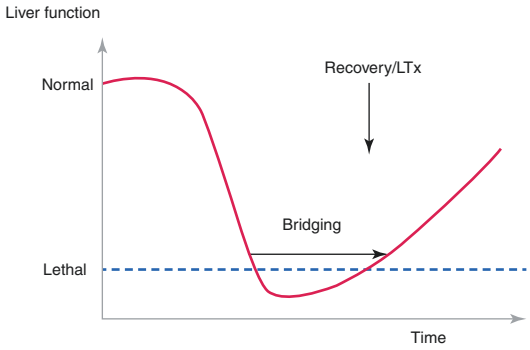

Fig. 46.1 Scheme illustrating the principle of extracorporeal liver support in the course of liver failure. *Ltx* liver transplantation. (Modified from Schaefer and Schmitt [56])

of increased intracranial pressure (e.g., pain, agitation, excessive cerebral blood flow), limitation of protein delivery, and elimination of ammonia-based waste products. The non-biological systems include hemofiltration, hemoperfusion, plasma exchange, and albumin dialysis. To perform these actions, there are currently several options for mechanical, or extracorporeal liver support systems: the molecular adsorbent recirculating system (MARS), Prometheus dialysis, therapeutic plasma exchange combined with hemodialysis (TPE/HD), and single-pass albumin dialysis (SPAD). Smaller reports are published on ELS systems such as open albumin dialysis (OPAL) and ADVanced Organ Support (ADVOS). The biological systems include extracorporeal whole liver perfusion, cross-circulation, and hybrid bioartificial liver support systems. This chapter focuses on the non-biological systems, which are increasingly applied in children with liver failure.

The four main ELS modalities are based on different technical approaches to remove protein-bound toxins. These consist of hemodialysis against a closed albumin circuit with additional toxin adsorbers (MARS), plasma separation followed by plasma purification and reinfusion (Prometheus), plasma separation in combination with hemodialysis, and single-pass albumin dialysis (SPAD). Knowledge about the specific advantages and shortcomings of each technology is vital in order to select the most appropriate liver support system available in a given critical care unit setting. Additionally, understanding the potential for using a multi-modal approach, incorporating standard continuous renal replacement therapy (CRRT) with TPE concurrent with an ELS modality such as MARS – so-called – hybrid ELS – is possible and has demonstrated encouraging preliminary results [6].

Indications for Extracorporeal Liver Support Therapy

Acute and Acute-on-Chronic Liver Failure

The liver plays a key role in a variety of bodily functions: maintains metabolic balance, the endocrine milieu, and acid–base status; synthesizes binding proteins, complement, and coagulation factors; metabolizes water soluble and albumin-bound endogenous and exogenous toxins; and neutralizes intestinal bacterial fragments. In patients with liver failure, all of these functions require careful consideration and appropriate therapeutic measures. Extracorporeal liver dialysis should be started in patients with ALF and in those with acute-on-chronic liver failure if a curative therapy, i.e., usually liver transplantation, or significant recovery of liver function can be expected (Tables 46.1 and 46.2). Of note, one-third of children with acute liver failure may recover [4], possibly in cases of intoxications, metabolic diseases, and autoimmune hepatitis,

Table 46.1 Potential clinical setting for liver replacement therapy

Acute liver failure
Bridging to LTX
Post LTX in case of primary organ dysfunction
Liver dysfunction after hepatobiliary surgery
Acute intoxication
Acute/chronic hepatitis (viral, autoimmune)
Secondary liver dysfunction (due to sepsis, systemic inflammatory response syndrome, multiorgan dysfunction syndrome)
Acute-on-chronic liver failure (biliary atresia, PFIC)
Cholestatic pruritus (biliary atresia, PFIC, ARPKD)

Legend: *LTX* liver transplantation, *PFIC* progressive familial intrahepatic cholestasis, *ARPKD* autosomal recessive polycystic kidney disease

Table 46.2 Potential indications for extracorporeal liver support

Indications	Relative indications
HE (≥3°)	Hemodynamic instability
Unconjugated bilirubin >25 mg/dl	Hepatorenal and -pulmonary syndrome
Coagulation failure	Plasma ammonia >200 µmol/l
	Increased intracranial pressure, HE 2°

Legend: No pediatric RCT available. RCT in adults comparing ELS for various indications and disease settings suggest reduced encephalopathy and lower mortality with ELS. *HE* hepatic encephalopathy. Of note, cut off values for bilirubin and ammonia are based on observational data only

and depending on the severity of liver damage, as assessed clinically (duration of encephalopathy) and by liver function tests.

The criteria to initiate ELS vary considerably, and recommendations have been made almost exclusively based on observational data. However, the following criteria should be taken into account in the decision process to start ELS therapy (Table 46.2): presence of hepatic encephalopathy stage 2 or higher, increased cerebral pressure, hepatic cardiomyopathy and cardiocirculatory instability, coagulopathy (INR >1.5–2.8), presence of hepatorenal failure, high plasma bilirubin concentrations, high plasma ammonium levels >200 µmol/l and high aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (>1500 U/l). All of these factors are dynamic and should be placed into the context of how liver function is changing over time (degree and rapidity of change).

The indication for ELS, procedure efficiency, and associated risks and complications should be evaluated prior to and after each treatment by thorough clinical examination, including assessment of coma scale and hepatic encephalopathy score, and by regular measurement of liver and dialysis-related biochemical parameters. These include bilirubin, ammonium, complete blood count, international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen, activated clotting time (ACT), bile acids, albumin, liver enzymes, C-reactive protein, creatinine, urea, electrolytes including phosphate, and acid–base status. Factor VII, the coagulation factor with the shortest half-life time (~4 h), is also a sensitive parameter to assess the capacity of liver synthesis.

Early ELS therapy initiation appears to be particularly justified in patients with rapid disease progression, although the scientific evidence for an improved outcome with this approach to ELS is still limited. The latter is primarily due to the relatively low incidence of ALF precluding large-scale clinical trials (even in adults), the heterogeneity of the underlying diseases and clinical presentations and the still limited availability of advanced technologies. Several authors have reported on the removal of water soluble toxins only [7–9] in children with liver failure and dialysis-dependent acute kidney injury. Kreuzer et al. reviewed data collected over 10 years which revealed better efficacy with continuous venovenous hemofiltration (CVVH) and lower mortality than with peritoneal dialysis (PD) [7]. In view of the severity of the often life-threatening conditions associated with ALF, with many protein-bound toxins accumulating and contributing to secondary kidney, lung and heart failure and a bleeding diathesis, selective removal of water soluble toxins should be limited to less severe cases, i.e., those with volume overload, less severe symptoms of intoxication, and sufficient coagulation. High sodium CVVH with regional citrate anticoagulation and online dialysate generation was used in 11 adult patients with ALF to precisely titrate serum sodium without undesirable fluctuations in extracellular fluid volume [8]. Whether such osmoregulatory effects are beneficial is uncertain.

Cholestatic Pruritus

Another indication of ELS is unbearable cholestatic pruritus that persists despite pharmacological treatment. Severe cholestatic pruritus prevents sleep and may result in heavy physical and psychological stress – ultimately resulting in depression and possible suicidal tendencies [10, 11]. In adults with intractable pruritus, intermittent MARS has provided good

results [12–14]. In children, MARS treatment every other week to twice weekly resulted in about a 60% reduction in serum bile acids per session and significant improvement of perceived pruritus [10, 15].

It should be emphasized that ELS modalities may be modified or discontinued when patients experience severe allergic reactions to components of the extracorporeal circuit, and they should be withheld in patients with circulatory failure and in cases where there is critical progression of the underlying disease or fatal complications precluding a positive outcome. The ongoing use of ELS varies globally and is influenced by the availability of resources, the expediency of transplantation, and local expertise. The collection of data pertaining to the use of ELS in children therefore becomes challenging – but especially important as best practice recommendations would be beneficial. It is without question that the decision to place children on ELS can affect the ability to list a patient for transplantation, and thus knowledge of the available options for ELS remains vital to the pediatric nephrologist, hepatologist, and intensivist.

Artificial Liver Support Devices

The MARS module (Gambro, Lund, Sweden) consists of a proprietary monitor system, which can be combined with conventional hemodialysis machines. A high-flux polysulfone dialyzer with a molecular cutoff around 50 kDa allows passage of both protein-bound and water soluble substances into a dialysate circuit, which contains 20% albumin. Hydrophilic substances are removed from the albumin circuit via a conventional hemofilter, whereas the albumin-bound substances are adsorbed to a charcoal filter and an anion exchange resin filter placed in series into the albumin circuit (Fig. 46.2).

Two different types of MARS filters are available; the adult system filter with 2.1 m^2 filter surface area and the MARSmini filter set with 0.6 m^2 filter surface area. The extracorporeal volumes are 152 and 57 mL, respectively, plus blood lines; the MARSmini system is recommended for patients less than 25 kg body weight. The albumin circuits are primed with about 500 (450 mL for MARSmini) of 20% human albumin. Urea and vitamin B12 clearances are 195 (34) and 149

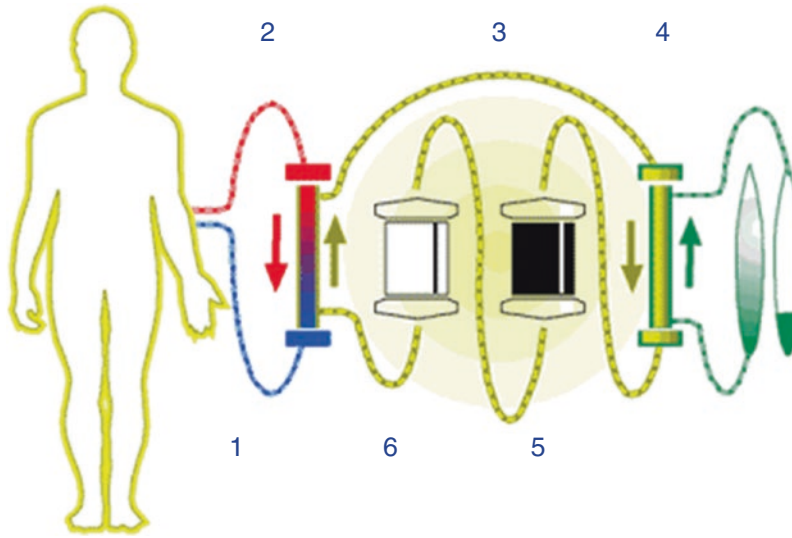

Fig. 46.2 MARS is a combination of a blood circuit with a polysulfone filter (1, 2) which dialyses against a primary circuit containing 20% albumin (3) and a secondary conventional hemodialysis circuit to remove water soluble toxins (4). While water soluble compounds are removed from the primary dialysate via the second dialysis circuit, the albumin-bound substances adhere to a charcoal filter (5) and an anion exchanger (6) placed in series into the albumin circuit

(25) mL/min with MARS (MARSmini) at 200 and 100 mL/min blood flow rates and 500 and 30 mL/min dialysate flow rates, respectively. The molar ratio of bilirubin to albumin in serum is approximately 20-fold higher than the respective dialysate ratio throughout the MARS sessions, giving a rough estimate of the MARS filter clearance capacity [16]. Due to its molecular cutoff of around 50 kD, proteins such as albumin, coagulation factors, and immunoglobulins are not removed with MARS.

The regulation of blood flow depends on multiple factors. Included in the determination of targeted blood flow are the metrics of weight, the stability of the patient, the speed and amount of detoxification deemed necessary by the clinical situation, and access. The albumin dialysate flow rate should equal the blood flow rate. The sum of the secondary dialysate turnover and ultrafiltration rate should not exceed 25% of the blood flow rate. The secondary dialysate flow rate should be at least two times the albumin flow rate. The efficacy of purification depends on the degree of intoxication and on the amount of toxins filtered and cleared via the albumin circuit.

MARS dialysis can be performed once daily for about 8 h until the adsorber systems are saturated, or continuously with system exchanges every 8 h, if required [17]. The 8 h limit is based upon the treatment time possible prior to saturation of the adsorbent filters; continuation of dialysis with the same system beyond 8 h for clearance of water soluble substances and ultrafiltration is feasible but may be less efficient. In addition to the general recommendations given above, MARS may not be applied or should be discontinued in children with active bleeding. The coagulation status often deteriorates during MARS therapy. The underlying mechanisms for bleeding include progressive failure of hepatic protein synthesis, mechanical platelet sequestration during blood passage through the filter, and membrane-induced immune-mediated coagulation factor consumption [18–20]. Hence, it should be emphasized that MARS therapy does not preclude the need for plasma protein supplementation.

The available data for MARS efficacy in children depend on the endpoints measured. In terms of improvement in hepatic encephalopathy (HE) and overall survival (transplant or no transplant), the range of improvement is anywhere from 17% to 100% in HE and 50–100% with respect to patient survival. The number of patients accounted for in these studies varies, but remains small compared to larger, adult studies [6, 21–24].

OPAL (Hepanet/Albutec GmbH – Hannover, Germany) was recently introduced to further improve ELS efficacy and patient outcome. This system incorporates an albumin circuit with a dialysis filter with a large surface area of contact with the charcoal adsorber, thereby potentially improving the regeneration rates and dialysis efficacy by allowing a higher concentration gradient between blood and the albumin dialysate. Priming of the circuit may be required in small children. To date, very few data are available based on the use of this modality. There are no published data on the effectiveness of the OPAL system as compared to the established MARS system, except for the case of a 15-year-old girl with liver transplantation and postoperative bile duct stenosis. OPAL was repeatedly compared to MARS and proved to be more effective in bile acid removal and relief of cholestatic pruritus [25].

ADVOS (ADVOS multi, Hepa Wash GmbH Munich, Germany) is another new type of albumin dialysis that provides rapid regeneration of toxin-binding albumin by two purification circuits altering the binding capacities of albumin by biochemical (changing of pH) and physical (changing of temperature) modulation of the dialysate. ADVOS efficiently eliminated water and protein-bound toxins in 14 patients with ALF [26], although pediatric data are scant.

The Prometheus device (Fresenius Medical Care, Bad Homburg, Germany) consists of two extracorporeal circuits. In the first, plasma is separated from blood via an albumin permeable polysulfone filter. The filtrate is purified via two adsorbers in series. The neutral resin exchanger retains albumin-bound substances such as bile

acids, hydrophobic amino acids, and phenolic substances. The anion exchanger retains negatively charged toxins such as bilirubin. Albumin, hormones, and electrolytes are not bound. The purified plasma is reinfused into the blood, which subsequently passes a conventional high-flux polysulfone dialyzer to eliminate water soluble toxins. Extracorporeal filter and blood line volumes amount to 340 mL. The volume can be somewhat reduced by exchanging the hemodialysis filter for an appropriate pediatric size high-flux filter. The extracorporeal plasma volume is 440 mL. Prometheus is mainly suitable for adolescents and adults. Its use in younger patients requires priming of the blood and plasma circuit with packed red blood cells, fresh frozen plasma, and albumin, respectively. Treatment time is typically 4–8 h, with a maximal time of 10 h per session.

Single-pass albumin dialysis (SPAD) is a continuous venovenous hemodialysis procedure against a standard dialysate solution enriched with 20% human albumin to a final concentration of 2–20%. The albumin dialysate is discarded after passage through the hemodialysis filter. When considering cost–efficacy, a 4–5% dialysate albumin concentration is usually considered adequate. The blood flow rate can be adjusted as recommended for standard CVVHD (3–5 mL/min/kg body weight). In adult patients, the albumin dialysate flow rate is often adjusted to 12–25 mL/min (10–20 ml/kg/h in a 75 kg patient); pediatric centers have used a 20–60 mL/kg/h albumin dialysate flow, which is feasible in small children for whom the absolute amount of human albumin solution is not excessive. SPAD can be combined with conventional hemodialysis at high dialysate flow rates (500–800 mL/min) [27] and with hemodiafiltration (Fig. 46.3). Solid efficacy data are lacking. Once daily sessions of 6–12 h duration have been reported to attenuate hepatic intoxication. Continuous SPAD may be performed to achieve higher clearance rates in children with severe hepatic failure, but at the expense of higher costs.

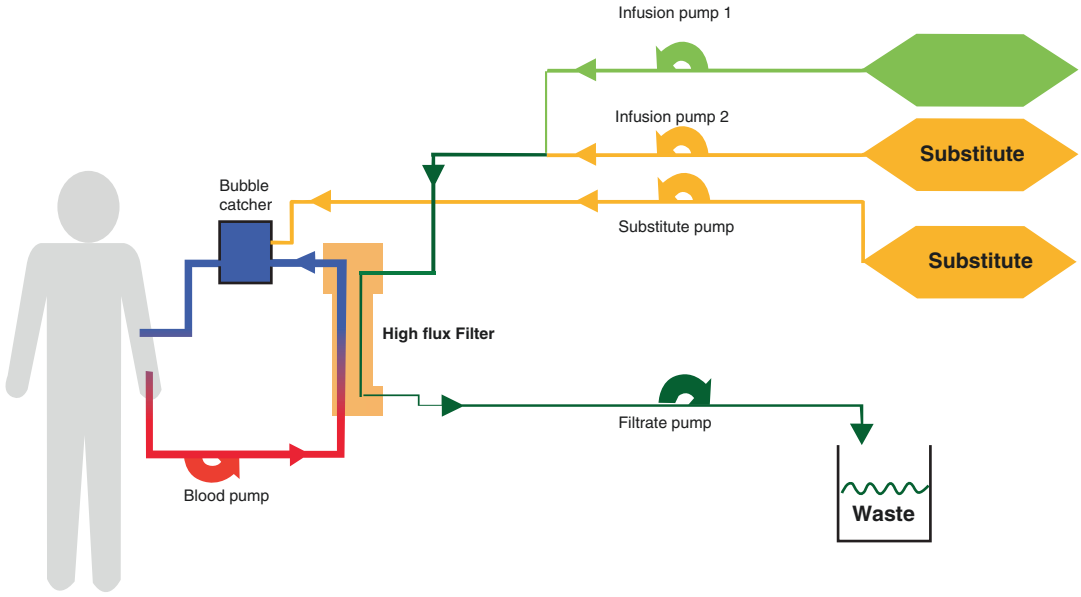

Fig. 46.3 Scheme of a single-pass albumin hemodiafiltration. Albumin solution (usually 4–5%) passes through a high-flux filter, which allows for ultrafiltration replaced by substitution fluid and net ultrafiltration in volume overloaded children

Combined Plasma Exchange and Hemodialysis Therapies

A type of ELS is the use of a hybrid therapy, combining extracorporeal hemodialysis and therapeutic plasma exchange (TPE). As an alternative to MARS and Prometheus, this approach can be performed using conventional hemodialysis machines and filters. The filter surface area should roughly equal the patient's body surface area. The standard plasma exchange volume is 150% per session, but can be adapted according to individual needs and should be replaced by fresh frozen plasma. Iso-oncotic albumin substitution can be considered only in the rare scenario of ALF with a still intact plasma coagulation status.

In emergency ALF situations with a need for rapid clearance of both albumin-bound and water soluble toxins such as ammonium, complicated by associated coagulation failure, it is possible to perform simultaneous plasmapheresis and hemodialysis by a single blood circuit passing serially through two dialysis machines encorporating a plasma and a high-flux hemodialysis filter system. Toxin elimination and volume- and nitrogen-neutral substitution of plasma proteins can be achieved simultaneously with a reduced workload. Total anticoagulation doses are slightly reduced as compared to sequential therapy. While dialysis machines have not been approved for such combinations, clinical experience is good [28] (Fig. 46.4).

The plasma turnover rate should not exceed 25% of the blood flow rate. If a relatively high blood flow rate is achieved, plasmapheresis can be accomplished within 2 h. While once daily plasmapheresis is sufficient in the majority of patients, the frequency can be adapted according to clinical needs, especially in the presence of hepatic encephalopathy. Limited experience using combined hemodialysis and plasma exchange with fresh frozen plasma has been reported to substantially improve the symptoms of liver failure [6, 28].

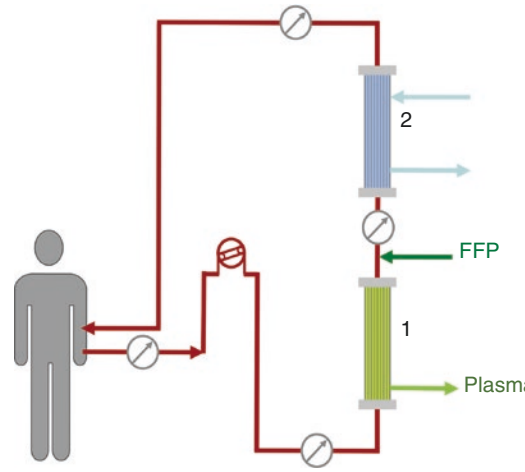

Fig. 46.4 Plasmapheresis and hemodialysis for liver support therapy can be performed simultaneously with a plasma separator and a conventional high-flux filter configured serially. Pressure measurements are placed at indicated positions (*crossed circles*). Variations may be required when other systems are combined

Bioartificial Liver Support Devices

As mentioned earlier, a biological approach can be used to treat ALF. The use of therapies such as MARS, TPE, CRRT, and Prometheus is technically nonbiological; however, the promising aim of bioartificial devices is to provide both liver detoxification and supplemental synthetic functions. HepatAssist (1) and the extracorporeal liver assist device (ELAD) (2) are the first bioartificial systems which have undergone testing in controlled trials in adult patients. HepatAssist contains porcine hepatocytes within the extracapillary compartment of a hollow fiber bioreactor, and ELAD uses human hepatoblastoma cells. Besides the safety of the systems [29, 30], one randomized controlled trial recently demonstrated an improvement in transplant-free survival with ELAD plus TPE and hemofiltration versus TPE and hemofitration [31]. Pediatric data are lacking. At present, bioartificial devices are not ready for routine clinical use in children.

Implementation of ELS

In the absence of the ability to provide clear evidence supporting a certain methodology, familiarity of use (particularly by nursing staff) is vital when deciding on ELS for patients with ALF. To prevent foreign protein exposure, and in children with cholestatic pruritus, albumin dialysis should be utilized. Albumin dialysis spans the range of single-pass albumin dialysis to MARS to Prometheus. There are no pediatric-specific recommendations on the adequate dose and duration of ELS. At present, ELS is dosed according to clinical and biochemical outcomes, i.e., improvement of hepatic encephalopathy, cardiac and kidney function, lowering of vasopressor requirements, and lowering of blood ammonia and serum bilirubin concentrations.

In patients treated with ELS for refractory cholestatic pruritus, monitoring of cholestasis markers such as serum bilirubin and bile acids should be performed to demonstrate the efficacy of the treatment. A visual analog scale may also be useful for monitoring the perceived improvement and to allow for individual adaptation of the treatment. For treatment of hepatic encephalopathy, a careful neurologic exam inclusive of the assessment for hyperreflexia and upper motor neuron function should ideally be performed at least every 2 h.

Anticoagulation therapy is required in the majority of ALF patients on ELS, even though coagulopathy is a cardinal feature of liver dysfunction, since pro- and anticoagulant factors are imbalanced and rapid clotting of the system may develop. Anticoagulation may be started if the endogenous activated clotting time (ACT) is below 160 s. In addition to the prevention of system clotting, anticoagulation reduces biofilm formation in the filter and thus preserves dialysis efficacy. Regional citrate anticoagulation is feasible in the majority of patients and is indicated when there is coagulation failure [9, 32, 33]. A second central intravenous (i.v.) line is usually required for the calcium infusion; otherwise, clotting of the venous dialysis catheter line is likely to occur. Hepatic citrate metabolism should be monitored as accumulation of citrate leads to metabolic acidosis and the "citrate lock" phenomenon (i.e., dissociation of ionized and total calcium levels). Whether citrate accumulation contributes to a poor outcome or whether the outcome is instead a reflection of the severity of liver failure is unclear. Observational studies in children and adults do not suggest associated untoward effects of the therapy [32, 33], whereas other factors such as a high lactate and low partial thromboplastin time (PTT) predict a poor outcome [34]. The high sodium load (3 sodium per citrate) also requires consideration and dialytic removal of sodium should hypernatremia develop.

Data for Extracorporeal Liver Support

Individual centers have developed their own policies and techniques for treating children with liver failure by ELS, often based on local availability of resources and appreciation of the limited scientific evidence. The available ELS systems have specific advantages and shortcomings (Table 46.3). The major advantage of MARS, Prometheus, and SPAD is the removal of protein-bound substances without administration of exogenous protein. Plasmapheresis replaces plasma with fresh frozen plasma or albumin and is thus associated with allergic and infectious risks. On the other hand, plasma exchange allows for removal of all plasma protein-bound toxins and for volume and nitrogen neutral correction of liver synthesis failure, in particular coagulation failure. Plasma exchange in combination with hemodialysis is an intermittent detoxification treatment, which can be repeated two to three times per day as required, or in severe cases may even be applied continuously. Even in infants below 1 year of age with ALF, continuous venovenous hemodiafiltration and plasma exchange have been reported to be well tolerated and has resulted in favorable outcomes [35]. Both methods can even be combined in a tandem setup to reduce treatment time and increase cost-effectiveness, which may be advantageous in critically ill patients who require rapid toxin

Table 46.3 Advantages and disadvantages of extracorporeal liver support systems

	MARS	Prometheus	SPAD	TPE/HD
Advantages	No exogenous protein delivery, no infectious and allergic risk Continuous administration feasible Good clinical tolerability	No exogenous protein delivery, no infectious and allergic risk Continuous administration feasible Good clinical tolerability	No exogenous protein delivery, no infectious and allergic risk Good clinical tolerability Relatively easy to perform	High detoxification capacity Efficient compensation of liver synthesis failure, reduces bleeding risk Volume and nitrogen neutral balance Cheaper Widely available
Drawbacks	Bleeding risk, additional plasma substitution is associated with volume and nitrogen load High costs and workload (system exchange q. 8–12 h)	Bleeding risk, additional plasma substitution is associated with volume and nitrogen load High costs and workload (system exchange q. 8–12 h) High extracorporeal volume	Bleeding risk, additional plasma substitution is associated with volume and nitrogen load High amounts of albumin required for extended treatment and large children	Intermittent therapy (TPE) Infectious and allergic risks related to exogenous protein load

MARS molecular adsorbent recirculating system, SPAD single-pass albumin dialysis, TPE/HD therapeutic plasma exchange combined with hemodialysis

removal [28]. Depending on the availability of resources and personnel expertise, as discussed earlier, the use of ELS, CRRT, and TPE should be adjudicated. Regardless of the choice, constant monitoring of coagulation and pressure in a multi-modal system is mandatory to avoid adverse events [28].

MARS and Prometheus therapies are usually performed for 6–8 h, but can be extended or may also be applied continuously in critical cases. System exchanges are required two to three times a day to maintain good purification efficacy. Of note, setup times are shorter and the material costs are usually lower (depending on patient size) with combined plasma exchange and hemodialysis than with MARS or Prometheus. Of course, cost-efficacy considerations must also take center-specific reimbursement policies into account.

Several randomized prospective studies have compared MARS and Prometheus with standard medical therapy. There does not appear to be any major differences in purification capacity with Prometheus and MARS, but one trial has suggested superior cardiovascular stability with MARS [36]. SPAD is a technically simple liver support system, which is feasible in small children. Several case reports including pediatric patients [37] suggest a dose- and time-dependent clearance efficacy of SPAD with respect to bilirubin, thyroxine, copper and, at least in vitro, of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). However, SPAD is associated with uncertain survival benefits as compared to standard medical treatment [38–42]. Experimental and clinical comparisons of SPAD and MARS have yielded conflicting findings: both similar to slightly better [43, 44] and inferior efficacy of SPAD [45, 46], presumably mainly depending on the intensity of the treatments in terms of duration, flow rates, and albumin concentrations.

Neither MARS nor Prometheus or SPAD have been compared in prospective trials with combined hemodialysis and plasma exchange, the most readily available and least expensive extracorporeal liver support therapy. Clinical observations in seven children, including an intraindividual comparison in five children, suggest better bilirubin removal and, not surprisingly, much better control of the coagulation status with combined TPE/HD as compared to

intermittent MARS therapy. The MARSmini system appeared particularly limited in this comparison [22].

Complications related to the constituents of ELS can add to the morbidity in these patients. Although very little data have been published in this regard, anecdotal and observational data highlight the importance of understanding the potential negative effects of albumin and use of multiple extracorporeal devices in tandem. Human serum albumin contains octanoate, a medium chain fatty acid, for stabilization during the manufacturing process. An involvement of this compound in the pathogenesis of hepatogenic encephalopathy, both by direct neurotoxicity and by competitive displacement of albumin-bound toxins, has been suggested. Markedly increased plasma octanoate levels have been described with MARS and even higher concentrations with SPAD [47]. No such accumulation should be observed with plasmapheresis. The relevance of octanoate accumulation on clinical outcomes is as yet unknown.

All extracorporeal devices cause mechanical platelet sequestration during blood passage through the filter and membrane-induced immune-mediated coagulation factor consumption, which has been associated with increased bleeding risk and major bleeding episodes [18, 19, 48]. Consumptive coagulopathy induced by preexisting bleeding from predilection sites may further aggravate a coagulation deficiency. Fresh frozen plasma and blood transfusions may insufficiently correct any coagulation failure and result in volume and protein overload; plasma exchange should be initiated in these children.

Outcome of ELS in Patients with Liver Failure

The removal of an array of toxins with albumin dialysis has repeatedly been demonstrated to be followed by pruritus relief [12, 13], improved mean arterial pressure, systemic vascular resistance, cardiac output, cerebral flow [49], intracranial pressure [50], kidney function, and hepatic encephalopathy [21, 49–54]. Several pediatric observational studies also suggest good clinical tolerability and efficacy of ELS in terms of biochemical correction of liver failure and improvement of hepatic encephalopathy [6, 22, 23, 33]. In addition to these early studies, seven RCTs in adults with different ELS modalities and different indications have been performed with varying doses of ELS. These were included in a recent meta-analysis together with 18 small-size prospective trials in adults with liver failure, altogether comprising a total of 1796 patients [55]. This analysis has suggested with moderate certainty an improved overall survival (RR 0.84; 95% CI 0.74, 0.96) and reduced hepatic encephalopathy (RR 0.71; 95% CI 0.60, 0.84, low certainty) with ELS. The risk of bleeding, hypotension, and thrombocytopenia was increased with ELS, but the quality of the studies precludes firm conclusions regarding these potential complications.

Conclusion

Taken together, there is increasing evidence that ELS improves hepatic encephalopathy and survival in patients with liver failure waiting for liver transplantation or recovery of liver function, which may be expected in one-third of patients depending on the underlying disease. In terms of the various devices available for ELS, plasma exchange together with hemodialysis/hemodiafiltration is easy to perform, widely available in pediatric dialysis centers, and cost-effective. Limited observational comparisons suggest comparable efficiency to MARS, while comparisons with other albumin-based ELS systems have not yet been performed. Children with otherwise refractory, unbearable cholestatic pruritus, can efficiently be treated with albumin dialysis without exposure to large amounts of foreign protein.

References

1. Narkewicz MR, Horslen S, Hardison RM, Shneider BL, Rodriguez-Baez N, Alonso EM, Ng VL, Leonis MA, Loomes KM, Rudnick DA, Rosenthal P, Romero R, Subbarao GC, Li R, Belle SH, Squires

RH. Pediatric acute liver failure study group. Clin Gastroenterol Hepatol. 2018;16(11):1801–10.
2. Arroyo V, Moreau R, Jalan R, Gines P, Study E-CCC. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol. 2015;62:131–43.
3. Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, Durkalski V, Larson AM, Liou I, Fix O, Schilsky M, McCashland T, Hay JE, Murray N, Shaikh OS, Ganger D, Zaman A, Han SB, Chung RT, Smith A, Brown R, Crippin J, Harrison ME, Koch D, Munoz S, Reddy KR, Rossaro L, Satyanarayana R, Hassanein T, Hanje AJ, Olson J, Subramanian R, Karvellas C, Hameed B, Sherker AH, Robuck P, Lee WM. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. Ann Intern Med. 2016;164:724–32.
4. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. J Pediatr Gastroenterol Nutr. 2005;40(5):575–81.
5. Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, Dhawan A, Rosenthal P, Rodriguez-Baez N, Murray KF, Horslen S, Martin MG, Lopez MJ, Soriano H, McGuire BM, Jonas MM, Yazigi N, Shepherd RW, Schwarz K, Lobritto S, Thomas DW, Lavine JE, Karpen S, Ng V, Kelly D, Simonds N, Hynan LS. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr. 2006;148(5):652–8.
6. Akcan Arikan A, Srivaths P, Himes RW, Tufan Pekkucuksen N, Lam F, Nguyen T, Miloh T, Braun M, Goss J, Desai MS. Hybrid extracorporeal therapies as a bridge to pediatric liver transplantation. Pediatr Crit Care Med. 2018;19(7):342–9.
7. Kreuzer M, Gähler D, Rakenius AC, Prüfe J, Jack T, Pfister ED, Pape L. Dialysis-dependent acute kidney injury in children with end-stage liver disease: prevalence, dialysis modalities and outcome. Pediatr Nephrol. 2015;30(12):2199–206.
8. Hamdi T, Yessayan L, Yee J, Szamosfalvi B. High sodium continuous veno-venous hemodialysis with regional citrate anticoagulation and online dialysate generation in patients with acute liver failure and cerebral edema. Hemodial Int. 2018;22(2):184–91.
9. Slowinski T, Morgera S, Joannidis M, Henneberg T, Stocker R, Helset E, Andersson K, Wehner M, Kozik-Jaromin J, Brett S, Hasslacher J, Stover JF, Peters H, Neumayer HH, Kindgen-Milles D. Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. Crit Care. 2015;19:349.
10. Schaefer B, Schaefer F, Wittmer D, Engelmann G, Wenning D, Schmitt CP. Molecular adsorbents recirculating system dialysis in children with cholestatic pruritus. Pediatr Nephrol. 2012;27(5):829–34.
11. Gross CR, Malinchoc M, Kim WR, Evans RW, Wiesner RH, Petz JL, Crippin JS, Klintmalm GB, Levy MF, Ricci P, Therneau TM, Dickson ER. Quality of life before and after liver transplantation for cholestatic liver disease. Hepatology. 1999;29(2):356–64.
12. Parés A, Cisneros L, Salmerón JM, Caballería L, Mas A, Torras A, Rodés J. Extracorporeal albumin dialysis: a procedure for prolonged relief of intractable pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2004;99:1105–10.
13. Bellmann R, Graziadei IW, Feistritzer C, Schwaighofer H, Stellaard F, Sturm E, Wiedermann CJ, Joannidis M. Treatment of refractory cholestatic pruritus after liver transplantation with albumin dialysis. Liver Transpl. 2004;10:107–14.
14. Leckie P, Tritto G, Mookerjee R, Davies N, Jones D, Jalan R. 'Out-patient' albumin dialysis for cholestatic patients with intractable pruritus. Aliment Pharmacol Ther. 2012;35(6):696–704.
15. Javouhey E, Ranchin B, Lachaux A, Boillot O, Martin X, Floret D, Cochat P. Long-lasting extracorporeal albumin dialysis in a child with end-stage renal disease and severe cholestasis. Pediatr Transplant. 2009;13(2):235–9.
16. Gong D, Ji D, Ren B, Tao J, Xu B, Ronco C, Li L. Significant decrease in dialysate albumin concentration during molecular adsorbent recirculating system (MARS) therapy. Int J Artif Organs. 2008;31(4):333–9.
17. Olin P, Hausken J, Foss A, Karlsen TH, Melum E, Haugaa H. Continuous molecular adsorbent recirculating system treatment in 69 patients listed for liver transplantation. Scand J Gastroenterol. 2015;50(9):1127–34.
18. Faybik P, Bacher A, Kozek-Langenecker SA, Steltzer H, Krenn CG, Unger S, Hetz H. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. Crit Care. 2006;10(1):2.
19. Bachli EB, Schuepbach RA, Maggiorini M, Stocker R, Müllhaupt B, Renner EL. Artificial liver support with the molecular adsorbent recirculating system: activation of coagulation and bleeding complications. Liver Int. 2007;27(4):475–84.
20. Doria C, Mandalà L, Smith JD, Caruana D, Scott VL, Gruttadauria S, Magnone M, Marino IR. Thromboelastography used to assess coagulation during treatment with molecular adsorbent recirculating system. Clin Transpl. 2004;18(4):365–71.
21. Novelli G, Rossi M, Morabito V, Pugliese F, Ruberto F, Perrella SM, Novelli S, Spoletini G, Ferretti G, Mennini G, Berloco PB. Pediatric acute liver failure with molecular adsorbent recirculating system treatment. Transplant Proc. 2008;40(6):1921–4.
22. Schaefer B, Schaefer F, Engelmann G, Meyburg J, Heckert KH, Zorn M, Schmitt CP. Comparison of molecular adsorbents recirculating system (MARS) dialysis with combined plasma exchange and haemodialysis in a children with acute liver failure. Nephrol Dial Transplant. 2011;26(11):3633–9.
23. Lexmond WS, Van Dael CM, Scheenstra R, Goorhuis JF, Sieders E, Verkade HJ, Van Rheenen PF, Kömhoff M. Experience with molecular adsorbent recircu-

lating system treatment in 20 children listed for high-urgency liver transplantation. Liver Transpl. 2015;21(3):369–80.
24. Rustom N, Bost M, Cour-Andlauer F, Lachaux A, Brunet AS, Boillot O, Bordet F, Valla F, Richard N, Javouhey E. Effect of molecular adsorbents recirculating system treatment in children with acute liver failure caused by Wilson disease. J Pediatr Gastroenterol Nutr. 2014;58(2):160–4.
25. Soo E, Sanders A, Heckert K, Vinke T, Schaefer F, Schmitt CP. Comparison of two different modes of molecular adsorbent recycling systems for liver dialysis. Pediatr Nephrol. 2016;31(11):2171–4.
26. Huber W, Henschel B, Schmid R, Al-Chalabi A. First clinical experience in 14 patients treated with ADVOS: a study on feasibility, safety and efficacy of a new type of albumin dialysis. BMC Gastroenterol. 2017;17(1):32.
27. Rosa Diez G, Greloni G, Gadano A, Giannasi S, Crucelegui M, Trillini M, Algranati S. Combined extended haemodialysis with single-pass albumin dialysis (SPAED). Nephrol Dial Transplant. 2007;22(9):2731–2.
28. Schaefer B, Ujszaszi A, Schaefer S, Heckert KH, Schaefer F, Schmitt CP. Safety and efficacy of tandem hemodialysis and plasma exchange in children. Clin J Am Soc Nephrol. 2014;9(9):1563–70.
29. Demetriou AA, Brown RS Jr, Busuttil RW, Fair J, McGuire BM, Rosenthal P, Am Esch JS 2nd, Lerut J, Nyberg SL, Salizzoni M, Fagan EA, de Hemptinne B, Broelsch CE, Muraca M, Salmeron JM, Rabkin JM, Metselaar HJ, Pratt D, De La Mata M, McChesney LP, Everson GT, Lavin PT, Stevens AC, Pitkin Z, Solomon BA. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg. 2004;239(5):660–7.
30. Ellis AJ, Hughes RD, Wendon JA, Dunne J, Langley PG, Kelly JH, Gislason GT, Sussman NL, Williams R. Pilot-controlled trial of the extracorporeal liver assist device in acute liver failure. Hepatology. 1996;24(6):1446–51.
31. Duan Z, Xin S, Zhang J, You S, Chen Y, Liu H, Zheng S, Li Z, Ashley R, Millis M. Comparison of extracorporeal cellular therapy (ELAD®) vs standard of care in a randomized controlled clinical trial in treating Chinese subjects with acute-on-chronic liver failure. Hepat Med. 2018;10:139–52.
32. Rodriguez K, Srivaths PR, Tal L, Watson MN, Riley AA, Himes RW, Desai MS, Braun MC, Akcan AA. Regional citrate anticoagulation for continuous renal replacement therapy in pediatric patients with liver failure. PLoS One. 2017;12(8):e0182134.
33. Lion RP, Tufan Pekkucuksen N, Srivaths P, Desai MS, Arikan AA. The safety and efficacy of regional citrate anticoagulation in albumin-assisted liver dialysis for extracorporeal liver support in pediatric patients. Blood Purif. 2019;47(1–3):23–7.
34. Schultheiß C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, Haller B, Einwächter H, Schmid RM, Huber W. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care. 2012;16(4):162.
35. Ide K, Muguruma T, Shinohara M, Toida C, Enomoto Y, Matsumoto S, Aoki K, Fukuda A, Sakamoto S, Kasahara M. Continuous veno-venous hemodiafiltration and plasma exchange in infantile acute liver failure. Pediatr Crit Care Med. 2015;16(8):e268–74.
36. Dethloff T, Tofteng F, Frederiksen HJ, Hojskov M, Hansen BA, Larsen FS. Effect of prometheus liver assist system on systemic hemodynamics in patients with cirrhosis: a randomized controlled study. World J Gastroenterol. 2008;14(13):2065–71.
37. Ringe H, Varnholt V, Zimmering M, Luck W, Gratopp A, König K, Reich S, Sauer IM, Gaedicke G, Querfeld U. Continuous veno-venous single-pass albumin hemodiafiltration in children with acute liver failure. Pediatr Crit Care Med. 2011;12(3):257–64.
38. Chawla LS, Georgescu F, Abell B, Seneff MG, Kimmel PL. Modification of continuous venovenous hemodiafiltration with single-pass albumin dialysate allows for removal of serum bilirubin. Am J Kidney Dis. 2005;45(3):51–6.
39. Koball S, Hickstein H, Gloger M, Hinz M, Henschel J, Stange J, Mitzner S. Treatment of thyrotoxic crisis with plasmapheresis and single pass albumin dialysis: a case report. Artif Organs. 2010;34(2):55–8.
40. Awad SS, Sawada S, Soldes OS, Rich PB, Klein R, Alarcon WH, Wang SC, Bartlett RH. Can the clearance of tumor necrosis factor alpha and interleukin 6 be enhanced using an albumin dialysate hemodiafiltration system? ASAIO J. 1999;45(1):47–9.
41. Karvellas CJ, Bagshaw SM, McDermid RC, Stollery DE, Bain VG, Gibney RT. A case-control study of single-pass albumin dialysis for acetaminophen-induced acute liver failure. Blood Purif. 2009;28(3):151–8.
42. Collins KL, Roberts EA, Adeli K, Bohn D, Harvey EA. Single pass albumin dialysis (SPAD) in fulminant Wilsonian liver failure: a case report. Pediatr Nephrol. 2008;23(6):1013–6.
43. Sauer IM, Goetz M, Steffen I, Walter G, Kehr DC, Schwartlander R, Hwang YJ, Pascher A, Gerlach JC, Neuhaus P. In vitro comparison of the molecular adsorbent recirculation system (MARS) and single-pass albumin dialysis (SPAD). Hepatology. 2004;39(5):1408–14.
44. Kortgen A, Rauchfuss F, Götz M, Settmacher U, Bauer M, Sponholz C. Albumin dialysis in liver failure: comparison of molecular adsorbent recirculating system and single pass albumin dialysis – a retrospective analysis. Ther Apher Dial. 2009;13(5):419–25.
45. Peszynski P, Klammt S, Peters E, Mitzner S, Stange J, Schmidt R. Albumin dialysis: single pass vs. recirculation (MARS). Liver. 2002;22(Suppl 2):40–2.
46. Sponholz C, Matthes K, Rupp D, Backaus W, Klammt S, Karailieva D, Bauschke A, Settmacher U, Kohl M, Clemens MG, Mitzner S, Bauer M, Kortgen A. Molecular adsorbent recirculating system and single-pass albumin dialysis in liver failure-a pro-

spective, randomised crossover study. Crit Care. 2016;20:2.
47. Klammt S, Koball S, Hickstein H, Gloger M, Henschel J, Mitzner S, Stange J, Reisinger EC. Increase of octanoate concentrations during extracorporeal albumin dialysis treatments. Ther Apher Dial. 2009;13(5):437–43.
48. Meijers BK, Verhamme P, Nevens F, Hoylaerts MF, Bammens B, Wilmer A, Arnout J, Vanrenterghem Y, Evenepoel P. Major coagulation disturbances during fractionated plasma separation and adsorption. Am J Transplant. 2007;7(9):2195–9.
49. Schmidt LE, Svendsen LB, Sørensen VR, Hansen BA, Larsen FS. Cerebral blood flow velocity increases during a single treatment with the molecular adsorbents recirculating system in patients with acute on chronic liver failure. Liver Transpl. 2001;7(8):709–12.
50. Sorkine P, Ben Abraham R, Szold O, Biderman P, Kidron A, Merchav H, Brill S, Oren R. Role of the molecular adsorbent recycling system (MARS) in the treatment of patients with acute exacerbation of chronic liver failure. Crit Care Med. 2001;29(7):1332–6.
51. Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, Berger ED, Lauchart W, Peszynski P, Freytag J, Hickstein H, Loock J, Löhr JM, Liebe S, Emmrich J, Korten G, Schmidt R. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl. 2000;6(3):277–86.
52. Steiner C, Mitzner S. Experiences with MARS liver support therapy in liver failure: analysis of 176 patients of the international MARS registry. Liver. 2002;22(Suppl 2):20–5.
53. Hassanein TI, Tofteng F, Brown RS Jr, McGuire B, Lynch P, Mehta R, Larsen FS, Gornbein J, Stange J, Blei AT. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46(6):1853–62.
54. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol. 2003;38(1):24–31.
55. Alshamsi F, Alshammari K, Belley-Cote E, Dionne J, Albrahim T, Albudoor B, Ismail M, Al-Judaibi B, Baw B, Subramanian RM, Steadman R, Galusca D, Huang DT, Nanchal R, Al Quraini M, Yuan Y, Alhazzani W, GUIDE Group. Extracorporeal liver support in patients with liver failure: a systematic review and meta-analysis of randomized trials. Intensive Care Med. 2020;46:1–16.
56. Schaefer B, Schmitt CP. The role of molecular adsorbent recirculating system dialysis for extracorporeal liver support in children. Pediatr Nephrol. 2013;28(9):1763–9.

47 Dialytic Therapy of Inborn Errors of Metabolism in Case of Acute Decompensation

Lucile Barcat, Patricia Monnier, Franz Schaefer, and Philippe Jouvet

Introduction

Some inborn errors of metabolism involve enzyme defects in the catabolic pathway of amino acids that induce a metabolic encephalopathy by accumulation of neurotoxic metabolites (endogenous intoxication). In these diseases, intermediate products of amino acid catabolism are not detoxified by the liver, accumulate, and contribute to neurologic symptoms (Fig. 47.1). Cerebral edema is frequently associated with these disorders and is mainly due to cytotoxic mechanisms [1, 2]. Since the encephalopathy is related to the accumulation of toxic metabolites, specific therapeutic strategies are required to decrease this accumulation and restore brain function, including dialysis. Rapid elimination of these metabolites is crucial in order to prevent irreversible neuronal damage since long-term outcome is correlated with the duration of the metabolic crisis. Metabolic crises are challenging indications for dialysis in several ways: the initial treatment is the institution of protein anabolism to suppress further neurotoxic metabolite production. It is important not to miss the time point when dialysis becomes necessary to prevent irreversible brain damage. Small infants and neonates, who usually have the most rapid and severe course of disease and the greatest need for efficient detoxification, are particularly challenging with respect to vascular access and methodological efficacy and accuracy. This chapter reviews the principles of anabolic treatment and management by dialysis of neonatal and pediatric metabolic emergencies.

Clinical Manifestations and Laboratory Investigations

In some circumstances, the patient's diagnosis is clear at the time of admission and clinical management can focus on specific treatment. This is the case in one-third of the neonates and two-thirds of the children with inborn errors of metabolism (IEM) who are admitted to the Pediatric Intensive Care Unit (PICU), in our experience [3]. Unfortunately, there is almost no exact report on the incidence of IEM in Neonatal Intensive Care Units [4]. Indeed, the first challenge is to quickly diagnose treatable disorders so as to ensure prompt treatment and recovery.

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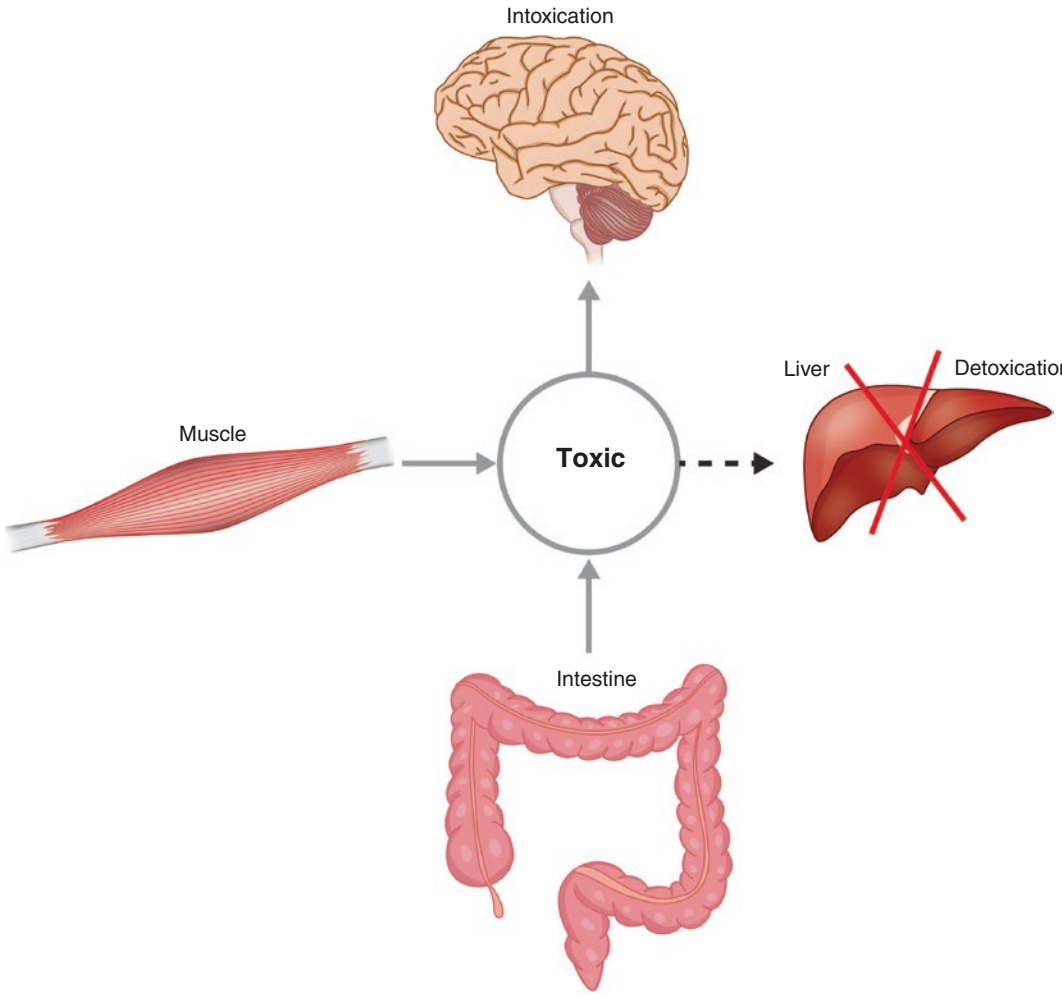

Fig. 47.1 Endogenous intoxication model: the toxic metabolite produced by the intestine and muscle amino acid catabolism (NH_3, propionic acid, etc., depending on the inborn error of metabolism) is not metabolized by the liver, resulting in toxic accumulation and brain damage. (Courtesy of D. Rabier (Biochemical Laboratory, Necker Hospital, France))

The initial clinical manifestations are characterized by nonspecific neurological abnormalities such as irritability, poor feeding, or somnolence, followed by rapid deterioration. The diagnosis is suspected based upon the combination of clinical course and laboratory investigations.

Metabolic crisis may occur at any age from the neonatal period to adulthood. A recent case report of a multifactorial non-cirrhotic hyperammonemic encephalopathy in adulthood recalls the importance of evaluating serum ammonia in front of any atypical clinical picture at any age of life [5]. Each attack can follow a rapid course that ends in either spontaneous improvement or unexplained death, despite supportive measures in the PICU. The following events may trigger acute decompensation by increasing neurotoxic metabolite production: prolonged fasting, anesthesia and surgery, infections, prolonged exercise, drugs (valproic acid, steroids, and adrenocorticotropic hormone), and high protein intake. Despite multiple etiologies, intercurrent infection is recognized as the leading cause of metabolic decompensation in patients with IEM. Some authors

have recently revisited the mechanism of impact of infection in the IEM patient and the central role of the liver as a metabolic and immunologic organ [6].

An inborn error of metabolism should be suspected when the following history is found (1): recurrent coma (2), unexplained death in the family or any neonatal death, even if it was attributed to another cause (e.g., sepsis, anoxia, etc.), and (3) consanguinity. Although most genetic disorders are hereditary and transmitted as recessive disorders, the majority of cases appear sporadically in developed countries because of small family sizes. Hepatomegaly, abnormal urine or body odor and myoglobinuria may help to refine the diagnosis [7].

General supportive measures and laboratory investigations should be undertaken as soon as metabolic encephalopathy is suspected. The initial approach for investigations is outlined in Table 47.1. It is important to perform these investigations as early as possible, and all laboratory tests should be obtained simultaneously, as most disorders may produce only intermittent abnormalities. The determination of plasma ammonia concentration is crucial when metabolic encephalopathy is suspected.

Etiologies

Inborn errors of metabolism with endogenous intoxication include urea cycle defects, maple syrup urine disease, and organic aciduria (propionic or methylmalonic aciduria). They are difficult to diagnose, and the biologic signs described in Table 47.2 and Fig. 47.2 should prompt consideration of such diseases. Metabolic acidosis with increased anion gap is observed in intermediate acid accumulation, such as organic acid disorders (propionic and methylmalonic acid). Severe hyperammonemia (>300 µmol/L) is observed in primary urea cycle defects, organic acid disorders, and fatty acid oxidation defects [8].

Treatment

The *principles of therapy* include (1) suppression of the de novo synthesis of toxic metabolites by adapted nutritional support including high caloric intake and no protein initially (2), pharmacological scavenging of ammonia by supplementation of substrates lacking physiological or alternative pathways, and (3) rapid removal of the small, water-soluble neurotoxic metabolites by dialysis.

Table 47.1 Laboratory investigations in inborn errors of metabolism

	Routine tests	Storage of samples and metabolic tests[a]
Urine	Smell (special odor) Look (special color) Ketones (Acetest) Ketoacids (DNPH)[b] pH	Fresh sample in the refrigerator, frozen sample at −20 °C, for metabolic testing (AAC, OAC, orotic acid)
Blood	Glucose Osmolality Blood gases Transaminases, bilirubin, γGT Ammonia Lactic acid Creatine kinase	Plasma heparinized at −20 °C (5 mL) for AAC, etc. Whole blood (10 mL) collected on EDTA at −20 °C (for molecular biology studies) Plasma or blood on filter paper for acylcarnitine dosage Redox status if lactate >10 mmol/L
Miscellaneous		Skin biopsy for fibroblast culture If death: liver and muscle biopsy

DNPH dinitrophenylhydrazine test, *AAC* amino acid chromatography, *OAC* organic acid chromatography

[a]Tests should be discussed with specialists in metabolic diseases

[b]This test screens for the presence of alpha-keto acids, as occur in maple syrup urine disease. It can be replaced by an amino acid chromatography, if available, in an emergency situation

Table 47.2 Etiologies of inborn errors of metabolism with neurotoxic accumulation, presenting with encephalopathy and which may be treated by dialysis

Clinical presentation	Predominant metabolic disturbances	Associated metabolic disturbances	Most frequent diagnoses
Metabolic coma without focal neurologic signs	Metabolic acidosis Hyperammonemia Hypoglycemia Hyperlactatemia	With ketosis Without ketosis Normal glucose Hypoglycemia With acidosis Without acidosis Normal glucose Hypoglycemia	Organic aciduria (MMA, PA), MSUD FAO[a] Urea cycle defects FAO[a] MSUD FAO[a] FAO[a] MCD FAO[a]
Neurologic coma with focal signs, seizures, severe intracranial hypertension, strokes, or stroke-like episodes	Biologic signs are variable, can be absent or moderate	Cerebral edema Hemiplegia or hemianopsia Extrapyramidal signs Stroke-like	MSUD OTC MSUD OTC MMA PA MMA Urea cycle defect MMA PA

MMA methylmalonic academia, *PA* propionic academia, *MSUD* maple syrup urine disease, *OTC* ornithine transcarbamylase, *FAO* fatty acid oxidation, *MCD* multiple carboxylase deficiency
[a]Usually not an indication for dialysis

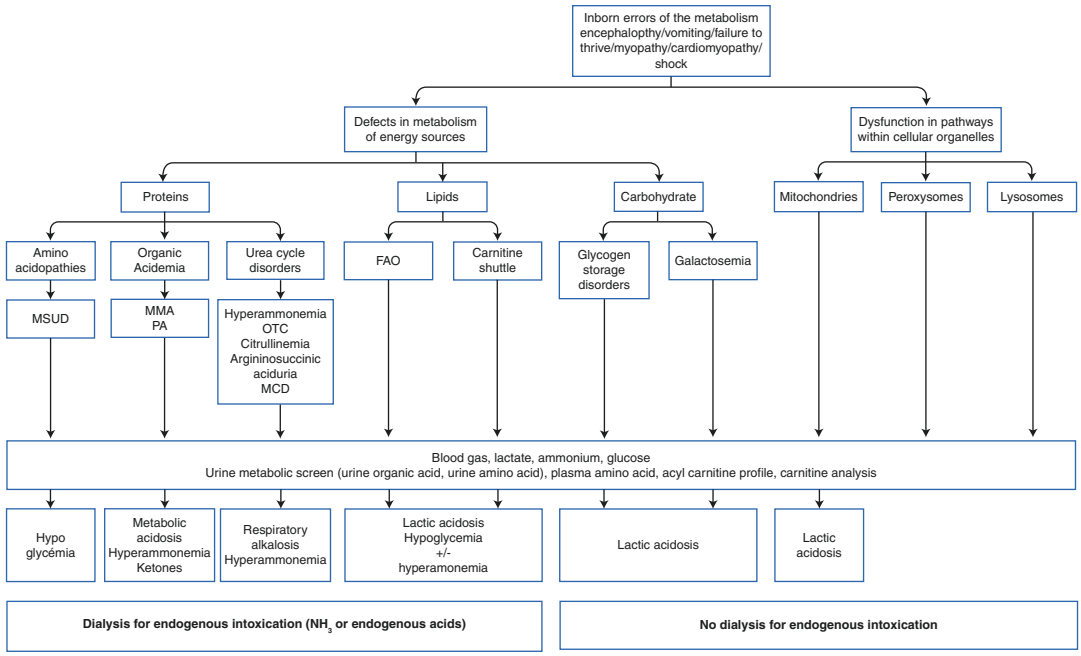

Fig. 47.2 Etiologies of inborn errors of metabolism with neurotoxic accumulation, presenting with encephalopathy, and which may or may not be treated by dialysis. MSUD, maple syrup urine disease; MMA, methylmalonic acidemia; PA, propionic acidemia; OTC, ornithine transcarbamylase; FAO, fatty acid oxidation; MCD, multiple carboxylase deficiency

Nutritional and Pharmacological Management

As soon as an endogenous intoxication is diagnosed, nutritional support should be discussed with the specialist, and it can include the following:

- *Rehydration first*: Many patients with metabolic defects are dehydrated at presentation as a result of poor oral fluid intake. Restoration of normal hydration to protect normal renal function and promote protein anabolism is crucial for effective treatment.
- *High caloric intake* to promote protein anabolism. Glucose is the only nutrient infused initially. The rate of glucose infusion should be high, so that enough energy is generated via glycolysis. Intravenous administration of 10% glucose with semi-normal saline solution is preferable to physiological saline solution in patients with hyperammonemia, since ammonia scavenging drugs contain large amounts of sodium [9]. When a central line is inserted, concentrated solutions of glucose are infused (>1000 kcal/m^2/day) which may require the addition of insulin infusion so as to avoid hyperglycemia. When the diagnosis is confirmed, nutritional support should be started, consisting of glucose and lipids (in the absence of a fatty acid oxidation defect) without protein, preferably by continuous enteral feeding with a caloric intake of at least 1500 kcal/m^2/day. Special amino acid mixtures are used to supply nontoxic amino acids. For example, in MSUD, the enzyme defect involves the branched chain amino acids (leucine, valine, and isoleucine). The mixtures used are initially free of these three branched chain amino acids but include the other essential amino acids.
- *Avoidance of any factor that promotes protein catabolism*, including steroid therapy (see above).
- *Specific medications* in some inborn errors of metabolism, such as ammonia removal drugs (see Table 47.3). Ammonia scavengers (sodium phenylacetate and sodium benzoate) with an initial loading dose are key treatments in case of hyperammonemia [10]. Carbamylglutamate has been used successfully in methylmalonic and propionic acidurias as an allosteric activator. Carbamylglutamate resulted in a dramatic decrease in ammonia blood levels with a similar effect to dialysis in some cases [11].

Metabolite Removal by Dialysis

Since the brain damage induced by neurotoxic metabolites is correlated with the duration of exposure to high levels of these metabolites, metabolic crises are considered emergency indications for dialysis requiring use of the most readily available and effective dialysis modality [7]. After 3–4 h of the nutritional and pharmacological treatment described above, medical management is evaluated with respect to neurological recovery, evolution of biochemical markers (serum ammonia, pH, etc.), and nutritional tolerance. However, this 4-h window should be used to prepare for having dialysis ready for nonresponders. The criteria for dialysis and the optimal modality to use are not yet well established for each disease and are currently based on individual institutional experience. The decision is made with a multidisciplinary approach that involves intensivists, specialists in metabolic diseases, and nephrologists. For technical aspects of each dialysis methods see corresponding chapters.

Hyperammonemic Disorders

In hyperammonemic disorders, increasing serum ammonia level or values persistently above 300–500 μmol/L are usual indications for dialysis [10, 12]. Since rapid toxic removal is crucial for limiting damage to susceptible tissues, particularly in hyperammonemic crises, the selection of dialysis modality must focus upon its efficacy of metabolite clearance. Other factors to consider in critically ill children are hemodynamic stability and intracranial hypertension. Dialysis is ended when ammonia blood levels are below 100 μmol/L [13–15].

Table 47.3 Specific treatments of inborn errors of metabolism

Drug	Effect	Indication (s)	Dose (s)	Administration
Sodium benzoate	Ammonia removal	NH_3 >200 µmol/L Urea cycle disease Ketotic hyperglycinemia	Loading dose: 500 mg/kg Maintenance: 500 mg/kg/24 h	IV 90 min IV 24 h
Sodium phenylacetate	Ammonia removal	NH_3 >200 µmol/L Urea cycle disease	Loading dose: 500 mg/kg Maintenance: 500 mg/kg/24 h	IV 90 min IV 24 h
Sodium phenylbutyrate	Ammonia removal	NH_3 >200 µmol/L Urea cycle disease	450–600 mg/kg/days 3–6 times a day max 20 g/day	PO
Arginine	Ammonia removal	NH3 >200 µmol/L Urea cycle disease	Loading dose: 600 mg/kg Maintenance: 600 mg/kg/day then 200 mg/kg/day	IV IV 24 h
Carglumic acid	Ammonia removal	NH_3 >200 µmol/L N acetylglutamate deficiency MMA PA FAO	100–250 mg/kg/day 2–4 doses	PO
Carnitine	Primary or secondary deficiency	Organic aciduria FAO Mitochondrial disorders	50–100 mg/kg/day in divided doses every 3–4 h	IVC or PO
Vitamin B12: hydroxycobalamin	Enzyme cofactor Methionine synthase deficiency	MMA	1–5 mg/kg/day	IM or IV
Metronidazole	Decreased toxin production by intestine bacteria	MMA PA	15–20 mg/kg/day divided in 2–3 doses	PO
Biotin	PC cofactor	PA Biotinidase deficiency Carboxylase deficiencies	5–20 mg once /day	PO
Riboflavin	Cofactor of acyl dehydrogenase	FAO	20–40 mg/day	IV or PO
Thiamine	Enzymatic cofactor	MSUD	50–200 mg/day	IV or IM

In suspected cases of IEM, the above specific treatments may be indicated in metabolic encephalopathy, after specialist consultation. Some therapies are specific for toxic accumulation (i.e., hyperammonemia) and some are specific a disease

MSUD maple syrup urine disease, *MMA* methylmalonic acidemia, *PA* propionic acidemia, *OTC* ornithine transcarbamylase, *FAO* fatty acid oxidation, *MCD* multiple carboxylase deficiency, *NH_3* ammoniac, *PC* pyruvate carboxylase, *IV* intravenous, *IVC* continuous intravenous infusion, *IM* intramuscular, *PO* per os

In hyperammonemic metabolic crises, experimental evidence suggests that ammonium is more efficiently removed by extracorporeal techniques than by peritoneal dialysis (PD) [16, 17]. PD is of limited efficacy in hyperammonemic patients, because normalization of blood ammonia levels occurs in no less than 24 h, continued dialysis is required over 1–5 days on average, and a failure to decrease ammonia levels is seen in individual cases [17–25]. Better results are obtained using continuous venovenous extrarenal therapies (CERT) including continuous hemofiltration [9] and continuous hemodialysis; blood ammonia is typically reduced 50% within 4–8 h and by >90% within 10 h, and therapy usually can be discontinued within 24 h [22, 26–29]. The most

efficient toxic removal is achieved by the use of intermittent hemodialysis (iHD), which reliably decreases blood ammonia concentrations by 75% within 3–4 h [17, 20, 21, 30–32]. However, repeated hemodialysis sessions or a switch to CERT are usually required due to rebound hyperammonemia [17, 20]. Hence, *continuous veno-venous hemodialysis* (CVVHD) until attainment of complete normalization of blood ammonium levels is considered the treatment of choice in most centers. The routine use of this technique has become feasible with the advent of dialysis machines specifically adjusted for use in small children.

Whatever the method used (iHD or CERT), the expected clearance should be greater than 40 mL/min/1.73 m^2. Metabolite clearance is measured by the formula:

$$\text{Clearance}\left(\text{mL}/\text{min}\right) = \text{blood flow}\left(\text{mL}/\text{min}\right) * \left(C_{\text{pre}} - C_{\text{post}}\right) / C_{\text{pre}},$$

where C_{pre} and C_{post} are the pre- and post-dialyzer metabolite blood concentrations.

Maple Syrup Urine Disease (MSUD)

The incidence rates of inborn metabolic diseases vary by country. MSUD is an autosomal recessive disease with an incidence ranging from 1/120,000 to 1/290,000 in the United States [33]. For some authors, dialysis is indicated if two of the three following criteria persist 3–4 h after initial treatment: coma, gastrointestinal intolerance, and plasma leucine levels ≥1700 μmol/L [34]. Dialysis is concluded when plasma leucine levels are below 1000 μmol/L.

In patients with MSUD, the low endogenous clearance of leucine and other branched chain-keto and amino acids is insufficient to reverse the accumulation of branched-chain amino acid (BCAA) that occurs during catabolic states. Since several fold higher BCAA clearance rates are achieved by PD, this technique has been regarded as the method of choice since its introduction in the 1980s [19, 23, 35]. More recently, 100–150% higher BCAA removal rates have been demonstrated experimentally with continuous extracorporeal blood purification techniques compared to PD (Fig. 47.3) [17, 36]. In clinical practice, CERT resulted in better leucine clearance than PD [27, 28, 37]. In children, iHD provided higher leucine clearance and required shorter sessions than CERT (5.4 ± 0.6 h vs. 17.1 ± 6.0 h). A leucine clearance ≥50 mL min^{-1}.1.73 m^{-2} resulted in a similar kinetic profile both with CERT and iHD [34, 38]. Currently, a major technical limit in monitoring the acute treatment of MSUD is the difficulty in obtaining rapidly serial plasma leucine levels during treatment. With CERT, leucine plasma levels decreased according to a bicompartmental model similar to that of non-protein-bound small-molecular-weight solutes such as urea or creatinine. This suggests that leucine clearance can be estimated from the creatinine clearance [38]. However, when extracorporeal technics are not available, there is one case report of successful treatment of acute MSUD with sodium phenylacetate/sodium benzoate and sodium phenylbutyrate [39].

Other Organic Aciduria

The incidence of these rare diseases is also variable. While individually rare, the cumulative incidence of inborn errors of metabolism has been shown to be upward of 1/800. To date, more than 1000 different IEM have been identified [40]. In methylmalonic or propionic aciduria, dialysis is indicated if two of the four following criteria persist 3–4 h after initial treatment: coma, gastrointestinal intolerance, and pH<7 or persistent high blood ammonia levels after carbamylglutamate treatment [41]. CERT or iHD are preferred (in these authors' experience). The other inherited metabolic diseases are not usual indications for dialysis. Extracorporeal removal therapy is sometimes initially instituted because an endoge-

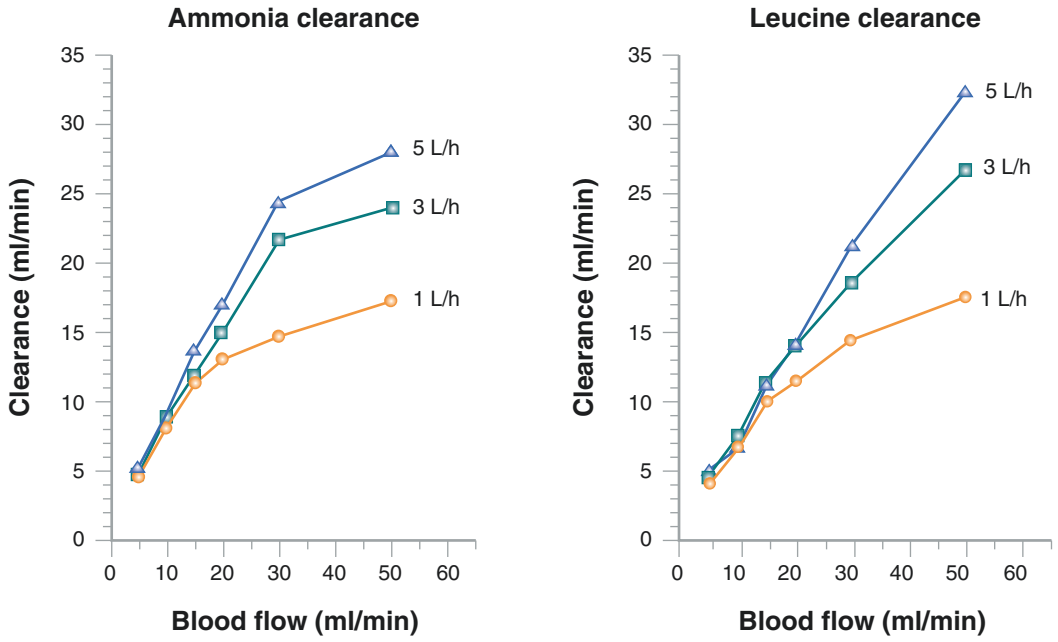

Fig. 47.3 Effect of blood and dialysate flow rate on ammonium and leucine removal by hemodialysis in a neonatal setting (simulation study using Baxter BM25 device and Bellco Spiraflo HFT02 dialyzer). (Modified from Schaefer et al. [17])

nous intoxication is thought to be the most likely diagnosis at the time of ICU admission.

Dialysis Equipment

Catheter

The choice of catheter has to balance between the aim of achieving an adequate blood flow and the risks of catheter insertion in a newborn. Ideally, a blood flow of 150 mL/min/m^2 should be attained, that is, 30–35 mL/min in an average neonate. This goal can be reached by inserting a 6.5-French double-lumen catheter (e.g., Gambro 6.5 Fr, 3.5 in.) into a femoral vein. This catheter provides excellent blood flow rates, but insertion may be difficult in small neonates. Alternatively, two 5-French single-lumen catheters (e.g., Medcomp 5 Fr, 3.0 in.) can be inserted [39]. Umbilical catheters are less suitable for dialysis because of high flow resistance determined by their length, but special extracorporeal setups involving two shortened umbilical catheters have been used anecdotally in small neonates.

Dialyzer

Polysulfone dialyzers should be preferred because of their superior biocompatibility and lower anticoagulation requirements. The surface of the dialyzer membrane should approximately match the body surface area of the patient. We have had excellent experience with the Fresenius FX paed (FMC, Bad Homburg, Germany) and the Spiraflo HFT02 (Bellco, Mirandola, Italy), which have fill volumes of 18 and 25 mL respectively.

Dialysis Machines and Tubing

In principle, emergency dialysis in neonates with inborn errors of metabolism can be performed using adjusted tubing systems on standard hemodialysis machines, such as the neonatal tubing

for the Fresenius 2008 or 4008 devices. These tubing sets have a fill volume of 47 mL. Even when used with the smallest neonatal dialyzers available, the total volume of the extracorporeal system exceeds 10% of the estimated blood volume of an average neonate. In that case, the circuit can be primed with blood or albumin to have a better hemodynamic tolerance at dialysis start. Another disadvantage is that an incorrect blood flow rate is displayed when small-volume neonatal tubes are used. Moreover, due to the fixed high dialysate flow rate of at least 500 mL/min with the 2008 device (300 mL/min with the 4008), critical depletions of phosphate and other solutes not present in the dialysis fluid may occur with prolonged use of this technique. Machines specifically designed for continuous renal replacement treatment in children are available, such as the BM25 (Baxter) or the PRISMAFLEX device (Gambro). The main advantages of these systems are the small volume of the extracorporeal system, accurate and fine-scaled setting of blood flow even in the low range typical for neonatal dialysis, precise control and variable choice of dialysate flow, and the mobile, reverse osmosis-independent device setup.

Dialysis Management

In order to achieve maximal treatment efficacy, blood flow should be set to the maximal value provided by the machine without alarms, which should be set as wide as possible. The dialysate flow rate required to achieve maximal clearance is determined by the blood flow achieved. In a neonatal dialysis simulation study, we found a linear relationship between blood flow and ammonium and leucine clearance up to the maximal blood flow rate usually achievable in neonates (i.e., 30 mL/min) with a dialysate flow rate of 5 L/h (Fig. 47.2). As a rule of thumb, extraction of these metabolites is maximal when dialysate flow exceeds blood flow by at least three times. This target can easily be achieved by passing bag dialysis fluid along the filter utilizing the filtration/substitution pump system of a pediatric continuous renal replacement machine such as the Prismaflex. Beginning by intermittent hemodialysis, to have a high removal of metabolite first, then continued by continuous hemodialysis to avoid rebound. Clearance is at least 35-50 mL/min/1.73 m^2.

The major complications to consider when dialyzing neonates or small infants with metabolic crises are *clotting* of the extracorporeal system, *hemodynamic instability,* and *risk of cerebral edema increase*, each of which can cause treatment interruptions and hence hazardous delays in the removal of toxic metabolites.

In order to prevent clotting, heparin should be administered at a dose sufficient to increase the activated clotting time (ACT) to 120–150 s. We use an initial bolus of 1500 IU/m^2 followed by continuous infusion of 300–600 IU/m^2/h. Anticoagulation should be monitored by hourly ACT measurements. Coagulation requirements are inversely related to the blood flow rate. However, with the goal to avoid adverse effects due to heparine, a prospective, non-randomized descriptive study on 18 pediatric patients and 119 treatments was published using citrasate (a citrate-based dialysate) with promising results [42].

Hemodynamic instability, leading to reduced cerebral perfusion pressure, is common in patients with a prolonged duration of hyperammonemia due to urea cycle disorders.

Another risk is a quick decrease in osmolarity during dialysis which may lead to intracellular water shift.

The challenge with both intermittent and continuous techniques is to accomplish rapid removal of ammonia without worsening cerebral edema by inducing hypotension and/or creating osmotic shifts. This is achieved by the following measures (1): NaCl 0.9% or albumin 5% infusion before the start of extracorporeal therapy (2), priming the circuit with blood when extracorporeal circuit volume exceeds 10% of the child's blood volume (80 mL/kg) (3), use of a dialysate fluid of osmolarity equal or greater than patient

osmolarity (4), no ultrafiltration, and (5) if neurologic deterioration is observed during therapy, the toxic clearance should be reduced and mannitol infused.

CERT seemed to significantly decrease inflammation when compared to intermittent hemodialysis in 22 children [43]. This supports the use of CERT in endogenous intoxications, as protein anabolism is one of the main goals of the treatment [43].

In 2001, it was suggested in a case report that moderate hypothermia (34 °C) could be considered in order to decrease metabolic activity in severe hyperammonemia [44]. This was confirmed later in a short series of seven cases [45]. This effect was attributed to a slowing of metabolic ammonia generation.

Clinical Outcomes

Metabolic encephalopathy due to inborn errors of metabolism represented 2% of admissions to a PICU serving a national reference center for metabolic diseases. The mortality rate of these patients was 28.6% [6], stable across the years despite an increased use of aggressive treatment [4]. In MSUD patients with neonatal onset who were dialyzed, good neurologic development is usually achieved. Neonatal onset of urea cycle defects (UCD) and propionic or methylmalonic aciduria (PA/MMA) is characterized by a less favorable outcome than MSUD and late-onset UCD and PA/MMA. F. Deodato et al. observed a mortality rate of 27.5% at 2 years and 48% at long-term follow-up, whereas late-onset patients showed only a 10% mortality rate [46]. Similarly, long-term cognitive development worsened in neonatal onset patients but did not deteriorate in late-onset ones.

Novel therapies are in development for inherited metabolic diseases including enzyme replacement therapy, hepatocyte transplantation followed by liver transplantation, and gene therapy [47–49]. For gene therapy the main obstacle to transfer in clinical practice remains the innate inflammatory acute response against the vector capsid protein, a complex and multifactorial phenomenon. If such therapies are successful, the main challenge that will remain is to make a rapid diagnosis and initiate efficient treatment at the first onset. However, a recent paper highlighted the difficulties of research in that field [50].

All these observations emphasize the importance of expeditious diagnosis and prompt referral of infants with suspected inborn errors of metabolism to hospitals with a multidisciplinary team that includes metabolic experts, a skilled pediatric dialysis team, intensivists, laboratory staff, and dieticians [51].

References

1. Jouvet P, Rustin P, Taylor DL, Pocock JM, Felderhoff-Mueser U, Mazarakis ND, et al. Branched chain amino acids induce apoptosis in neural cells without mitochondrial membrane depolarization or cytochrome c release: implications for neurological impairment associated with maple syrup urine disease. Mol Biol Cell. 2000;11(5):1919–32.
2. Ratnakumari L, Qureshi IA, Butterworth RF. Effects of congenital hyperammonemia on the cerebral and hepatic levels of the intermediates of energy metabolism in spf mice. Biochem Biophys Res Commun. 1992;184(2):746–51.
3. Jouvet P, Touati G, Lesage F, Dupic L, Tucci M, Saudubray JM, et al. Impact of inborn errors of metabolism on admission and mortality in a pediatric intensive care unit. Eur J Pediatr. 2007;166(5):461–5.
4. Meng M, Zhang Y-P. Impact of inborn errors of metabolism on admission in a neonatal intensive care unit: a 4-year report. J Pediatr Endocrinol Metab. 2013;26(7–8):689–93.
5. Triplett KE, Murray R, Anstey M. Multifactorial non-cirrhotic hyperammonaemic encephalopathy. BMJ Case Rep. 2018;2018:bcr-2017-223245.
6. Tarasenko TN, McGuire PJ. The liver is a metabolic and immunologic organ: a reconsideration of metabolic decompensation due to infection in inborn errors of metabolism (IEM). Mol Genet Metab. 2017;121(4):283–8.
7. Jouvet P, Lortie A, Maranda B, Tasker R. Metabolic encephalopathies in children. In: Nichols D, editor. Rogers textbook of pediatric intensive care. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2008. p. 973–83.
8. Fernandes J, Saudubray J-M, van den Berghe G, Walter JH, editors. Inborn metabolic diseases: diagnosis and treatment [Internet]. 4th ed. Berlin/Heidelberg: Springer-Verlag; 2006. [Cited 18 Feb 2019]. Available from: https://www.springer.com/la/book/9783540287858.

9. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138(1):S30–9.
10. Enns GM, Berry SA, Berry GT, Rhead WJ, Brusilow SW, Hamosh A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med. 2007;356(22):2282–92.
11. Gebhardt B, Dittrich S, Parbel S, Vlaho S, Matsika O, Bohles H. N-Carbamylglutamate protects patients with decompensated propionicaciduria from hyperammonaemia. J Inherit Metab Dis. 2005;28(2):241–4.
12. Picca S, Bartuli A, Dionisi-Vici C. Medical management and dialysis therapy for the infant with an inborn error of metabolism. Semin Nephrol. 2008;28(5):477–80.
13. Diane Mok TY, Tseng M-H, Chiang M-C, Lin J-L, Chu SM, Hsu J-F, et al. Renal replacement therapy in the neonatal intensive care unit. Pediatr Neonatol. 2018;59(5):474–80.
14. Gupta S, Fenves AZ, Hootkins R. The role of RRT in hyperammonemic patients. Clin J Am Soc Nephrol. 2016;11(10):1872–8.
15. Cho H. Renal replacement therapy in neonates with an inborn error of metabolism. Korean J Pediatr. 2019;62(2):43–7.
16. Semama DS, Huet F, Gouyon JB, Lallemant C, Desgres J. Use of peritoneal dialysis, continuous arteriovenous hemofiltration, and continuous arteriovenous hemodiafiltration for removal of ammonium chloride and glutamine in rabbits. J Pediatr. 1995;126(5 Pt 1):742–6.
17. Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant. 1999;14(4):910–8.
18. Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. J Pediatr. 1980;97(6):893–900.
19. Saudubray JM, Ogier H, Charpentier C, Depondt E, Coudé FX, Munnich A, et al. Hudson memorial lecture. Neonatal management of organic acidurias. Clinical update. J Inherit Metab Dis. 1984;7(Suppl 1):2–9.
20. Donn SM, Swartz RD, Thoene JG. Comparison of exchange transfusion, peritoneal dialysis, and hemodialysis for the treatment of hyperammonemia in an anuric newborn infant. J Pediatr. 1979;95(1):67–70.
21. Wiegand C, Thompson T, Bock GH, Mathis RK, Kjellstrand CM, Mauer SM. The management of life-threatening hyperammonemia: a comparison of several therapeutic modalities. J Pediatr. 1980;96(1):142–4.
22. Lettgen B, Bonzel KE, Colombo JP, Fuchs B, Kordass U, Wendel K, et al. Therapy of hyperammonemia in carbamyl phosphate synthase deficiency with peritoneal dialysis and venovenous hemofiltration. Monatsschr Kinderheilkd. 1991;139(9):612–7.
23. Gortner L, Leupold D, Pohlandt F, Bartmann P. Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. Acta Paediatr Scand. 1989;78(5):706–11.
24. Siegel NJ, Brown RS. Peritoneal clearance of ammonia and creatinine in a neonate. J Pediatr. 1973;82(6):1044–6.
25. Snyderman SE, Sansaricq C, Phansalkar SV, Schacht RC, Norton PM. The therapy of hyperammonemia due to ornithine transcarbamylase deficiency in a male neonate. Pediatrics. 1975;56(1):65–73.
26. Ring E, Zobel G, Stöckler S. Clearance of toxic metabolites during therapy for inborn errors of metabolism. J Pediatr. 1990;117(2 Pt 1):349–50.
27. Thompson GN, Butt WW, Shann FA, Kirby DM, Henning RD, Howells DW, et al. Continuous venovenous hemofiltration in the management of acute decompensation in inborn errors of metabolism. J Pediatr. 1991;118(6):879–84.
28. Falk MC, Knight JF, Roy LP, Wilcken B, Schell DN, O'Connell AJ, et al. Continuous venovenous haemofiltration in the acute treatment of inborn errors of metabolism. Pediatr Nephrol 1994;8(3):330–3.
29. Arbeiter AK, Kranz B, Wingen A-M, Bonzel K-E, Dohna-Schwake C, Hanssler L, et al. Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. Nephrol Dial Transplant. 2010;25(4):1257–65.
30. Rajpoot DK, Gargus JJ. Acute hemodialysis for hyperammonemia in small neonates. Pediatr Nephrol. 2004;19(4):390–5.
31. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int. 1994;45(3):903–6.
32. Rutledge SL, Havens PL, Haymond MW, McLean RH, Kan JS, Brusilow SW. Neonatal hemodialysis: effective therapy for the encephalopathy of inborn errors of metabolism. J Pediatr. 1990;116(1):125–8.
33. Levy HL. Genetic screening. Adv Hum Genet. 1973;4:1–104.
34. Phan V, Clermont M-J, Merouani A, Litalien C, Tucci M, Lambert M, et al. Duration of extracorporeal therapy in acute maple syrup urine disease: a kinetic model. Pediatr Nephrol. 2006;21(5):698–704.
35. Wendel U, Becker K, Przyrembel H, Bulla M, Manegold C, Mench-Hoinowski A, et al. Peritoneal dialysis in maple-syrup-urine disease: studies on branched-chain amino and keto acids. Eur J Pediatr. 1980;134(1):57–63.
36. Lim VS, Bier DM, Flanigan MJ, Sum-Ping ST. The effect of hemodialysis on protein metabolism. A leucine kinetic study. J Clin Invest. 1993;91(6):2429–36.
37. Jouvet P, Jugie M, Rabier D, Desgrès J, Hubert P, Marie Saudubray J, et al. Combined nutritional support and continuous extracorporeal removal therapy in the severe acute phase of maple syrup urine disease. Intensive Care Med. 2001;27(11):1798–806.
38. Jouvet P, Hubert P, Saudubray JM, Rabier D, Man NK. Kinetic modeling of plasma leucine levels during continuous venovenous extracorporeal removal

therapy in neonates with maple syrup urine disease. Pediatr Res. 2005;58(2):278–82.
39. Köse M, Canda E, Kagnici M, Uçar SK, Çoker M. A patient with MSUD: acute management with sodium phenylacetate/sodium benzoate and sodium phenylbutyrate [Internet]. Case Rep Pediatr. 2017 [Cited 13 Feb 2019]. Available from: https://www.hindawi.com/journals/cripe/2017/1045031/.
40. Mak CM, Lam C, Siu W, Law C, Chan W, Lee HC, et al. OPathPaed service model for expanded newborn screening in Hong Kong SAR, China. Br J Biomed Sci. 2013;70(2):84–8.
41. Filippi L, Gozzini E, Fiorini P, Malvagia S, la Marca G, Donati MA. N-carbamylglutamate in emergency management of hyperammonemia in neonatal acute onset propionic and methylmalonic aciduria. Neonatology. 2010;97(3):286–90.
42. Fajardo C, Sanchez CP, Cutler D, Sahney S, Sheth R. Inpatient citrate-based hemodialysis in pediatric patients. Pediatr Nephrol. 2016;31(10):1667–72.
43. Ağbaş A, Canpolat N, Çalışkan S, Yılmaz A, Ekmekçi H, Mayes M, et al. Hemodiafiltration is associated with reduced inflammation, oxidative stress and improved endothelial risk profile compared to high-flux hemodialysis in children. PLoS One. 2018;13(6):e0198320.
44. Whitelaw A, Bridges S, Leaf A, Evans D. Emergency treatment of neonatal hyperammonaemic coma with mild systemic hypothermia. Lancet. 2001;358(9275):36–8.
45. Lichter-Konecki U, Nadkarni V, Moudgil A, Cook N, Poeschl J, Meyer MT, et al. Feasibility of adjunct therapeutic hypothermia treatment for hyperammonemia and encephalopathy due to urea cycle disorders and organic acidemias. Mol Genet Metab. 2013;109(4):354–9.
46. Deodato F, Boenzi S, Rizzo C, Abeni D, Caviglia S, Picca S, et al. Inborn errors of metabolism: an update on epidemiology and on neonatal-onset hyperammonemia. Acta Paediatr Suppl. 2004;93(445):18–21.
47. Puppi J, Tan N, Mitry RR, Hughes RD, Lehec S, Mieli-Vergani G, et al. Hepatocyte transplantation followed by auxiliary liver transplantation--a novel treatment for ornithine transcarbamylase deficiency. Am J Transplant. 2008;8(2):452–7.
48. Brunetti-Pierri N, Clarke C, Mane V, Palmer DJ, Lanpher B, Sun Q, et al. Phenotypic correction of ornithine transcarbamylase deficiency using low dose helper dependent adenoviral vectors. J Gene Med. 2008;10(8):890–6.
49. Wilhelm M, Chung W. Inborn errors of metabolism. In: Nichols D, editor. Rogers textbook of pediatric intensive care. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2008. p. 1685–97.
50. Talele SS, Xu K, Pariser AR, Braun MM, Farag-El-Massah S, Phillips MI, et al. Therapies for inborn errors of metabolism: what has the orphan drug act delivered? Pediatrics. 2010;126(1):101–6.
51. Echeverri OY, Guevara JM, Espejo-Mojica ÁJ, Ardila A, Pulido N, Reyes M, et al. Research, diagnosis and education in inborn errors of metabolism in Colombia: 20 years' experience from a reference center. Orphanet J Rare Dis [Internet]. 2018 [Cited 13 Feb 2019];13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6097205/.

Therapeutic Apheresis in Children

48

Christina Taylan and Scott M. Sutherland

Introduction

The term "apheresis" is derived from the Greek word "Αφαίρεσης," which means removal. In the most traditional sense, it refers to the large-scale separation or elimination of a blood component. For example, plasmapheresis is the removal of plasma and leukapheresis is the removal of white blood cells (WBCs). The technique, in various forms, has been utilized for over a century [1]. However, the first use of the technique as we know it today occurred during World War II [2]. At that time, Dr. Edwin Cohn developed both a technique and a device for isolating the serum albumin fraction of blood plasma. Indeed, transfusions of this purified albumin component were responsible for rescuing thousands of soldiers from hypovolemic shock. After the war, Cohn worked to develop systems by which every component of donated blood could be used, ensuring that nothing would be wasted. The final result was a device with reusable parts capable of separating donor plasma "online" during whole blood donation [3].

True therapeutic apheresis procedures became feasible after notable trends in the design of instruments improved safety, hygiene, and efficiency. For example, lower extracorporeal volumes reduced the risk of hypovolemia and red blood cell (RBC) depletion; monitors and alarms were developed to detect clotting, air accumulation, and dangerous device and access pressures; anticoagulation began to be individualized for patient requirements; the size and weight of the devices decreased, allowing greater portability. Therapeutic plasma exchange was first used manually in 1952 to treat a patient with multiple myeloma and hyperviscosity; whole blood was removed from the patient, RBCs were separated gravitationally and returned to the patient, and the plasma component was discarded [4]. Several years later, in 1965, the engineer Jodson in collaboration with the physician Freireich created a centrifugal machine capable of removing WBCs from a patient with acute leukemic disease [5]. This automated process was initially used to collect white blood cells and platelets; however, it was ultimately modified to be used for plasma exchange in 1970 [6]. Today a number of therapeutic apheresis devices are available and the procedure is safe and easy to perform; technical improvements have made procedures quicker, safer, more convenient for instrument operators, and more comfortable for patients [7].

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In children, therapeutic apheresis requires selected modifications given a child's smaller size, blood volume, and developmental stage. Often, RBC priming is used to prevent hemodilution and hypovolemia. Although peripheral access may be used in older patients, the majority of pediatric patients require double lumen central venous catheters if the therapy will be needed for an extended period of time. Often diversional activities appropriate for the child's developmental age are provided to allay anxiety, divert attention, and elicit cooperation. That said, if the infrastructure of an apheresis center is appropriately designed, a child's size and clinical condition are not exclusionary criteria for apheresis. This chapter will give an overview of therapeutic apheresis techniques in general and will describe some of the issues that are unique to the application of apheresis techniques in pediatrics.

Principles of Separation

Apheresis involves the removal of whole blood from an individual and the subsequent separation of that blood into cellular elements and plasma; it is generally performed for the purpose of removing or exchanging one of these blood components. There are two techniques which can be used to achieve this separation: mechanical centrifugation and membrane filtration. During mechanical centrifugation, blood cells and components are separated based upon their density. Centrifugal apheresis can target blood cells or plasma and is very efficient, achieving nearly 80% plasma extraction efficiency. Notably, it requires relatively low blood flow rates and therefore can be performed using either peripheral or central venous access. Additionally, centrifugation can utilize intermittent or continuous flow. Intermittent flow centrifugation processes small volumes of blood in cycles (a cycle consists of blood being drawn, processed, and re-infused); continuous flow centrifugation simultaneously removes, processes, and re-infuses blood. Intermittent flow techniques can be performed using a single venous access site; however, the procedure time is longer and larger extracorporeal blood volumes are required; it is rarely used for therapeutic apheresis. Continuous flow centrifugation is faster but requires two vascular access sites (or a dual lumen central catheter), one for withdrawal of blood and a second for its return. Membrane filtration devices, on the other hand, selectively remove plasma along with high-molecular-weight proteins based upon differing membrane pore sizes (pore range 0.2–0.6 μm, Table 48.1). As a result, membrane filtration devices are capable of plasma removal and exchange but not cytapheresis. Notably, these devices are less efficient with lower plasma extraction efficiency (about 30%), require higher blood flow rates which tends to necessitate central vascular access, and require continuous flow.

Regardless of the method of extraction, all apheresis systems have certain aspects in common. First, all devices employ single-use, disposable, biocompatible plastic-ware to maintain sterility during the procedure. Second, these devices all incorporate safety features such as air traps to prevent air embolism, filters to prevent reinfusion of aggregates, pressure monitors to ensure safe access and intra-device pressures, and appliances to infuse an anticoagulant to prevent clot formation in the extracorporeal circulation. Finally, all automated separators have an obligate extracorporeal volume (ECV) which must be in the instrument's tubing during the apheresis procedure. The necessary ECV varies depending both on the type of device used and the type of procedure being performed. The temporary loss of these volumes is usually well tolerated by adults, but volume and RBC balance must be taken into careful consideration when automated apheresis is performed in small children,

Table 48.1 Size of cellular blood components

Cell type	Diameter
Plasma	N/A
Platelets	1–4 μm
Erythrocytes	6–8 μm
Lymphocytes	6–10 μm
Eosinophils	9–15 μm
Basophils	10–15 μm
Neutrophils	12–15 μm
Monocytes	10–30 μm

especially if the ECV represents >10–15% of the patient's total blood volume.

Pediatric-Specific Technical Considerations

The use of apheresis in children is feasible regardless of the size of the patient, as long as adequate vascular access can be established. However, apheresis procedures in young children must be customized to the situation and to the size of the patient because apheresis equipment and the software that controls it are, in general, designed for use in adults.

Vascular Access

Although apheresis procedures can be performed using peripheral venous access, most pediatric patients will not have antecubital veins large enough to support adequate flows. The access for drawing blood from the patient is of paramount importance as it must be capable of tolerating the pressures generated by the device; frequently, this necessitates placement of a 16 or 17-gauge steel needle (similar to those used to access arteriovenous fistulas). The return access can be a standard, plasticized peripheral intravenous line; however, it needs to be of larger bore as well (18 to 20-gauge). As a result, the vast majority of children who receive apheresis do so via a double lumen central venous catheter, utilizing the same access for both draw and return. In these situations, it is preferable to draw from the proximal port and reinfuse through the distal point to minimize recirculation; however, in practice the more patent lumen with superior flows is usually chosen for the draw access. The length and gauge of the catheter will depend on the child's physical size and vein quality; however, in all cases the wall of the catheter must be resilient enough to withstand the negative pressure generated during the apheresis procedure. Although catheters designed for dialysis are commonly used for apheresis procedures, newer "power injectable" central lines such as the PowerHickman® (Bard, Tempe, Arizona, United States) can be used as well. These catheters are capable of tolerating the pressures generated by the apheresis devices but are smaller, more flexible, and allow greater customization of length. For larger patients who are likely to require apheresis chronically, several companies make "power injectable" ports through which procedures can be performed. Unfortunately, standard softer central venous catheters such as those commonly used in oncology patients and the intensive care unit are not suitable apheresis access. Although they may be used for return of the blood, they are not stiff enough to be used for drawing of the blood into the device. Table 48.2 provides general guidelines for apheresis access across weight categories. It is worth noting that in situations where patients already have some type of extracorporeal circulation (i.e., extracorporeal membrane oxygenation, cardiopulmonary bypass, or continuous renal replacement therapy), most apheresis devices can be attached directly to these circulations without the need for alternate venous access.

Extracorporeal Volume and Blood Priming

One of the most important considerations when adapting apheresis instruments designed for adults for use in children is the extracorporeal volume (ECV) of the device. The actual ECV varies from approximately 200 to 400 mL depending on the device employed and the procedure performed. Although adult-sized patients may tolerate the transient loss of such a volume, smaller pediatric patients almost certainly will not. Generally speaking, if the ECV of the device exceeds 10–15% of the child's blood volume, blood priming of the device should be employed. Although the ECV for all apheresis devices/procedures is clearly defined, patients total blood volume must always be estimated. Traditionally, pediatricians estimate total blood volume to be 65–85 mL/kg depending on age. However, most apheresis devices contain more complex, empirically derived formulas for blood volume estimation that take into account gender, weight,

Table 48.2 Weight-based apheresis line choices for children

Catheter selection for all apheresis therapies based on patient weight and expected duration of therapy		
	Expected usage ≤14 days	Expected usage >14 days
<5 kg	7Fr x 10 cm (uncuffed dialysis catheter)	N/A[a]
5–10 kg	7Fr x 10 cm (uncuffed dialysis catheter)	8Fr (cuffed dialysis catheter)
10–15 kg	7Fr x 10 cm (uncuffed dialysis catheter)[b] 8Fr (cuffed or uncuffed dialysis catheter)[b]	8Fr (cuffed dialysis catheter)
15–20 kg	8Fr (cuffed or uncuffed dialysis catheter)	8Fr (cuffed dialysis catheter)
20–30 kg	8Fr (cuffed or uncuffed dialysis catheter)[b] 9.5 Fr (cuffed Power Hickman, Bard)[b]	8Fr (cuffed or uncuffed dialysis catheter)[b] 9.5 Fr (cuffed Power Hickman, Bard)[b]
30–40 kg	9.5 Fr (cuffed Power Hickman, Bard)	9.5 Fr (cuffed Power Hickman, Bard) 12 Fr Dual Lumen Apheresis Port (Vortex®, Powerflow®)[c]
40–50 kg	9.5 Fr (cuffed Power Hickman, Bard)	9.5 Fr (cuffed Power Hickman, Bard) 12 Fr Dual Lumen Apheresis Port (Vortex®, Powerflow®)[c]
>50 kg	9.5 Fr (cuffed Power Hickman, Bard)	9.5 Fr (cuffed Power Hickman, Bard) 12 Fr Dual Lumen Apheresis Port (Vortex®, Powerflow®)[c] Two 8Fr single lumen Apheresis Ports (Vortex®, Powerflow®)[d]

[a]No cuffed, permanent solution available for children <5 kg
[b]Choice of catheters should be based upon both patient size and vein size
[c]Apheresis ports can be placed in some patients less than 40 kg; however, patient and vein size will ultimately determine feasibility. These ports cannot be used earlier than 7–21 days after placement
[d]Two 8Fr single lumen Apheresis ports have an effective combined lumen size of ~ 16Fr; thus they can only be used in patients >50 kg. These ports cannot be used earlier than 7–21 days after placement

and height programed directly into the software [8]. Often, the apheresis instrument is primed by filling all of the tubing with red blood cells at a predetermined hematocrit before starting; however, priming can also be accomplished by infusing red cells or fluids directly into the patient at the start of the procedure while the machine is filling with blood coming directly from the patient. With proper planning, it is possible to perform an apheresis procedure in a small child with no change in the patient's blood volume or red cell mass during the procedure. The technical details of priming for pediatric apheresis procedures are discussed in detail elsewhere [9, 10].

Anticoagulation

Apheresis requires anticoagulation to prevent clotting in the device and extracorporeal circulation. Most commonly, the anticoagulant employed is sodium citrate which prevents clotting through the chelation of calcium; the clotting cascade is highly dependent on calcium and lowering calcium levels prevents activation. One substantial benefit of citrate anticoagulation is its regional nature; citrate allows anticoagulation of the circuit without exposing the patient to the bleeding risks of systemic anticoagulation. On the other hand, citrate can lead to transient hypocalcemia. The severity of this side effect depends primarily on the rate of infusion and the rate of hepatic citrate metabolism; smaller children and those with hepatic dysfunction are at the greatest risk for hypocalcemia. The symptoms of hypocalcemia during apheresis can range from mild (perioral, hand, and foot tingling and paresthesias) to severe (tremors, muscle spasms, tetany, seizures, and arrhythmias) [11–14]. Thus, patients undergoing apheresis using citrate anticoagulation should be monitored for early signs of citrate accumulation and hypocalcemia by focused symptom history or measurement of ionized calcium levels. In small children or sedated/unconscious patients who are incapable of verbalizing their symptoms frequent vital signs

monitoring is warranted along with serial calcium determination. Mild symptoms (tingling) can be treated by reducing the citrate infusion rate, stopping the procedure temporarily, or administering oral calcium supplements. Severe symptoms such as seizures, tetany, or EKG changes should be managed by terminating the procedure and administering calcium intravenously. Heparin can also be used as the anticoagulant for apheresis procedures. In this case, the patient typically receives a therapeutic dose of heparin during the procedure with resultant systemic and extracorporeal anticoagulation; these patients should be considered at risk for bleeding during and immediately after the procedure. For patients at greater bleeding risk it is safest to monitor the degree of heparinization during the procedure and adjust the infusion rate accordingly. In pediatric apheresis, it is particularly important to pay attention to the rate at which the anticoagulant is administered to the patient. Since the anticoagulant is added to the blood drawn from the patient in a constant ratio of volume of anticoagulant per volume of blood, the rate of blood draw determines the dose of anticoagulant that the patient ultimately receives. Apheresis procedures in children are often performed at relatively higher flow rates than adults (relative to weight). Thus, the dose anticoagulant (citrate or heparin) will be higher in a child than in an adult on a per kilogram basis. Specific anti-coagulation protocols will vary between institutions and are dependent on the device being used. For many devices, the anticoagulant dose is expressed as a ratio relative to the blood flow rate. For example, the default blood flow to anticoagulant ratio for plasma exchange at our institution is 10:1, meaning that for every 10 mL of blood that passes through the device, 1 mL of anticoagulant (ACD-A) is added; typical ratios for ACD-A are between 8:1 and 15:1 where higher ratios provide less aggressive anticoagulation. We typically use heparin only to provide photopheresis, primarily due to device specifications. In this scenario, depending on the patient's platelet count, 7500–10,000 units of heparin is added to 500 mL of normal saline and anticoagulation is provided at a ratio of 8:1 to 12:1. It is important to note that these ranges are merely guidelines and that it is important that anticoagulation is tailored to the individual.

Volumetric Control

The rates at which blood is drawn, processed, and returned during an apheresis procedure are determined by computerized algorithms that control the peristaltic pumps that move the blood through the tubing. While it is beyond the scope of this chapter to discuss these algorithms in detail, a few general points are worth noting. First, within certain limits, the patient's net balance of volume and the net balance of red cell mass can be manipulated independently during an apheresis procedure. This means, for example, that it is possible to administer a red cell transfusion during plasmapheresis with no net increase in the patient's intravascular volume, a maneuver that can be very advantageous for a patient with anemia and oliguric kidney failure. Second, it is possible to perform a plasmapheresis procedure that results in a net removal of plasma volume from the patient, or in a net fluid gain. It is important to note, however, that while these manipulations are feasible, using apheresis procedures as a method of volumetric control is not ideal; patients who need true ultrafiltration will be better served by some form of renal replacement therapy. However, subtle manipulations in volume can be helpful for patients who are exquisitely volume sensitive.

Apheresis Treatment Modalities and Procedures

Historically, there have been four primary therapeutic apheresis procedures: plasmapheresis, erythrocytapheresis, leukapheresis, and plateletpheresis. All four can be performed safely and effectively in pediatric patients with various modifications. This section will discuss these four primary procedures as well as several more specialized techniques.

Plasmapheresis

Plasmapheresis involves separation and removal of plasma from the cellular components of blood. During the procedure, a patient's plasma is collected and discarded into a waste bag while the cells themselves are mixed with a replacement fluid and returned to the patient. Therapeutic plasma exchange is generally employed in two situations. The first would be a scenario where a patient's plasma compartment contained a non-physiologic or undesirable protein or substance. An example of this is Goodpasture's disease; in this case, the pathogenesis of the patient's disease is the presence of circulating antibodies against the glomerular basement membrane. The antibodies are contained within the plasma component and are removed along with the plasma. Normovolemia is restored by replacing the discarded plasma with an equal volume of an osmotically equivalent fluid. Options primarily include donated fresh frozen plasma (FFP) or 5% albumin. Often, 5% albumin is used in isolation as it allows the procedure to be performed with minimal concern for transfusion-transmitted infectious disease, blood product allergic reactions, or transfusion-associated lung injury (TRALI) [15]. However, removal of plasma and replacement with 5% albumin leads to depletion of important plasma proteins (i.e., non-pathologic immunoglobulins and coagulation cascade components). As an example, as shown in Fig. 48.1, plasmapheresis of one plasma volume without concomitant replacement with a plasma product will reduce the levels of coagulation proteins by about 60–65%. This may be associated with a fibrinogen level below 100 mg/dL and prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT); however, it is not usually associated with clinical bleeding. Generally speaking, if the rate of hepatic regeneration of these coagulation factors is normal, performing plasmapheresis on an alternate day schedule tends not to require exogenous replacement with FFP. However, if daily plasmapheresis is required or the patient has synthetic hepatic dysfunction, a concomitant coagulopathy, or significant bleeding risk, at least a portion of the replacement fluids must be comprised of FFP. Often, institutions will

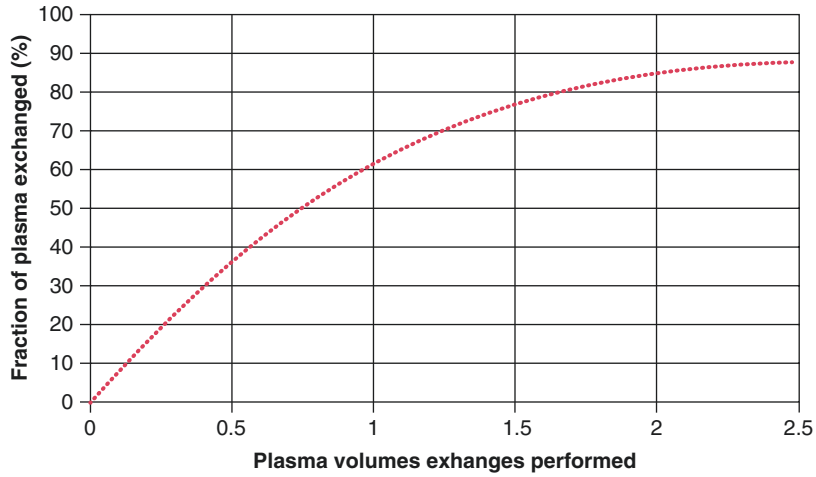

Fig. 48.1 Relationship between TPE volume exchanges and plasma turnover. As larger fractions of plasma are exchanged, each successive increase becomes less efficient. This is due to the fact that the process is provided continuously; the patient's plasma becomes mixed with the donor plasma during the course of the therapy. A single-volume exchange replaces approximately 65% of the patient's plasma, a 1.5x volume exchange replaces approximately 75% of a patient's plasma, and a double-volume exchange replaces approximately 85% of a patient's plasma. The diminishing returns suggest that exchanges larger than 2x volume are unlikely to provide significant incremental effect

set a pre-therapy fibrinogen threshold of 150–180 mg/dL and patients due to undergo plasmapheresis who have fibrinogen levels lower than this threshold will receive FFP as part of the replacement fluid; while some situations may require 100% of the replacement fluid to be FFP, often a mixture of 50% FFP and 50% 5% albumin will suffice. The second scenario where plasmapheresis is employed is in the setting of a blood protein or component deficiency. The best example of this is likely thrombotic thrombocytopenic purpura (TTP). In this case, the goal is not only removal of a pathologic substance but also the replacement of an absent physiologic one. In these situations, the replacement fluid must consist entirely of FFP. Although some patients with mild deficiencies may respond to plasma infusion alone, the vast majority require a large enough plasma volume to restore normal protein levels that plasma exchange is necessary to prevent massive volume overload.

A very important aspect of plasma exchange is the concept of efficiency and dose. As plasma is removed from the patient, the replacement fluid or fluids of choice must be given concurrently to maintain intravascular volume and oncotic pressure. As a result of this, the replacement fluids become admixed with the patient's plasma, thereby diluting it. Subsequently, a portion of the plasma removed throughout the procedure is technically the replacement fluid itself. At the beginning of a treatment, the majority of the removed fluid is the patient's plasma, whereas at the end of the plasmapheresis, much of what is removed is actually replacement fluid. The relationship between the amount of plasma removed (expressed as multiples of the patient's plasma volume) and the fraction of the original plasma remaining is given in Fig. 48.1. A plasmapheresis procedure that exchanges a volume equal to the patient's plasma volume (single-volume exchange) will achieve about 63% removal of the original plasma, with 37% remaining in the patient, as shown in the figure. Removal of twice the patient's plasma volume (double-volume exchange) will remove 86% of the original plasma. From the figure, it is apparent that the additional benefit of prolonging a plasmapheresis past two volumes is marginal. Finally, the overall efficiency of a single plasmapheresis procedure, or of a series of treatments, is also affected by the distribution between intra- and extravascular compartments of the targeted substance and on other metabolic characteristics such as rate of synthesis and degradation [16]. Figure 48.2 illustrates two commonly utilized regimens, daily single-volume exchanges (Fig. 48.2a) and alternate-day 1.5x volume exchanges (Fig. 48.2b). Each regimen is capable of achieving similar effective clearance albeit over shorter and longer timeframes, respectively. While alternate-day regimens are associated with greater inter-treatment rebound and longer effective clearance times, they also allow the body to re-accumulate physiologic components of hematologic homeostasis (i.e., clotting factors). The use of single-, 1.5x, or double-volume exchanges as well as delivery of the therapy on a daily or alternate day schedule depends on the manner in which these aspects are prioritized.

Erythrocytapheresis

Erythrocytapheresis involves separation of RBCs from the plasma and other cellular components. The RBCs are discarded and the volume replaced with an equal volume of replacement fluid or donor RBCs. When the patient's RBCs are replaced with donated RBCs, the procedure is commonly referred to as an automated exchange transfusion. This technique is most often employed in hemoglobinopathies; however, it has also been used to manage diseases caused by intra-erythrocytic parasites such as babesiosis and malaria [17]. In children and adults, however, the primary applications of erythrocytapheresis are in sickle cell disease. In patients with sickle cell disease, automated exchange transfusion can be used urgently to manage acute chest syndrome and/or cerebrovascular events. On a non-urgent basis, it can be used pre-operatively, during pregnancy, and in lieu of manual transfusion therapy. The apheresis machines can be programmed to achieve a desired post-procedure hemoglobin S level which can lead to more effective and effi-

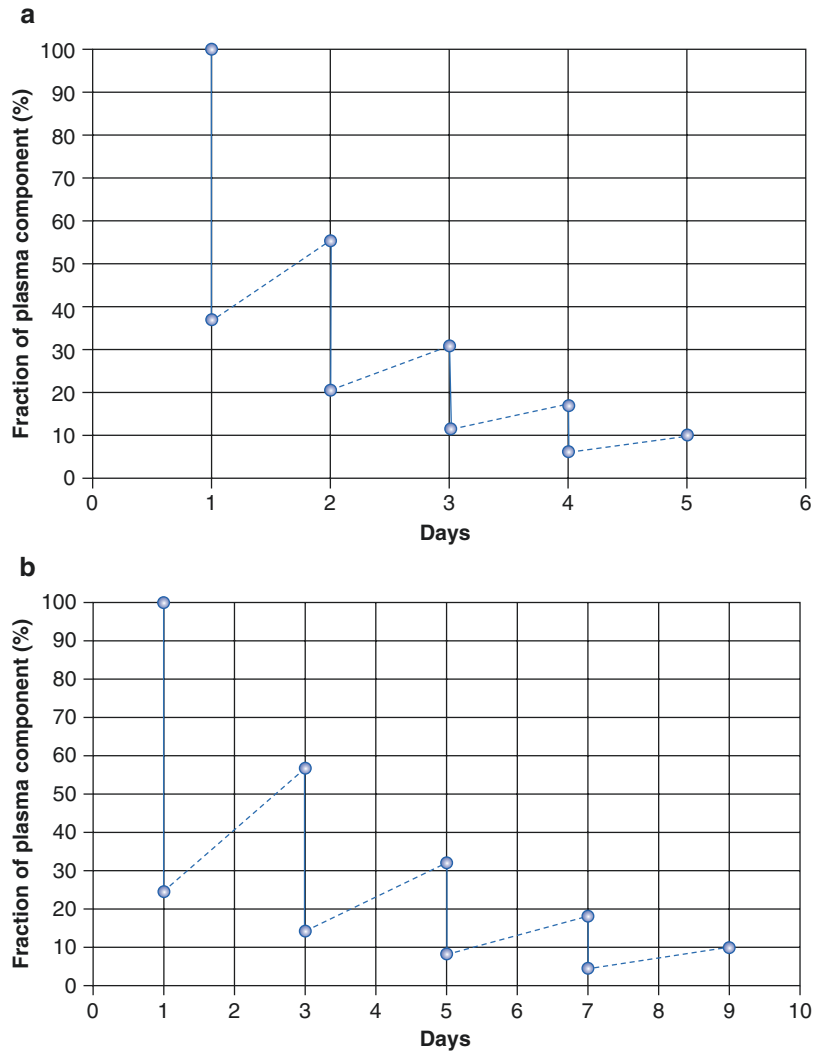

Fig. 48.2 Comparison of daily and alternate day plasma exchange regimens. Figure 48.2a depicts daily, single-volume exchanges whereas Fig. 48.2b depicts alternate-day exchanges of 1.5x volume. Similar effective clearances can be achieved over 4 or 7 days, respectively. While alternate day regimens allow greater inter-treatment rebound of pathologic blood components (i.e., autoantibodies), they also allow for synthesis and reaccumulation of physiologic compounds necessary for hematologic homeostasis (i.e., clotting factors)

cient disease management than that achieved with manual transfusion approaches. Automated exchange transfusions also prevent dramatic increases in effective circulating volume and are associated with reduced risk for iron overload [18, 19].

Leukapheresis

Leukapheresis is the process by which leukocytes are removed from whole blood while the plasma, platelets, and red cells are returned to the patient. Historically, the most common indication for leukapheresis has been malignancy-associated hyperleukocytosis. Hyperleukocytosis in the setting of leukemia can cause severe pulmonary and neurologic complications; traditionally, rapid reduction of the leukocyte count by automated therapeutic leukapheresis was thought to reduce the risk of these complications through a reduction in circulating WBC mass and blood viscosity [20–22]. Newer data, however, has suggested that leukapheresis may not significantly improve outcomes [23–25]. Based upon the best currently available data, leukapheresis tends to be considered when the WBC count is >300–400×10^9/L [26–28]; if initiated, it is often performed until the WBC falls below 50–100×10^9/L [26, 28]. Though its use in pediatric hematologic malig-

nancies can be debated, there is ample data to suggest that it can be performed safely even in very small children [26, 29]. Additionally, variations of this leukapheresis technique can be used to harvest peripheral blood mononuclear cells from allogeneic or autologous donors for stem cell transplantation or cell-based therapies [30, 31]. Leukapheresis allows harvest of peripheral blood progenitor cells which can then be used in stem cell transplantations. Alternatively, leukapheresis can be used to harvest T-cell lymphocytes which are manipulated ex-vivo and used therapeutically in the setting of malignancy [32, 33].

Plateletpheresis

In plateletpheresis whole blood from healthy donors is separated into platelet-poor plasma (PPP), platelet-rich plasma (PRP), and red cells. The PRP is retained as a single-donor platelet concentrate, while the PPP and red cells are returned to the donor. This is the single most frequent application of apheresis technology and harvested platelets are used to treat thrombocytopenia of various causes and severities. Plateletpheresis can also be used as a therapeutic procedure to remove excess platelets from the circulation in patients with symptomatic thrombocytosis [34, 35].

Photopheresis

Photopheresis is a specialized variation of the leukapheresis procedure. In photopheresis, leukocytes are collected and then exposed to a photosensitizing agent and ultraviolet A light; the photo-activated leukocytes are then returned to the patient [36]. When it was first introduced, the photosensitizing agent was administered systemically (orally); however, the currently employed procedure utilizes an agent which can be administered to the leukocytes ex vivo during the procedure [37]. This has increased effectiveness and tolerability, the latter of which is especially significant in pediatric patients [10, 37]. This therapy was first employed in the setting of cutaneous T-cell lymphoma [38–41] and has since been used to treat graft-versus-host disease, solid organ allograft rejection, and some autoimmune diseases [36, 38, 42–48]; in children, the most common indications are graft versus host disease and acute rejection of solid organ transplants [10]. Although it has been utilized since the 1980s, the mechanism of action remains poorly understood [10, 37–39, 49, 50]. The prevailing data suggests that the procedure mediates immunomodulation via induction of lymphocyte apoptosis [36, 37]. At our institution (SMS), a closed photopheresis system is utilized (CELLEX®, Therakos, Mallinckrodt Pharmaceuticals, Bedminster NJ, USA). This device has a priming volume of ~ 250 mL and a blood prime is recommended for patients <35 kg [51]. The manufacturer recommends heparin anticoagulation; however, the use of citrate has been successfully described [52]. Although special accommodations are required, this technique can be performed effectively and safely in small children with appropriately trained staff [10, 52, 53].

Lipoprotein Apheresis

Lipid apheresis (also described as LDL apheresis) refers to the process by which circulating lipoproteins are removed from the circulation via an extracorporeal circuit [54]. The definitive indication for LDL apheresis is familial hypercholesterolemia (FH), an autosomal dominant form of hypercholesterolemia. At our institution (CT), its heterozygous form has an estimated prevalence of approximately 1 in 500 persons, but a prevalence as high as 1 in 72 persons has been described in certain populations; the reported prevalence of the homozygous form ranges from 1 in 30,000 to 1 in 860,000 [55]. Patients with FH experience increased LDL-cholesterol (LDL-C) levels, extraplasmatic deposition of LDL-C, and an increased risk for premature coronary heart disease (CHD). In general, this risk and the atherosclerotic burden are dependent on the severity of the disease and the duration of exposure to elevated LDL-C levels [56]. Although CHD generally does not manifest before adulthood, two

indicators of early atherosclerotic development, namely, endothelial dysfunction and thickening of the arterial vessel wall, can be found in children with the homozygous form of the disease [57]; it is particularly important to identify these cases early so that aggressive lipid-lowering therapies can begin promptly in childhood [58]. Although LDL apheresis can be used in other forms of hypercholesterolemia, this approach is not as universally accepted and should not be considered unless patients have failed medical management. When performed, LDL-apheresis treatments take between 2 and 4 hours depending on the system and regimen. The goal of each treatment is a reduction in LDL-C of at least 60% and, in patients with established atherosclerotic lesions, target LDL cholesterol levels should be <100 mg/dL. Of note, inter-treatment rebound is common and variable amongst patients. Thus, if therapeutic targets are not met, the frequency should be increased to weekly or, if necessary, twice weekly [58]. It is important to note that in 2015, the FDA approved a medical anti-LDL therapy which may be used in lieu of LDL-apheresis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be used in patients with FH or in those with clinical evidence of atherosclerotic cardiovascular disease who have inadequately controlled LDL levels despite optimized statin therapy. These inhibitors bind and inactivate PCSK9 which augments LDL receptor recirculation and increases LDL-C clearance [59, 60].

Although a complete discussion of LDL apheresis is beyond the scope of this chapter, it is important to highlight the various LDL apheresis removal techniques:

1. *Immunoadsorption columns containing matrix-bound sheep antiapoB antibodies.* After plasma separation, the elimination of LDL and Lp (a) particles occurs by binding to polyclonal sheep anti-human apolipoprotein B-100 antibodies. Since the mechanism is very specific for apoB-100-containing particles, there is no significant elimination of other plasma components such as HDL and fibrinogen. Therefore, there is no restriction regarding the treated plasma volume.
2. *Direct adsorption of lipoprotein using hemoperfusion*. In this method, whole blood passes through an absorber containing porous polyacrylamide beads having polyacrylic acid on their surface. The negatively charged polyacrylic acid reversibly binds the apolipoprotein-B100 portion of LDL and Lp(a) and little fibrinogen.
3. *Heparin extracorporeal LDL precipitation.* In this LDL-Apheresis method the separated blood plasma is buffered with heparin acetate, lowering the plasma pH which results in crosslinking of LDL, fibrinogen and Lp(a) with heparin. This precipitate is then eliminated by a filter and excess heparin is removed by adsorption.
4. *Double Filtration Plasmapheresis (DFPP)*. After separation, plasma is processed through a second hollow fiber filter which is permeable to particles with a molecular weight below 50,000–100,000 Da; HDL, albumin, and smaller immunoglobulins pass through and are returned to the patient, whereas LDL, Lp(a), VLDL, and chylomicrones (as well as larger immunoglobulins like IgM) are retained and discarded.
5. *Dextran sulfate columns*. In this method, positively charged apolipoprotein B-100 contained in LDL, VLDL, and Lp(a) is bound to immobilized, negatively charged low-molecular-weight dextran. There are 2 different methods to achieve this. Whole blood can be passed directly through an absorber or, alternatively, plasma can be separated first via a membrane plasma separator; the separated plasma is then passed through the absorber before being returned to the whole blood.

Immunoadsorption

Immunoadsorption refers to the selective removal of a plasma constituent. In this technique, plasma is separated from the other blood components and then passed into a plasma absorption column. Pathogenic substances bind to the column (absorption) and are removed based upon the

selective binding between ligands on a given column and the pathogenic substances themselves. Unlike the non-selective substance removal achieved with plasmapheresis, immunoadsorption selectively removes specific protein types such as IgG or even individual (such as ABO) antibodies. In addition to its high efficiency, the technique maintains fluid homeostasis without the requirement of a replacement fluid and avoids exposure of the patient to foreign plasma, minimizing the risks of sensitization, allergic reactions, and infection. Hence, if available, immunoadsorption should be considered as a first-line option when the underlying disease is supposed to be caused by circulating agents that can be removed from the blood. The technical suitability of immunoadsorption in children depends on the size of the absorber and the resultant extracorporeal volume, which should not exceed 15% of the patient's total blood volume. Columns are commercially available for both single use and patient-specific re-use. The binding capacity of a column is limited to about 2 g of human IgG so two columns are often utilized; multiple-use absorbers can be regenerated during the treatment and the flow of plasma is diverted from the saturated column to the newly stripped one. The columns can be preserved and reused following a session; columns are typically reused 5 to 20 times depending on the system employed. Several of the more commonly used absorption columns are described in Table 48.3.

Immunoadsorption is associated with the standard side effects of extracorporeal procedures including hypotension, anemia, clotting, vascular access problems, and hemolysis. Notably,

Table 48.3 Plasma adsorbers used for immunoadsorption

Adsorber	Matrix	Binding	Remark
Coraffin	Sepharose/synthetic peptide	ß1-adrenerge receptor Ab	PV 60 Dilatative cardiomyopathy
Globaffin	Pure synthetic peptide Peptid GAM®	IgG1, IgG2, IgG4	Multiple use PV 60 ml
Glycosorb	Sepharose/BG antigen	Anti-A/anti-B-Ab	Single use PV 150 ml AB0 incompatible transplantation
Immunosorba	Sepharose/ Staphylococcus protein A	High affinity to Fc fraction of IgG immunoglobulins of the subclasses IgG1, IgG2, and IgG4	Multiple use PV 63 ml
Immusorba PH 350 L	Phenylalanine immobilized polyvinylalcohol gel	Immune complexes and anti-DNA antibody	Single use PV 300 ml Autoimmune diseases (systemic lupus erythematosus, malignant rheumatoid arthritis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis
Immusorba TR 350 L	Tryptophan immobilized polyvinylalcohol gel	Anti-acetylcholine receptor antibodies and immune complexes	Single use PV 300 ml Neurologic antibody-mediated disease
Selesorb	Dextran sulfate/ cellulose	DNA-Ab, Cardiolipin-Ab, immune complexes	Multiple use PV 150 ml Systemic lupus erythematosus
Therasorb	Sepharose/polyclonal sheep-IgG	IgG (subclasses 1–4) IgM, IgA, IgE, IgD, circulating immune complexes Rheumatoid factors Fragments of immunoglobulins	Multiple use PV 300 ml

Table 48.4 Indications for immunoadsorption by system

Dermatology	Dermatomyositis/polymyositis Pemphigus vulgaris/foliaceus and bullous pemphigoid Atopic dermatitis
Hematology	Thrombotic microangiopathies Acquired inhibitory hemophilia
Nephrology	ABO incompatible kidney transplantation Antibody-mediated rejection ANCA-associated vasculitis Cryoglobulinemic vasculitis Focal segmental glomerulosclerosis
Neurology	Multiple sclerosis Myasthenia gravis and Lambert Eaton myasthenia syndrome Neuromyelitis optica Chronic inflammatory demyelinating polyneuropathy
Ophthalmology	Age-related macular degeneration (AMD)
Otorhinolaryngology	Acute hearing loss, idiopathic sudden sensorineural hearing loss (SSHL)

angiotensin-converting enzyme (ACE) inhibitors have been associated with potentially severe reactions which occur shortly after the start of the apheresis procedures. The belief is that the contact of the blood with the negatively charged surfaces of the absorber activates bradykinin release; ACE inhibitors, in turn, block bradykinin degradation resulting in hypotension, dizziness, vomiting, and skin rashes. Because of this, ACE inhibitors must be stopped 24 hours before an immunoadsorption procedure is performed; angiotensin-receptor blockers (ARBs) are not associated with this issue and can be prescribed in lieu of ACE inhibitors if similar antihypertensive effect is required. The use of immunoadsorption is growing and indications are becoming more common. A decade ago, its use was limited to rheumatoid arthritis, hemophilia, and a few kidney diseases. However, immunoadsorption has become an important part of the overall therapeutic paradigm in a number of different diseases across a spectrum or organ systems (Table 48.4) [61–72].

Indications for Apheresis Techniques

The American Society for Apheresis periodically publishes guidelines on indications for therapeutic apheresis; the most recent update was in 2019 [17]. Guidelines such as these are extraordinarily important since although apheresis has many theoretical applications, in practice, only some are supported by existing data. These particular guidelines classify indications by category (Table 48.5) which define disorders according to whether therapeutic apheresis is a first-line therapy (Category I), a second-line therapy (Category II), a therapy of uncertain benefit (Category III), or a therapy known to be harmful or ineffective (Category IV). Therapeutic apheresis should be used for all Category I and II indications and considered for Category III indications; it should not be employed to treat Category IV disorders. The guidelines also describe each therapeutic recommendation as strong (Grade 1) or weak (Grade 2) and the data supporting the recommendation as high (A), moderate (B), or low quality (C). Using this combined rating system, one is capable of determining the likely benefit of any given therapy in any given disease. The Category I indications (therapeutic apheresis in first line therapy) are shown in Table 48.6; Category II indications (therapeutic apheresis is second-line therapy) are shown in Table 48.7 [17]. A complete discussion of all the potential indications for therapeutic apheresis is beyond the scope of this chapter; however, we have included more in-depth discussions of some of the more common pediatric indications below.

ANCA-Associated Glomerulonephritis

Antineutrophil cytoplasmic antibody (ANCA)–associated diseases are vasculitides which affect

Table 48.5 Indications and grading of recommendations for therapeutic apheresis

Categories of therapeutic indications		
I	Disorders for which apheresis is accepted as *first-line therapy,* either as a primary standalone treatment or in conjunction with other modes of treatment	
II	Disorders for which apheresis is accepted as *second-line therapy,* either as a standalone treatment or in conjunction with other modes of treatment	
III	Optimum role of apheresis is not established. Decision making should be individualized	
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.	
Grading of recommended indications		
1A	Strong recommendation	High-quality evidence
1B	Strong recommendation	Moderate-quality evidence
1C	Strong recommendation	Low-quality evidence
2A	Weak recommendation	High-quality evidence
2B	Weak recommendation	Moderate-quality evidence
2C	Weak recommendation	Low-quality evidence

Adapted from Padmanabhan et al. [17]

small and medium-sized blood vessels. The two most common diseases, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), present primarily with glomerulonephritis, severe renal failure, and pulmonary hemorrhage [73]. The prompt diagnosis and treatment of these diseases is crucial as delays increase the risk for morbidity and mortality. The cornerstone of ANCA-associated disease management is systemic immunosuppression; commonly this involves the use of high-dose corticosteroids and an additional agent, typically cyclophosphamide or rituximab [74–77]. However, there is ample data to suggest additional benefit from therapeutic apheresis in certain circumstances. The majority of prospective studies suggest that while plasma exchange is not beneficial in milder

Table 48.6 Category I apheresis indications

Therapeutic Plasma Exchange	
Disease	Grade
Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome	1A
Acute liver failure (high-volume TPE)	1A
ANCA-associated rapidly progressive glomerulonephritis (microscopic polyangiitis, granulomatosis with polyangiitis, renal limited vasculitis) *Diffuse alveolar hemorrhage* *Creatinine ≥5.7 mg/dL or dialysis dependence*	1C 1A
Anti-glomerular basement membrane disease (Goodpasture syndrome) *Diffuse alveolar hemorrhage* *Dialysis independence*	1C 1B
Catastrophic antiphospholipid syndrome (CAPS)	2C
Chronic inflammatory demyelinating polyradiculopathy	1B
Focal segmental glomerulosclerosis recurrence in renal transplant (+/− immunoabsorption)	1B
Hyperviscosity in hypergammaglobulinemia *Symptomatic* *Prophylaxis for rituximab*	1B 1C
Liver transplantation (desensitization of ABO incompatible living donor)	1C
Myasthenia gravis (acute short-term treatment +/− immunoabsorption)	1B
N-methyl D-aspartate receptor antibody encephalitis (+/− immunoabsorption)	1C
Paraproteinemic demyelinating neuropathies/chronic acquired demyelinating polyneuropathy *IgG/IgA/IgM*	1B
Renal transplant *Antibody-mediated rejection (+/− immunoadsorption)* *Desensitization, living donor (+/− immunoadsorption)* *ABO incompatible, living donor (+/− immunoadsorption)*	1B 1B 1B
Thrombotic microangiopathy, complement mediated (factor H antibody)	2C
Thrombotic microangiopathy, drug mediated (ticlopidine)	2B
Thrombotic thrombocytopenic purpura	1A
Wilson's disease, fulminant	1C
Photopheresis	
Cutaneous T-cell lymphoma, mycosis fungoides, Sezary syndrome (erythrodermic)	1B

(continued)

Table 48.6 (continued)

LDL apheresis	
Familial hypercholesterolemia (homozygous)	1A
Erythrocytapheresis/RBC exchange	
Hereditary hemochromatosis	1B
Polycythemia vera	1B
Sickle cell disease *Acute stroke* *Stroke prophylaxis/iron overload prevention*	1C 1A
Immunoadsorption	
Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome	1B

Adapted from Padmanabhan et al. [17]

Table 48.7 Category II apheresis indications

Therapeutic plasma exchange	
Disease	Grade
Acute disseminated encephalomyelitis	2C
Age-related macular degeneration, dry (high risk)	2B
Autoimmune hemolytic anemia (severe cold agglutinin disease)	2C
Cardiac transplantation, desensitization	1C
Cryoglobulinemia, symptomatic/severe	2A
Familial hypercholesterolemia (homozygous/heterozygous)	1B
Hematopoietic stem cell transplant (ABO incompatible) *Major HPC, marrow* *Major HPC, apheresis*	1B 2B
Lambert-Eaton myasthenic syndrome	2C
Multiple sclerosis, acute attack, or relapse	1A
Mushroom poisoning	2C
Myasthenia gravis, long-term treatment (+/− immunoadsorption)	2B
Myeloma cast nephropathy	2B
Neuromyelitis optica spectrum disorders, acute attack, or relapse	1B
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, Sydenham's chorea	1B
Phytanic acid storage disease (Refsum's disease, +/− immunoabsorption)	2C
Polyarteritis nodosa, hepatitis B virus associated	2C
Renal transplantation, ABO incompatible, antibody mediated rejection (+/− immunoabsorption)	1B

Table 48.7 (continued)

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)	2C
Systemic lupus erythematosus, severe complications	2C
Thyroid storm	2C
Voltage-gated potassium channel antibodies (+/− immunoabsorption)	1B
Leukapheresis	
Hyperleukocytosis, symptomatic	2B
Behcet's disease (adsorption granulocytapheresis)	1C
Immunoadsorption	
Cryoglobulinemia, symptomatic/severe	2B
Dialysis related amyloidosis (β2 microglobulin column)	2B
Dilated cardiomyopathy, idiopathic	1B
Multiple sclerosis, acute attack, or relapse	1B
Neuromyelitis optica spectrum disorders, acute attack or relapse	1C
Photopheresis	
Cardiac transplantation *Cellular/recurrent rejection* *Rejection prophylaxis*	1B 2A
Graft versus host disease *Acute* *Chronic*	1C 1B
Lung transplantation, bronchiolitis obliterans syndrome	1C
LDL apheresis	
Familial hypercholesterolemia (heterozygous)	1A
Focal segmental glomerulosclerosis, recurrence in renal transplant OR steroid resistance disease in native kidney	2C
Lipoprotein (a) hyperlipoproteinemia with progressive atherosclerotic cardiovascular disease	1B
Peripheral vascular disease	1B
Phytanic acid storage disease (Refsum's disease)	2C
Erythrocytapheresis/RBC exchange	
Babsiosis	2C
Sickle cell disease, acute (severe acute chest syndrome)	1C
Sickle cell disease, non-acute *Pregnancy* *Recurrent vaso-occlusive pain crisis*	2B 2B
Platletpheresis	
Thrombocytosis, symptomatic	2C

Adapted from Padmanabhan et al. [17]

ANCA-associated disease cases, in patients who have severe renal involvement, the use of plasma exchange improves outcomes. The largest study to date, MEPEX (Methylprednisone versus Plasma Exchange), demonstrated that in patients who have severe renal dysfunction, the use of plasma exchange improved the rate of renal recovery and reduced progression to end-stage renal disease at 1 year [78]. The regimen utilized was seven plasmapheresis sessions delivered over 14 days; our practice (SMS) is to perform 1–1.5x volume exchanges on alternate days for a total of 7 treatments. In most cases, 5% albumin can be used as the replacement fluid. However, patients who are at high risk for bleeding and those who have undergone or will undergo a procedure (i.e., kidney biopsy) should receive at least partial replacement with fresh frozen plasma. Plasma exchange is also recommended in patients with ANCA-associated disease who have concurrent anti-glomerular basement membrane (GBM) antibodies regardless of the severity of renal involvement; this recommendation is extrapolated from the data showing a benefit in the setting of isolated anti-GBM disease [79]. Finally, although not universally recommended, plasma exchange is commonly used in ANCA patients who have evidence of pulmonary hemorrhage independent of the severity of renal involvement [80, 81]. No randomized controlled trials to date have examined this; however, the recommendation is based upon observational studies and the demonstrated benefit in anti-GBM associated pulmonary hemorrhage. The regimens employed in the two aforementioned situations mirror that used to treat severe ANCA-associated renal disease described above.

Thrombotic Microangiopathies

Thrombotic microangiopathy (TMA) is a general term for conditions which are characterized by thrombocytopenia, microangiopathic hemolytic anemia, and end organ damage [82]. Although TMA can be secondarily associated with certain diseases (i.e., systemic lupus erythematosis, or stem cell transplantation) and medications (i.e., calcinurin inhibitors), the most archetypal TMAs are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) [82]. TTP is particularly common in adults and, in addition to thrombocytopenia and microangiopthic hemolytic anemia, patients with TTP often develop fever, mental status change, and acute kidney injury. TTP has been associated with severe ADAMSTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) deficiency; indeed the hallmark of TTP is an ADAMSTS13 activity level of <5–10% [83, 84]. In patients with TTP, the first-line therapy of choice is therapeutic plasma exchange [83–86]. Typical regimens include 1–1.5x volume exchanges performed on a daily basis until recovery has occurred. Although there is no standard definition for recovery, many practitioners perform plasma exchange until the platelet count is $>150 \times 10^9$/L and lactate dehydrogenase (or other markers of hemolysis) levels begin to normalize [17]. It is important to note that the replacement fluid in this particular indication needs to be FFP since one of the main goals of the therapy is to restore normal levels of ADAMSTS13. Plasma exchange alone is rarely adequately effective, and comprehensive management strategies include the use of immunosuppressive agents (i.e., steroids and rituximab) [17, 87, 88]. Although TTP is common in adults, it is relatively rare in children and pediatric practitioners are far more likely to manage HUS which tends to be further subdivided into diarrheal-associated HUS (D+ HUS) and atypical HUS (aHUS) [88]. D+ HUS is classically caused by shiga-toxin producing Escherichia coli (STEC) and tends to be managed conservatively. Currently there is no official indication for plasma exchange in D+ HUS unless there is underlying evidence of complement activation (i.e., STEC or diarrheal illness triggers a presentation of atypical HUS) [89, 90]. However, it is often employed

in children with D+ HUS when there is evidence of severe neurologic involvement given the clinical overlap with TTP. Atypical HUS, on the other hand, was historically managed with plasma exchange. Atypical disease is commonly due to mutations affecting the alternative complement pathway (i.e., Factor H, Factor I, MCP, CFHR1 thrombomodulin, complement factor B (CFB), and C3) [91]. Plasma exchange is effective and was utilized due to its ability to remove defective mutant complement proteins or autoantibodies as well as its ability to replace these defective/deficient proteins with fully functional versions [92]. However, plasma exchange has been largely replaced by complement blockade agents. One such agent, eculizumab, is a monoclonal antibody against C5 which prevents formation of the membrane attack complex (MAC), thereby blocking activation of the terminal component of the complement cascade [93]. Although plasma exchange can still be used to treat aHUS, it should be considered second-line therapy in the vast majority of cases.

Focal Segmental Glomerulosclerosis (Recurrent)

Focal segmental glomerulosclerosis (FSGS) is a descriptive, histologic term which encompasses several genetic and non-genetic conditions which are associated with nephrotic syndrome [94]. In children, approximately 10% of nephrotic syndrome cases will exhibit steroid resistance and FSGS accounts for the majority of these cases [95]. Immunosuppression and renin-angiotensin-aldosterone system (RAAS) blockade are the cornerstones of therapy; however, these interventions are often only partially effective and a significant number of children with FSGS progress to end-stage renal disease (ESRD). In these children transplantation is offered; however, recurrence of FSGS is quite common with rates between 20–40% [96]. Although not necessarily effective for primary FSGS, therapeutic apheresis is effective in the treatment of FSGS recurrence following renal transplantation [97–99]. Although the physiology is not fully understood, conventional teaching is that FSGS recurrence is due to a circulating permeability factor which can be removed by plasmapheresis [99]. Plasmapheresis is usually provided in conjunction with augmented immunosuppression and seems to be more effective if initiated early in the course of the recurrence [100–102]. Although several regimens have been described, our practice (SMS) is to perform daily plasma exchange until some semblance of response is seen (i.e., reduction in spot urinary protein/creatinine ratio, higher serum albumin levels, improved renal allograft function, less severe hypertension). Following this, plasmapheresis is weaned serially to determine the minimum effective therapeutic frequency; patients may often require plasmapheresis one to two times per week indefinitely. While we believe aggressive, early daily apheresis carries the highest likelihood of success; it is time and resource intensive and often necessitates the use of FFP as a replacement fluid. Alternate-day regimens or short daily courses followed by early transition to alternate-day therapy may be equally effective. Many centers also perform plasmapheresis immediately prior to kidney transplantation in children with FSGS in an attempt to prevent or reduce the risk of recurrence. Preventative use of plasmapheresis has not been universally effective; however, given the ramifications of disease recurrence its use is fairly common [98, 103]. Recently, post-transplant FSGS recurrence has been treated successfully with immunoadsorption [104]. Compared with plasmapheresis, immunoadsorption offers similar efficacy but eliminates the risks related to foreign plasma exposure such as allergic reactions and sensitization. Immunoadsorption can be performed weekly or bi-weekly with 200% plasma exchange volume. Monitoring should consist of, at a minimum, plasma fibrinogen levels (safety and factor depletion) and proteinuria (efficacy).

Solid Organ Transplantation

Therapeutic apheresis can be used before and/or after solid organ transplantation in a variety of circumstances. The primary transplant-associated

indications are the mitigation of sensitization, the treatment of antibody-mediated rejection (AMR), and ABO-incompatible transplantation. Across all organs, sensitization is becoming more common; sensitization refers to the presence of pre-formed HLA antibodies [105, 106]. Sensitization occurs most commonly due to prior transplantation, blood product administration, pregnancy (rare in children but common in adults), and immunizations [107]. Regardless of the cause, the presence of pre-formed anti-HLA antibodies makes transplantation more difficult and puts allograft recipients at greater immunological risk for rejection [105, 107]. Desensitization strategies aim to mitigate or eliminate the anti-HLA antibody burden, thereby allowing transplantation to proceed and reducing future risk of antibody mediated rejection. Anti-HLA desensitization has been performed most commonly for kidney, heart, and lung allograft recipients; potential interventions include intravenous immunoglobulin (IVIG), rituximab, bortezomib, and plasma exchange [105–112]. A complete discussion of desensitization is beyond the scope of this chapter; however, it will be useful to highlight some of the apheresis-related concepts. Plasma exchange is rarely used in isolation as without some additional antibody control mechanism, rebound can occur; as a result, it is used most commonly with IVIG at a minimum and, at times, in conjunction with rituximab or bortezomib [113–116]. Since plasma exchange non-selectively removes antibody-sized proteins, it is imperative that immunologic agents such as these are administered after apheresis. Additionally, once administered, apheresis should not be performed again until the agent has had adequate time to achieve its desired effect. The one exception is IVIG as small doses of IVIG are often given after each apheresis episode in many desensitization protocols [113]. When employed, therapeutic plasma exchange if often performed daily or on an alternate-day basis with single or 1.5x volume exchanges. Replacement can consist of either 5% albumin or FFP depending on proximity to a surgical procedure, bleeding risk, and intensity of the exchange regimen. Plasma exchange is far more effective in the setting of living donation as antibody strength can be monitored and serial cross matches can be performed. This is only an option for renal transplantation; however, apheresis prior to living donation often results in complete elimination of a previously positive cross match. The use of plasmapheresis in the setting of antibody-mediated rejection is based upon similar pathophysiology. The hallmark of AMR is the presence of circulating anti-HLA antibodies specifically directed against the HLA antigens present on the donated organ [117]. Similar to desensitization, in the setting of AMR, plasmapheresis is designed to remove the offending antibodies from circulation. However, plasmapheresis has not been shown to be effective in isolation. It has been used with IVIG, rituximab, bortezomib, and eculizumab with varying degrees of success [110, 117–125]. Most apheresis regimens are performed daily or on alternate days until there is evidence of effect; this may be manifest by a reduction in the strength or number of anti-HLA donor specific antibodies (DSA), histologic evidence of AMR mitigation, or improvement in allograft function. Just as in desensitization, monitoring the strength of anti-HLA antibodies is an important facet of AMR management. Whenever available, immunoadsorption is a valid alternative in patients who experience plasmapheresis-related side effects or have an inadequate response to therapy. Tryptophan and Globaffin absorbers are very effective and remove IgG selectively. Immunoadsorption has been used safely for extended periods of time and should be considered a viable therapeutic option in these situations. Lastly, therapeutic apheresis is used in the setting of transplantation across ABO blood groups. Typically, transplantation across blood groups (i.e., transplanting an allograft from a blood type B donor into a blood type A recipient) should not be performed since the recipient's immune system will rapidly recognize and attack the foreign proteins on the transplanted allograft; without intervention, transplantation across blood groups is associated with acute antibody-mediated rejection [126–129]. However, therapeutic plasma exchange has been successfully used to perform ABO-incompatible liver and kidney transplants [127, 129]. The typical regi-

men is to perform 1–1.5x volume exchanges both prior to and (if necessary) after transplantation [17]. Regimens differ from center to center; however, the strength of the antibody titer dictates the frequency of exchange and the ultimate number of treatments will depend on the rate of antibody production and rebound, the strength of the titer, and the response to therapy [130]. In Europe immunoadsorption, in combination with plasma exchange, has become first-line therapy for ABO-incompatible transplantation [131]. Anti-A or anti-B columns can be used to specifically eliminate circulating ABO antibodies directed against donor cells. The plasma exchange volume and number of sessions required will depend on the strength of the antibody titer, which is measured before and after every immunoadsorption session and should be lowered prior to transplantation to a target titer of ≤1:4. Although there have not been any controlled trials of plasma exchange or immunoadsorption in liver or kidney transplantation, observational studies have suggested that mid- to long-term allograft outcomes are similar to those seen in ABO compatible transplants [132–134].

Summary

Apheresis is an effective extracorporeal therapy for a broad swath of diseases and pathophysiologic states. The technique is capable of targeted removal of cellular blood components and less-specific removal of plasma proteins and components; specific removal of certain substances can be achieved with immunoadsorptive or hybrid apheresis/immunoadsorptive approaches.

Additionally, apheresis can be used to replace a deficient plasma protein or exchange defective cellular components for fully functional ones. Though the blood flows required to perform therapeutic apheresis are not as high as those required for renal replacement therapy, they are rapid enough to require placement of specialized access which can make the therapy challenging in small infants. However, with the appropriate processes in place and specialized experience managing pediatric patients, all apheresis techniques performed in adults can be delivered in children effectively and safely.

References

1. Krumbhaar ACEB. A history of medicine. New York: Alfred A. Knopf; 1941.
2. Mousavi Hosseini K, Ghasemzadeh M. Implementation of plasma fractionation in biological medicines production. Iran J Biotechnol. 2016;14(4):213–20.
3. Millward BL, Hoeltge GA. The historical development of automated hemapheresis. J Clin Apher. 1982;1(1):25–32.
4. Adams WS, Blahd WH, Bassett SH. A method of human plasmapheresis. Proc Soc Exp Biol Med. 1952;80(2):377–9.
5. Freireich EJ, Judson G, Levin RH. Separation and collection of leukocytes. Cancer Res. 1965;25(9):1516–20.
6. Lockwood CM, Rees AJ, Pearson TA, Evans DJ, Peters DK, Wilson CB. Immunosuppression and plasma-exchange in the treatment of Goodpasture's syndrome. Lancet (London, England). 1976;1(7962):711–5.
7. McLeod BC, Sniecinski I, Ciavarella D, Owen H, Price TH, Randels MJ, et al. Frequency of immediate adverse effects associated with therapeutic apheresis. Transfusion. 1999;39(3):282–8.
8. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51(2):224–32.
9. Kim HC. Therapeutic pediatric apheresis. J Clin Apher. 2000;15(1–2):129–57.
10. DeSimone RA, Schwartz J, Schneiderman J. Extracorporeal photopheresis in pediatric patients: practical and technical considerations. J Clin Apher. 2017;32(6):543–52.
11. Strauss R, McLeod B. Adverse reactions to therapeutic apheresis. Bethesda: AABB Press; 1996.
12. Dzik WH, Kirkley SA. Citrate toxicity during massive blood transfusion. Transfus Med Rev. 1988;2(2):76–94.
13. Olson PR, Cox C, McCullough J. Laboratory and clinical effects of the infusion of ACD solution during plateletpheresis. Vox Sang. 1977;33(2):79–87.
14. Szymanski IO. Ionized calcium during plateletpheresis. Transfusion. 1978;18(6):701–8.
15. Mair DC, Hirschler N, Eastlund T. Blood donor and component management strategies to prevent transfusion-related acute lung injury (TRALI). Crit Care Med. 2006;34(5 Suppl):S137–43.
16. Chopek M, McCullough J. Protein and biochemical changes during plasma exchange. Bethesda: AABB Press; 1980.
17. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines

on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing Committee of the American Society for apheresis: the eighth special issue. J Clin Apher. 2019;34(3):171–354.
18. Adams DM, Schultz WH, Ware RE, Kinney TR. Erythrocytapheresis can reduce iron overload and prevent the need for chelation therapy in chronically transfused pediatric patients. J Pediatr Hematol Oncol. 1996;18(1):46–50.
19. Kim HC, Dugan NP, Silber JH, Martin MB, Schwartz E, Ohene-Frempong K, et al. Erythrocytapheresis therapy to reduce iron overload in chronically transfused patients with sickle cell disease. Blood. 1994;83(4):1136–42.
20. Eisenstaedt RS, Berkman EM. Rapid cytoreduction in acute leukemia. Management of cerebral leukostasis by cell pheresis. Transfusion. 1978;18(1):113–5.
21. Lane TA. Continuous-flow leukapheresis for rapid cytoreduction in leukemia. Transfusion. 1980;20(4):455–7.
22. Bug G, Anargyrou K, Tonn T, Bialleck H, Seifried E, Hoelzer D, et al. Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. Transfusion. 2007;47(10):1843–50.
23. Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol. 1997;98(2):433–6.
24. Nguyen R, Jeha S, Zhou Y, Cao X, Cheng C, Bhojwani D, et al. The role of leukapheresis in the current management of hyperleukocytosis in newly diagnosed childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2016;63(9):1546–51.
25. Abla O, Angelini P, Di Giuseppe G, Kanani MF, Lau W, Hitzler J, et al. Early complications of hyperleukocytosis and leukapheresis in childhood acute leukemias. J Pediatr Hematol Oncol. 2016;38(2):111–7.
26. Greze V, Chambon F, Merlin E, Rochette E, Isfan F, Demeocq F, et al. Leukapheresis in management of hyperleukocytosis in children's leukemias. J Pediatr Hematol Oncol. 2014;36(8):e513–7.
27. Lowe EJ, Pui CH, Hancock ML, Geiger TL, Khan RB, Sandlund JT. Early complications in children with acute lymphoblastic leukemia presenting with hyperleukocytosis. Pediatr Blood Cancer. 2005;45(1):10–5.
28. Veljkovic D, Kuzmanovic M, Micic D, Serbic-Nonkovic O. Leukapheresis in management hyperleucocytosis induced complications in two pediatric patients with chronic myelogenous leukemia. Transfus Apher Sci. 2012;46(3):263–7.
29. Zeng F, Huang H, Fu D, Huang Q, Fan L, Wei S. Leukapheresis in 15 patients weighing 20kg or less: a single centre experience. Transfus Apher Sci. 2017;56(6):889–93.
30. Torrabadella M, Olive T, Ortega JJ, Massuet L. Enhanced HPC recruitment in children using LVL and a new automated apheresis system. Transfusion. 2000;40(4):404–10.
31. Gorlin JB, Humphreys D, Kent P, Galacki D, Kevy SV, Grupp S, et al. Pediatric large volume peripheral blood progenitor cell collections from patients under 25 kg: a primer. J Clin Apher. 1996;11(4):195–203.
32. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509–18.
33. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018;24(1):20–8.
34. Adami R. Therapeutic thrombocytapheresis: a review of 132 patients. Int J Artif Organs. 1993;16(Suppl 5):183–4.
35. Liumbruno G, Centoni PE, Ceretelli S, Sodini ML. Rapid reduction of platelet numbers in thrombocytosis. Ther Apher. 2000;4(5):374–6.
36. Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, Gennery AR, et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis society. Br J Haematol. 2017;177(2):287–310.
37. Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, Laroche L, et al. Guidelines on the use of extracorporeal photopheresis. J Eur Acad Dermatol Venereol. 2014;28(Suppl 1):1–37.
38. Zic JA, Miller JL, Stricklin GP, King LE Jr. The North American experience with photopheresis. Ther Apher. 1999;3(1):50–62.
39. Rook AH, Suchin KR, Kao DM, Yoo EK, Macey WH, DeNardo BJ, et al. Photopheresis: clinical applications and mechanism of action. J Investig Dermatol Symp Proc. 1999;4(1):85–90.
40. Knobler R, Jantschitsch C. Extracorporeal photochemoimmunotherapy in cutaneous T-cell lymphoma. Transfus Apher Sci. 2003;28(1):81–9.
41. Greinix HT, Volc-Platzer B, Rabitsch W, Gmeinhart B, Guevara-Pineda C, Kalhs P, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood. 1998;92(9):3098–104.
42. Shinoda T. Photopheresis and leukocytapheresis: cytapheresis treatment against immune-mediated diseases. Ther Apher. 2002;6(4):245–6.
43. Schneider M. Plasma- and lymphapheresis in autoimmune diseases. Z Rheumatol. 1996;55(2):90–104.
44. Costanzo-Nordin MR, Hubbell EA, O'Sullivan EJ, Johnson MR, Mullen GM, Heroux AL, et al. Photopheresis versus corticosteroids in the therapy of heart transplant rejection. Preliminary clinical report. Circulation. 1992;86(5 Suppl):Ii242–50.
45. Meiser BM, Kur F, Reichenspurner H, Wagner F, Boos KS, Vielhauer S, et al. Reduction of the incidence of rejection by adjunct immunosuppression

with photochemotherapy after heart transplantation. Transplantation. 1994;57(4):563–8.
46. Schneiderman J. Extracorporeal photopheresis: cellular therapy for the treatment of acute and chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program. 2017;2017(1):639–44.
47. Calore E, Marson P, Pillon M, Tumino M, Tison T, Mainardi C, et al. Treatment of acute graft-versus-host disease in childhood with extracorporeal photochemotherapy/photopheresis: the Padova experience. Biol Blood Marrow Transplant. 2015;21(11):1963–72.
48. Weitz M, Strahm B, Meerpohl JJ, Schmidt M, Bassler D. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. Cochrane Database Syst Rev. 2015;(12):Cd009898.
49. Dunbar NM, Raval JS, Johnson A, Abikoff CM, Adamski J, Cooling LL, et al. Extracorporeal photopheresis practice patterns: an international survey by the ASFA ECP subcommittee. J Clin Apher. 2017;32(4):215–23.
50. Lim HW, Edelson RL. Photopheresis for the treatment of cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 1995;9(5):1117–26.
51. Rangarajan HG, Punzalan RC, Camitta BM, Talano JA. The use of novel Therakos Cellex(R) for extracorporeal photopheresis in treatment of graft-versus-host disease in paediatric patients. Br J Haematol. 2013;163(3):357–64.
52. Rutella S, Valentini CG, Ceccarelli S, Romano MT, Brescia LP, Milano GM, et al. Extracorporeal photopheresis for paediatric patients experiencing graft-versus-host disease (GVHD). Transfus Apher Sci. 2014;50(3):340–8.
53. DeSimone RA, Wontakal SN, Lyashchenko AK, Schwartz J. Acute mechanical hemolysis as a complication of extracorporeal photopheresis in a low-weight child. J Clin Apher. 2017;32(6):571–3.
54. Julius U. History of lipidology and lipoprotein apheresis. Atheroscler Suppl. 2017;30:1–8.
55. Walzer S, Travers K, Rieder S, Erazo-Fischer E, Matusiewicz D. Homozygous familial hypercholesterolemia (HoFH) in Germany: an epidemiological survey. ClinicoEco Outcomes Res. 2013;5:189–92.
56. Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis. 2014;233(1):219–23.
57. Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet (London, England). 2004;363(9406):369–70.
58. Taylan C, Schlune A, Meissner T, Azukaitis K, Udink Ten Cate FE, Weber LT. Disease control via intensified lipoprotein apheresis in three siblings with familial hypercholesterolemia. J Clin Lipidol. 2016;10(6):1303–10.
59. Seidah NG. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors in the treatment of hypercholesterolemia and other pathologies. Curr Pharm Des. 2013;19(17):3161–72.
60. Mollaki V, Progias P, Drogari E. Familial Hypercholesterolemia in Greek children and their families: genotype-to-phenotype correlations and a reconsideration of LDLR mutation spectrum. Atherosclerosis. 2014;237(2):798–804.
61. Freiburghaus C, Berntorp E, Ekman M, Gunnarsson M, Kjellberg BM, Nilsson IM. Immunoadsorption for removal of inhibitors: update on treatments in Malmo-Lund between 1980 and 1995. Haemophilia. 1998;4(1):16–20.
62. Nilsson IM, Freiburghaus C. Apheresis. Adv Exp Med Biol. 1995;386:175–84.
63. Uehlinger J, Button GR, McCarthy J, Forster A, Watt R, Aledort LM. Immunoadsorption for coagulation factor inhibitors. Transfusion. 1991;31(3):265–9.
64. Bohmig GA, Regele H, Saemann MD, Exner M, Druml W, Kovarik J, et al. Role of humoral immune reactions as target for antirejection therapy in recipients of a spousal-donor kidney graft. Am J Kidney Dis. 2000;35(4):667–73.
65. Braun N, Kadar JG, Risler T. Therapeutic immunoadsorption--its role in clinical practice. Transfus Sci. 1998;19(Suppl):65–9.
66. Bygren P, Freiburghaus C, Lindholm T, Simonsen O, Thysell H, Wieslander J. Goodpasture's syndrome treated with staphylococcal protein a immunoadsorption. Lancet (London, England). 1985;2(8467):1295–6.
67. Esnault VL, Besnier D, Testa A, Coville P, Simon P, Subra JF, et al. Effect of protein A immunoadsorption in nephrotic syndrome of various etiologies. J Am Soc Nephrol. 1999;10(9):2014–7.
68. Dantal J, Bigot E, Bogers W, Testa A, Kriaa F, Jacques Y, et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med. 1994;330(1):7–14.
69. Haas M, Bohmig GA, Leko-Mohr Z, Exner M, Regele H, Derfler K, et al. Peri-operative immunoadsorption in sensitized renal transplant recipients. Nephrol Dial Transplant. 2002;17(8):1503–8.
70. Hickstein H, Korten G, Bast R, Barz D, Nizze H, Schmidt R. Immunoadsorption of sensitized kidney transplant candidates immediately prior to surgery. Clin Transpl. 2002;16(2):97–101.
71. Matic G, Bosch T, Ramlow W. Background and indications for protein A-based extracorporeal immunoadsorption. Ther Apher. 2001;5(5):394–403.
72. Paglialonga F, Schmitt CP, Shroff R, Vondrak K, Aufricht C, Watson AR, et al. Indications, technique, and outcome of therapeutic apheresis in European pediatric nephrology units. Pediatr Nephrol. 2015;30(1):103–11.

73. Moussi-Frances J, Sallee M, Jourde-Chiche N. Apheresis to treat systemic vasculitis. Joint Bone Spine. 2018;85(2):177–83.
74. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670–80.
75. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221–32.
76. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211–20.
77. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116(6):488–98.
78. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18(7):2180–8.
79. Bolton WK. Goodpasture's syndrome. Kidney Int. 1996;50(5):1753–66.
80. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003;42(6):1149–53.
81. Cigarran S, Castro MJ, Pousa M, Paredes S, Bernardo H, Porteiro M. Plasmapheresis in diffuse alveolar hemorrhage as perinuclear antineutrophil cytoplasmic antibody-associated vasculitis relapse on hemodialysis. Ther Apher Dial. 2010;14(3):368–72.
82. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol. 2018;13(2):300–17.
83. Shatzel JJ, Taylor JA. Syndromes of thrombotic microangiopathy. Med Clin North Am. 2017;101(2):395–415.
84. Williams LA, Marques MB. Pathology consultation on the diagnosis and treatment of thrombotic microangiopathies (TMAs). Am J Clin Pathol. 2016;145(2):158–65.
85. Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the writing Committee of the American Society for apheresis: the seventh special issue. J Clin Apher. 2016;31(3):149–62.
86. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991;325(6):393–7.
87. Kremer Hovinga JA, Coppo P, Lammle B, Moake JL, Miyata T, Vanhoorelbeke K. Thrombotic thrombocytopenic purpura. Nat Rev Dis Primers. 2017;3:17020.
88. Trachtman H. HUS and TTP in children. Pediatr Clin N Am. 2013;60(6):1513–26.
89. Loos S, Ahlenstiel T, Kranz B, Staude H, Pape L, Hartel C, et al. An outbreak of Shiga toxin-producing Escherichia coli O104:H4 hemolytic uremic syndrome in Germany: presentation and short-term outcome in children. Clin Infect Dis. 2012;55(6):753–9.
90. Boyce TG, Swerdlow DL, Griffin PM. Escherichia coli O157:H7 and the hemolytic-uremic syndrome. N Engl J Med. 1995;333(6):364–8.
91. Waters AM, Licht C. aHUS caused by complement dysregulation: new therapies on the horizon. Pediatric nephrology (Berlin, Germany). 2011;26(1):41–57.
92. Walsh PR, Johnson S. Treatment and management of children with haemolytic uraemic syndrome. Arch Dis Child. 2018;103(3):285–91.
93. Nester CM, Brophy PD. Eculizumab in the treatment of atypical haemolytic uraemic syndrome and other complement-mediated renal diseases. Curr Opin Pediatr. 2013;25(2):225–31.
94. Sethna CB, Gipson DS. Treatment of FSGS in children. Adv Chronic Kidney Dis. 2014;21(2):194–9.
95. Trautmann A, Schnaidt S, Lipska-Zietkiewicz BS, Bodria M, Ozaltin F, Emma F, et al. Long-term outcome of steroid-resistant nephrotic syndrome in children. J Am Soc Nephrol. 2017;28(10):3055–65.
96. Baum MA. Outcomes after renal transplantation for FSGS in children. Pediatr Transplant. 2004;8(4):329–33.
97. Kashgary A, Sontrop JM, Li L, Al-Jaishi AA, Habibullah ZN, Alsolaimani R, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: a systematic review and meta-analysis of 77 case-reports and case-series. BMC Nephrol. 2016;17(1):104.
98. Verghese PS, Rheault MN, Jackson S, Matas AJ, Chinnakotla S, Chavers B. The effect of peri-transplant plasmapheresis in the prevention of recurrent FSGS. Pediatr Transplant. 2018;22(3):e13154.
99. Weber S, Tonshoff B. Recurrence of focal-segmental glomerulosclerosis in children after renal transplantation: clinical and genetic aspects. Transplantation. 2005;80(1 Suppl):S128–34.
100. Garcia CD, Bittencourt VB, Tumelero A, Antonello JS, Malheiros D, Garcia VD. Plasmapheresis for recurrent posttransplant focal segmental glomerulosclerosis. Transplant Proc. 2006;38(6):1904–5.
101. Taylan C, Goebel H, Beck BB, Dotsch J, Nuesken KD, Hoppe B, et al. Quiz page December 2016: anuria on the second day following kidney transplantation. Am J Kidney Dis. 2016;68(6):A18–a21.

102. Pradhan M, Petro J, Palmer J, Meyers K, Baluarte HJ. Early use of plasmapheresis for recurrent post-transplant FSGS. Pediatr Nephrol. 2003;18(9):934–8.
103. Gonzalez E, Ettenger R, Rianthavorn P, Tsai E, Malekzadeh M. Preemptive plasmapheresis and recurrence of focal segmental glomerulosclerosis in pediatric renal transplantation. Pediatr Transplant. 2011;15(5):495–501.
104. Allard L, Kwon T, Krid S, Bacchetta J, Garnier A, Novo R, et al. Treatment by immunoadsorption for recurrent focal segmental glomerulosclerosis after paediatric kidney transplantation: a multicentre French cohort. Nephrol Dial Transplant. 2018;33(6):954–63.
105. Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2011;11(2):196–202.
106. Chih S, Patel J. Desensitization strategies in adult heart transplantation-will persistence pay off? J Heart Lung Transplant. 2016;35(8):962–72.
107. Mamode N, Marks SD. Desensitization protocols for prospective pediatric renal transplant recipients. Pediatr Nephrol. 2016;31(10):1549–51.
108. Asante-Korang A, Jacobs JP, Ringewald J, Carapellucci J, Rosenberg K, McKenna D, et al. Management of children undergoing cardiac transplantation with high panel reactive antibodies. Cardiol Young. 2011;21(Suppl 2):124–32.
109. Chang DH, Kobashigawa JA. Desensitization strategies in the patient awaiting heart transplantation. Curr Opin Cardiol. 2017;32(3):301–7.
110. Everly MJ. Donor-specific anti-HLA antibody monitoring and removal in solid organ transplant recipients. Clin Transpl. 2011:319–25.
111. Requiao-Moura LR, de Sandes-Freitas TV, Marcelo-Gomes G, Rangel EB. Bortezomib in kidney transplant: current use and perspectives. Curr Drug Metab. 2017;18(12):1136–46.
112. Snyder LD, Gray AL, Reynolds JM, Arepally GM, Bedoya A, Hartwig MG, et al. Antibody desensitization therapy in highly sensitized lung transplant candidates. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2014;14(4):849–56.
113. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. 2011;365(4):318–26.
114. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242–51.
115. Jordan SC, Choi J, Kahwaji J, Vo A. Progress in desensitization of the highly HLA sensitized patient. Transplant Proc. 2016;48(3):802–5.
116. Abu Jawdeh BG, Cuffy MC, Alloway RR, Shields AR, Woodle ES. Desensitization in kidney transplantation: review and future perspectives. Clin Transpl. 2014;28(4):494–507.
117. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. N Engl J Med. 2018;379(12):1150–60.
118. Chehade H, Rotman S, Matter M, Girardin E, Aubert V, Pascual M. Eculizumab to treat antibody-mediated rejection in a 7-year-old kidney transplant recipient. Pediatrics. 2015;135(2):e551–5.
119. Colvin MM, Cook JL, Chang P, Francis G, Hsu DT, Kiernan MS, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2015;131(18):1608–39.
120. Kulkarni HS, Bemiss BC, Hachem RR. Antibody-mediated rejection in lung transplantation. Curr Transplant Rep. 2015;2(4):316–23.
121. Pape L, Becker JU, Immenschuh S, Ahlenstiel T. Acute and chronic antibody-mediated rejection in pediatric kidney transplantation. Pediatr Nephrol. 2015;30(3):417–24.
122. Pearl MH, Nayak AB, Ettenger RB, Puliyanda D, Palma Diaz MF, Zhang Q, et al. Bortezomib may stabilize pediatric renal transplant recipients with antibody-mediated rejection. Pediatric Nephrol. 2016;31(8):1341–8.
123. Taner T, Stegall MD, Heimbach JK. Antibody-mediated rejection in liver transplantation: current controversies and future directions. Liver Transpl. 2014;20(5):514–27.
124. Thrush PT, Pahl E, Naftel DC, Pruitt E, Everitt MD, Missler H, et al. A multi-institutional evaluation of antibody-mediated rejection utilizing the pediatric heart transplant study database: incidence, therapies and outcomes. J Heart Lung Transplant. 2016;35(12):1497–504.
125. Twombley K, Thach L, Ribeiro A, Joseph C, Seikaly M. Acute antibody-mediated rejection in pediatric kidney transplants: a single center experience. Pediatr Transplant. 2013;17(7):E149–55.
126. Stegall MD, Dean PG, Gloor JM. ABO-incompatible kidney transplantation. Transplantation. 2004;78(5):635–40.
127. Morath C, Zeier M, Dohler B, Opelz G, Susal C. ABO-incompatible kidney transplantation. Front Immunol. 2017;8:234.
128. Song GW, Lee SG, Hwang S, Kim KH, Ahn CS, Moon DB, et al. ABO-incompatible adult living donor liver transplantation under the desensitization protocol with rituximab. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2016;16(1):157–70.
129. Warner PR, Nester TA. ABO-incompatible solid-organ transplantation. Am J Clin Pathol. 2006;125(Suppl):S87–94.
130. Tobian AA, Shirey RS, Montgomery RA, Cai W, Haas M, Ness PM, et al. ABO antibody titer and risk of antibody-mediated rejection in ABO-

incompatible renal transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2010;10(5):1247–53.
131. Saliba F, Ichai P, Azoulay D, Habbouchi H, Antonini T, Sebagh M, et al. Successful long-term outcome of ABO-incompatible liver transplantation using antigen-specific immunoadsorption columns. Ther Apher Dial. 2010;14(1):116–23.
132. Opelz G, Morath C, Susal C, Tran TH, Zeier M, Dohler B. Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. Transplantation. 2015;99(2):400–4.
133. Lee EC, Kim SH, Park SJ. Outcomes after liver transplantation in accordance with ABO compatibility: a systematic review and meta-analysis. World J Gastroenterol. 2017;23(35):6516–33.
134. Mysore KR, Himes RW, Rana A, Teruya J, Desai MS, Srivaths PR, et al. ABO-incompatible deceased donor pediatric liver transplantation: novel titer-based management protocol and outcomes. Pediatr Transplant. 2018;22(7):e13263.

49

Evaluating and Preparing the Pediatric Dialysis Patient for Kidney Transplantation

Sandra Amaral and Lars Pape

Introduction

Historical Context

The field of transplantation is fairly new in the context of medical history. The first successful kidney transplant occurred in identical twin young adult brothers in December 1954 in Boston, Massachusetts in the United States. The recipient died 8 years later of causes unrelated to the transplant [1]. In the 1960s, the majority of children with end-stage renal failure died because no adequate treatments were available. It was not until the mid-late 1960s that immunosuppressive treatments were developed to enable successful transplantation using either living or deceased donors and across immunological barriers. In the mid-seventies, pediatric and adolescent hemodialysis and transplantation programs were set up in many industrialized countries, increasing the chances of survival for the first time for patients with end-stage renal failure. At that time, approximately 120 children and adolescents with end-stage renal failure underwent kidney transplant surgery each year per 100 million population. With an incidence rate of approximately 120 new cases of end-stage renal failure per 100 million population, the number of children and adolescents on the transplant list has remained stable with approximately 6–8 children per one million children <18 years old in industrialized countries [2].

Benefits of Transplant Over Dialysis

In the current era, over 75% of children reaching end-stage renal failure receive dialysis prior to transplantation (USRDS). Unfortunately, in the United States, only about 20% of children who reach end-stage renal disease circumvent the need for dialysis through preemptive transplant. Dialysis in children and adolescents is fraught with numerous complications with long-term sequelae. Even effective dialysis therapy cannot usually guarantee more than 15–20% of normal kidney function. Consequently, pediatric dialysis patients suffer from a number of secondary complications, including uremia, growth impairment, renal osteodystrophy, renal anemia, metabolic acidosis, accelerated atherosclerosis, and cardiovascular disease. Medical complications are often accompanied by impaired psychosocial development and can have adverse effects on education.

The deleterious effects of dialysis on children cannot be overstated. In a US cohort of over 7500 children <18 years of age from 2000 to 2012, compared with children transplanted pre-emptively, children on dialysis >1 year had

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a 52% higher risk of graft failure (HR 1.52; 95% CI: 1.22–1.89) and those on dialysis >18 months had an 89% higher risk of mortality (HR 1.89; 95% CI: 1.32–2.70) [3]. Similarly, a large-scale study in Australia and New Zealand of 1634 children and adolescents starting renal replacement therapy before the age of 20 showed a four-fold (hemodialysis) to five-fold (peritoneal dialysis) increase in the mortality rate with dialysis therapy compared to successful renal transplantation [4]. The benefits of renal transplantation versus dialysis therapy in terms of survival rates were outlined most impressively in a recent report of the United States Renal Data System (USRDS). Compared to dialysis therapy, successful renal transplantation improved life expectancy in all age groups, with the most striking increase being noted in children and adolescents [2]. In children aged 0–14 years, successful renal transplantation improved the remaining life expectancy post-transplantation by 30 years; the average life expectancy for this age group is 50 years. For adolescents between 15 and 19 years of age, life expectancy is improved by 25 years with a mean life expectancy of 40 years.

Therefore, kidney transplantation is clearly the treatment of choice for any form of childhood end-stage renal failure. The complications associated with uremia and dialysis therapy can be avoided or at least reduced after prompt, successful renal transplantation [4]. Moreover, quality of life is considerably better after a successful renal transplant compared to chronic dialysis treatment [5, 6]. Patients can lead a virtually normal life, and apart from the need to take medication and attend outpatient clinics, there are only a few restrictions on everyday life. Even growth and physical development are almost normal following successful transplantation [7].

Transplant Referral: Timing and Indications

Given the clear survival and health-related quality of life benefits to children with a kidney transplant versus chronic dialysis, prompt referral for transplantation is essential for all children in advanced stages of kidney disease. The purpose of the pediatric transplant evaluation is to identify any potentially modifiable surgical, medical, and psychosocial barriers that may adversely impact optimal patient and graft survival. To this end, a robust, multi-disciplinary approach is essential to promote safe and effective transplantation for children and their families. Typical components of the pediatric kidney transplant evaluation are presented in Table 49.1. The evaluation is by necessity comprehensive and can be time-consuming. Preparations for kidney transplantation are usually initiated when the estimated glomerular filtration rate (eGFR) falls below 20–25 ml/min/1.73 m^2. In the United States, children may be waitlisted for deceased donor kidney transplantation at any level of eGFR. This is in contrast to other countries, like those of the Eurotransplant group, or adults over 18 years of age in whom the eGFR must be ≤20 ml/min/1.73 m^2. The absence of an eGFR cut-off for waitlisting children in the United States reflects recognition that children with advanced stages of chronic kidney disease may experience substantially impaired growth and nutrition, impaired neurocognitive development, and other medical complications related to their kidney disorder before their eGFR reaches <20 ml/min/1.73 m^2. Further, many children have syndromic or multi-organ conditions, such as methylmalonic acidemia or polycystic kidney disease, in which kidney transplantation may be needed earlier in conjunction with liver transplantation, for example.

Many transplant centers require a minimum bodyweight of 8–10 kg for transplant evaluation as it may otherwise prove impossible to safely position the transplanted organ due to the anatomy. Although small pediatric donor kidneys may be transplanted en bloc (as a pair), very small pediatric kidney transplant recipients are at heightened risk of surgical complications, acute thrombosis**,** and early graft failure [8].

Transplant eligibility is based on two constructs: (1) favorable probability of successful graft survival and (2) direct benefit to the child

Table 49.1 Key elements of the transplant evaluation

Consultant	Rationale
Required	
Nurse or Advance Practice Provider/Transplant Educator	Provide overview of transplantation process. Sets expectations. Provides education regarding living donation.
Transplant Nephrologist	Review medical history in detail to identify any issues which might impact success of transplant.
Transplant Nephrologist	Planning of immunosuppressive therapy.
Transplant Surgeon	Review surgical history and anatomy to identify any issues which might impact success of transplant.
Psychologist	Assess baseline psychosocial factors that may affect treatment adherence and help develop plan for intervention to optimize transplant readiness.
Social Worker	Assess baseline social support and resources available to support transplant and identify any potential concrete barriers to treatment adherence.
Transplant Pharmacist	Explain anticipated treatment regimen, including risk profiles, drug interactions, and side effects. Elicits potential adherence barriers related to medication regimen.
Transplant Dietician	Assess overall nutritional status and discusses anticipated changes to diet and nutritional support post-transplant.
Financial Counselor	Assess insurance coverage (if applicable) and explains anticipated financial expectations and burdens after transplant (USA).
Urology	Required assessment for all children with CAKUT.
Recommended	
Infectious Disease	Review vaccine history, assess antibody responses, and recommend any outstanding vaccinations to optimize infectious disease protection prior to transplant.
Cardiology	Obtain echocardiogram or EKG as indicated.
Anesthesiology	Review anesthesia history pre-operatively to assess any required modifications or concerns.
Other considerations	
Dentist	Identify and treat any dental caries prior to transplant.
Ophthalmologist	Obtain baseline fundoscopic exam to rule out increased intraocular pressure, cataracts, etc.
Gynecologist	For all menstruating females

through improved quality and/or duration of life. *Absolute contraindications* to childhood renal transplantation include florid infections, malignancies, and severe concomitant diseases (e.g., cardiovascular, bronchial/lung, and liver disorders), which may prove life-threatening during transplantation or which could compromise the long-term successful outcome of transplant surgery. Physical or intellectual disability is not a contraindication to transplantation [9]. Relative contraindications to kidney transplantation include nonadherence and lack of family support or supervision to the extent that these conditions would impair successful transplant maintenance.

Surgical Considerations

In children, the timing of transplantation may be heavily impacted by disease etiology. Unlike adults, the most common cause of end-stage renal failure in children is congenital anomalies of the kidney and urinary tract (CAKUT), estimated to account for between 30% and 60% of cases worldwide, as reflected by various national and international registries [10]. For children with significant urological impairment in childhood, the involvement of pediatric urology prior to transplant is critical. Patients with severe vesicoureteral reflux or frequently recurring urinary tract infections may require single or bilateral

ureteronephrectomy to avoid the risk of urosepsis as a result of immunosuppressive therapy administered after transplantation. Patients with significant voiding dysfunction will usually require urodynamic studies to ensure adequate bladder drainage to support successful transplantation. Both bladder capacity and compliance should be assessed in children with CAKUT pre-transplant whenever feasible [11]. Children with high pressure and small capacity bladders that are refractory to catheterization regimens may require urological reconstruction prior to transplantation to ensure reliable urinary drainage and to reduce the risk of urinary tract infection and allograft injury. Occasionally, it may be necessary to augment a small bladder prior to transplantation using material taken from the intestine or ureter.

Nephrotic syndrome, focal segmental glomerulosclerosis (FSGS), and other secondary forms of glomerulonephritis account for 5–30% of pediatric chronic kidney disease [10] and also demand thoughtful surgical planning in advance of transplantation. Nephrotic states will pose increased risk for acute thrombosis, and consequently, children with actively nephrotic end-stage renal disease may require nephrectomies with interim dialysis until hypoalbuminemia and proteinuria improve.

Besides active nephrosis, there are a few other conditions in which nephrectomies are performed either in advance or at the time of transplant. Pre-transplant nephrectomy is generally performed in children with genetic predisposition to renal malignancies, i.e., Wilms tumor/Denys-Drash syndrome [11]. Nephrectomies are also often necessary for children with autosomal recessive polycystic kidney disease, due to the large renal mass of the native kidneys which may limit the space available for the newly transplanted organ.

Lastly, surgical evaluation of a pediatric candidate is also focused on ensuring that there is a suitable location for vascular anastomoses that will provide adequate venous outflow. Any child with known or suspected thrombosis of the pelvic vessels will require abdominal imaging for surgical planning. Inferior vena cava (IVC) thromboses make kidney transplantation extremely challenging [12, 13]. Femoral hemodialysis catheters pose a significant risk for IVC thromboses and should be avoided in children with chronic kidney disease as much as possible [13]. Similarly, in children on peritoneal dialysis, the complexity of transplant surgery is increased in children who have experienced encapsulating peritoneal sclerosis, and all efforts should be made to follow national and international guidelines and care bundles to reduce the risk of peritoneal infections [14–16]. There is some international variation when peritoneal catheters are removed after transplant, but there is a risk of peritonitis and exit site infections when catheters are not removed at the time of transplant [17]. Timing of removal of either hemodialysis or peritoneal catheters will depend on the likelihood of delayed graft failure or risk of recurrent disease after transplant and should be discussed as part of advanced surgical planning.

Medical and Immunological Considerations

Whenever possible, living donation is preferred as it is associated with graft and patient survival benefits compared with deceased donation. Living donors are most commonly parents and immunologically well-matched, but there have been trends toward more unrelated donors [18]. Some centers offer kidney paired exchange programs, in which an incompatible donor for recipient candidate A can donate to recipient candidate B and recipient candidate B's incompatible donor donates to recipient candidate A. Such exchanges can occur over many more than two recipient–donor pairs and are an excellent option for increasing access to living donation for children and adults, particularly for those patients who are highly sensitized [19, 20].

Typically, children are transplanted with ABO compatible organs, although AB0 blood-group incompatibility is no longer considered an absolute immunological contraindication. Some pediatric transplant centers have successfully achieved long-term results with ABO-incompatible kidneys similar to the outcomes achieved following

ABO blood group-compatible procedures [22]. However, the organ recipient must undergo conditioning treatment prior to transplantation in the form of antigen-specific immunoadsorption to remove blood group antibodies. Due to the device-related extracorporeal volume, immune adsorption is less problematic to carry out in older children than in infants. In addition, the protocols currently used for living kidney donors who are incompatible with the ABO blood groups advocate more intensive immunosuppressant induction therapy with the B-cell-depleting antibody rituximab, which potentially increases the risk of infection. A notable exception to this higher immunologic risk is the transplantation of A2 and A2B kidneys into B and O blood type recipients when there are low (≤4) anti-A IgG isoagglutinin titers. In such a situation, immunosuppressive regimens and long-term outcomes are favorable and similar to ABO-compatible transplantation [23].

The issue of specific immunological risks should be broached during discussions with the recipient and their family members. Previous graft losses due to immunological causes have an adverse effect on subsequent graft survival. The presence of pre-formed class I or class II cytotoxic anti-human leukocyte antigen (HLA)-specific antibodies in the blood is also critical, especially if these have originated through a previous transplant or transfusion. A complete HLA-typing is needed, and tests for pre-formed, panel-reactive antibodies should be repeated at least quarterly, especially after blood transfusions.

Children with FSGS are at risk of recurrence of nephrotic syndrome following kidney transplantation. Caregivers of children with FSGS should be counseled about this possibility. However, children with FSGS associated with an identified mutation(s) are at negligible risk and thus genetic testing may be helpful to better understand the risk of post-transplant recurrence. A recent US study of children with steroid-resistant nephrotic syndrome found that overall, 41% recurred in their renal allograft. Disease recurrence was much more common among children with late-steroid resistance (78%) vs. children with primary steroid resistance (40%) [24].

Screening for congenital or acquired thrombophilia is also strongly recommended in order to plan anticoagulation therapy for the transplant procedure (Table 49.1).

When children are on dialysis, there are numerous opportunities to promote the long-term success of their transplant through optimal chronic kidney disease management. For example, appropriate use of erythropoietin-stimulating agents and iron can reduce the need for pre-transplant blood transfusions which ultimately reduces the risk of human leukocyte antigen (HLA) sensitization. Although blood transfusions can be administered as leukocyte-reduced, this procedure does not entirely eliminate the risk of sensitization. Vascular access should be preserved to the extent possible, ideally avoiding the pelvic vessels as previously noted. Optimizing growth through the use of recombinant growth hormone and nutritional supplements with or without feeding tubes can help a child reach the minimal bodyweight for transplant eligibility and also provide long-term benefits in terms of growth and nutritional status. Pre-transplant growth failure has been associated with faster time to reduced kidney function after transplant [25].

The leading causes of mortality in transplant recipients are cardiovascular and infectious complications. Achieving optimal blood pressure control and fluid management can reduce long-term cardiovascular risks [26]. Generally, children under transplant evaluation are required to receive all age-appropriate vaccinations, particularly vaccinations with live vaccines, to reduce the risk of vaccine-preventable infections. Of note, pediatric transplant recipients have been shown to have impaired vaccine responses compared with healthy children, children with chronic kidney disease, and children on dialysis. Whether additional vaccine doses or altered dosing schedules are needed is not clear based on current evidence and should be discussed on a case-by-case basis [26, 27]. In turn, cautious infection prophylaxis is crucial prior to elective transplantation. Potential infectious foci (urinary tract, skin, teeth, and paranasal sinuses) must be cleansed. Furthermore, family members and medical staff coming into close contact with the

patient should have an up-to-date vaccination schedule to promote herd immunity.

Pediatric transplant candidates should also meet with a renal dietician for assessment of their baseline growth and nutritional needs and discussion of anticipated changes post-transplant. As suggested above, many younger patients may require g-tube placement prior to transplant to promote growth and nutrition and reach minimum bodyweight for surgery. Although many children will experience increased appetite after transplant, particularly if they are on steroid-based immunosuppressive regimens, some children will have ongoing problems with speech and feeding disorders and may require long-term g-tubes and enteral support to meet nutritional needs and fluid goals. Attention to pre-transplant nutritional status is critical, both to identify underweight and growth failure conditions, as well as obesity and overweight conditions. Aberrant weight and growth in children pre-transplant are associated with poorer transplant outcomes across numerous studies [25, 29–31]. In a US study of 18,261 pediatric kidney transplant recipients, obesity was associated with greater odds of delayed graft function (OR 1.3; 95% CI: 1.13–1.49), acute rejection ((OR 1.23; 95% CI: 1.06–1.43), graft failure (HR 1.08; 95% CI: 1.05–1.22), and mortality (HR 1.19; 95% CI: 1.05–1.35) [29]. Obesity post-transplant has also been associated with a higher cardiometabolic risk [31].

Transplant pharmacists also play a key role in the pediatric transplant evaluation. The transplant pharmacist reviews the anticipated post-transplant medications and common adverse effects with patients and families and identifies any potential allergies or drug interactions. Further, the transplant pharmacist can identify potential barriers to children receiving their medications as directed. For example, a pharmacist may identify that a child has difficulty swallowing pills or an oral aversion which can alert the transplant team of the need to create plans for liquid formulations of required medications or g-tube administration. Pharmacists may also be the first to recognize that a child or parent has difficulty understanding directions and can help the team determine how to promote adherence in the setting of poor health literacy [32]. Pharmacists will discuss and reinforce the importance of timing and consistency in medication administration. They also help identify ways to reduce treatment complexity, such as reducing the number of different pharmacies from which a patient receives medication or setting up mail-order pharmacy services. Establishing a relationship between transplant pharmacy and the pre-transplant candidate may also prove beneficial in the post-transplant setting. The participation of transplant pharmacists in the interdisciplinary kidney transplant team has been associated with improved medication management, discharge planning, and patient education for transplant recipients [32].

Psychosocial Considerations

Although transplantation is the preferred treatment modality for end-stage renal disease over dialysis, transplant still incurs substantial demands on the patient and family and requires rigorous adherence to a complex treatment regimen. Assessment of any psychosocial barriers that might impair a patient or family's ability to obtain daily immunosuppressive medications or required laboratory studies and clinic visits is essential prior to moving forward with transplantation. A psychosocial assessment is generally mandated by regulatory and government agencies to be part of the transplant evaluation; however, how the psychosocial assessment is attained may vary. In many transplant centers, the assessment is performed by a pediatric clinical psychologist and a social worker. The clinical psychologist's focus is generally two-fold: (1) to assess the child's psychosocial abilities and co-morbidities and (2) to assess the family structure [33]. An understanding of the child's neurocognitive abilities with respect to their potential for independent healthcare self-management is critical to formulate realistic expectations regarding how much assistance a child will need to adhere to their treatment regimen as they transition into adolescent and young adulthood. Adolescence is a high-risk period for allograft

loss and risk factors for nonadherence may be identified pre-transplant to help alert the transplant team about patients who may need additional post-transplant support [33]. Screening for psychiatric co-morbidities, such as depression, should also be performed as these disorders may also pose a risk for difficulties in adhering to treatment regimens [34]. The psychologist also assesses family dynamics to understand the child's emotional support structure. Abnormal family dynamics, including parental distress and a lack of family cohesion, are well-recognized risk factors for poor transplant outcomes in children [35]. The psychologist must also evaluate the child and family coping abilities, identifying any fears and anxieties surrounding transplantation. The evaluation conducted by the social worker generally focuses on assessment of concrete resources, such as travel logistics for attending appointments and obtaining laboratory studies and anticipated insurance and out-of-pocket costs. Social workers may also help liaise with a child's school and caregiver's employer to create plans for supporting a child's education and a family's financial stability during the post-transplant period.

Evaluation to Transplant

Once a child has completed the required components of the transplant evaluation, the multidisciplinary transplant selection committee meets to determine eligibility. In most cases, a child is approved to either be placed on a deceased donor waiting list or scheduled to receive a living donor transplant. In the United States (but not in Eurotransplant countries), a child may be listed inactive status (a condition in which the child can accrue waiting time but not receive organ offers) until certain criteria, such as demonstration of consistent adherence or completion of vaccines, are met. The actual time between reaching end-stage renal disease, completing transplant evaluation, and receiving transplantation depends on numerous factors. Access to living donation vs. deceased donation kidneys varies internationally, by country and cultural values.

Deceased Donation

Although children generally receive priority for deceased donor kidney transplantation, waiting times for deceased donation vary from months to years, depending on national allocation schemes, deceased donor organ supply and demand issues, and individual-level factors such as blood type and sensitization.

As examples, the allocation systems of Eurotransplant and of the United Network for Organ Sharing (UNOS) in the United States are described. In the case of many European centers, listing is managed by the Eurotransplant Foundation in Leiden (the Netherlands), which is the central European distribution center for donor organs. In Eurotransplant, kidneys are initially allocated for transplantation according to histocompatibility criteria and secondly based on the level of immunization and patient waiting times. This allocation procedure is widely accepted in Europe as extensive data corroborate the important role of histocompatibility in confirming early and late graft survival. Children under 16 years of age are given preferential treatment for organ donation. The aim of carrying out early transplantation of a deceased donor kidney during childhood is often impossible today due to the high number of dialysis patients, the declining willingness of the population to donate organs, and the inevitable increase in waiting times for transplantation. The average waiting time for children under 16 is currently 1.5–2 years in Eurotransplant countries, depending on blood group. In contrast to children, adolescents aged 16 and over have closed growth plates and are viewed as adults by the Eurotransplant organ location center – hence the average waiting time for this age group is currently 3.6–9 years. The Eurotransplant allocation guidelines for pediatric renal transplants were consequently changed from 1.12.2010 to ensure that adolescents aged 16 and over, who still have the potential to grow, i.e., with open epiphyseal plates, receive the same benefits as younger children. The waiting time was reduced by adding extra pediatric points and allocating the kidneys of donors under 16 years of age to pediatric recipients [4].

In the United States, the United Network for Organ Sharing (UNOS) manages the national organ allocation, and organs are generally distributed locally, then regionally and nationally. Similar to the Eurotransplant system, organs are allocated first based on blood type compatibility and then by sensitization and waiting times. Pediatric priority is provided to children who are waitlisted at <18 years of age, the age of majority in the United States. Multi-organ transplant recipients (e.g., heart-kidney, kidney-pancreas), highly sensitized candidates, and prior living donors are prioritized ahead of children. Donor organs are classified by a risk index, the Kidney Donor Profile Index, and more favorable kidneys are preferentially allocated to children, young adults, and the top 20% of donors with the greatest estimated post-transplant survival. Waiting times vary geographically, but median waiting times are less than 1 year [36]. Other countries around the world have different allocation systems, and the primary donor source, living or deceased, may vary depending on cultural and religious values and healthcare system access and resources [10, 37, 38].

It is still important to achieve a good HLA match for children since this is relevant not only for ensuring optimum renal graft survival, but also for avoiding HLA sensitization that might preclude a second or third transplant in the future [39]. A good HLA match also enables less intensive immunosuppressant medication and thus reduces the risk of infection and oncological complications such as the much feared post-transplant lymphoproliferative disease (PTLD). In particular, transplant kidneys with two mismatches on the HLA-DR locus should only be accepted in exceptional cases.

Long-term data also show that the transplantation of grafts from older deceased donors >50 years of age is linked to poor graft survival – hence only a kidney from a deceased donor <50 years old should be accepted for a pediatric recipient, where possible. The 50-year-old age limit does not apply to a living donor. In this particular case, good long-term results can be achieved following a careful selection process to obtain healthy kidneys from older living donors (e.g., grandparents). The extent to which donor organs from young children <5 years should be accepted for pediatric recipients is a controversial issue as the transplantation of these very small organs to very young recipients can lead to early organ loss due to increased incidence of arterial and venous thrombosis. Last but not least, the successful implementation of more complex transplantation procedures depends on the vascular/surgical expertise of the transplant surgeon. Based on Eurotransplant guidelines, kidneys must be harvested en-bloc from deceased pediatric donors <2 years old. The en-bloc harvesting technique is also recommended for donors between 2 and <5. Some transplant surgeons recommend a recipient with a bodyweight of 20–50 kg for an en-bloc renal transplant, as the outcomes have not been as good in smaller or larger recipients. Other centers accept en-bloc kidneys also for very small recipients with good results [40].

Living Donation

Between 20% and 60% of kidney transplants currently performed in children and adolescents up to 18 years of age involve living donor kidneys. The majority of living donor kidneys are procured from parents, although there has been an increase in the number of unrelated donors over the last decade [18]. Potential donors are informed about the process and the potential risks of being a living donor in detailed discussions with doctors and psychologists. Generally, the transplant team evaluating the donor is separate from the team evaluating the recipient to reduce potential conflict of interest and bias. In the United States, living donor candidates must meet with an impartial living donor advocate to attest to their willingness to donate freely and without coercion. In Europe, The Living Donor Commission of the respective competent Medical Association must consent to the live donation in a discussion with the potential donor and, depending on age, with the recipient. For living donation, children may have differential access to living donors based on their family and social

support structure and inheritance patterns of their underlying disease. In addition, opportunities for living donation may increase in places where there are kidney exchange programs or access to ABO-incompatible transplantation.

The transplantation of a kidney donated by a living donor offers several advantages compared to a deceased donor: (i) the kidney donors are generally young and healthy and have undergone thorough screening; (ii) the procedure can be planned appropriately over time; (iii) immunological tolerance is usually better due to the haploid entity between parent and child compared to a deceased donor kidney – hence less intense immunosuppressant therapy is often required with consequently fewer side effects, and (iv) prolonged organ preservation is not needed so the structure and function of the transplant are improved. These factors therefore explain, at least in part, why the 5-year graft survival rate is approximately 10% better with a living kidney donor compared to a deceased kidney donor. Furthermore, a pre-emptive approach (i.e., prior to dialysis therapy) is also more feasible with a living kidney donor, thereby preventing any potential dialysis-related complications [3].

The advantages of living kidney donation must be weighed against a very small surgical risk to the donor. The peri-operative mortality risk associated with living kidney donation is very low (0.03%). The risks immediately associated with surgery, i.e., active hemorrhage, corrective surgery, and thrombosis, range from less than 1% to less than 5%. The overall risk of developing any complication is less than 9%. Long-term, life expectancy is similar to the general population. However, the risk to the donor increases slightly compared to healthy non-donors in terms of developing end-stage renal failure (absolute risk of approximately 0.8%). Nevertheless, the living donor actually has a slightly lower probability of developing end-stage kidney failure compared to the normal population as living kidney donors have been thoroughly pre-screened for renal disease risk and will usually undergo regular nephrological follow-up. There is also a slightly elevated risk that the donor will develop arterial hypertension and/or proteinuria [41].

The donor will have approximately 80% of normal kidney function after donating a kidney. An annual check-up is therefore required in order to promptly identify any further impairment of kidney function or the development of arterial hypertension. In the Eurotransplant countries, the annual check-up comprises a 24-h blood pressure recording on an outpatient basis, determination of kidney function and urine protein elimination, an ultrasound scan of the remaining kidney, completion of a questionnaire or advice in terms of quality of life, and the offer of psychological support, if required. In the United States, living donor follow-up is mandated to be reported by the transplant center at 6 months, 1 year, and 2 years after donation [42].

Compared to the normal population, the majority of kidney donors comment in questionnaires that they feel better and have a positive feeling about kidney donation. Occasionally, there will be negative feedback from the kidney donor, essentially due to surgical complications and dissatisfaction expressed by the recipient following transplant, and a reduction in the quality of life. In this context, there have been individual reports of the onset of an adaptation disorder (diminished performance, withdrawal from social circles, and depressive episodes) [43]. A 4-week recovery phase should be planned following living donor surgery. Physical ability returns to pre-existing levels after approximately 3 months. The donor can then resume work, but decisions must be made on an individual basis. This information is often helpful to present to families during the child's evaluation since the potential donor may also be the pediatric recipient's caregiver. Assistance in developing a plan for additional family support in the household after transplant should be discussed with the transplant social worker. For example, living donors are not able to drive for several weeks after transplant and, thus, a driver to bring the child to the hospital for the child's post-transplant clinic visits should be identified a priori.

Even if living donation is deemed the best option for the recipient from a medical perspective, deceased organ donation is almost always offered as an alternative. In view of the decrease

in organ donations and long waiting times, when considering children with end-stage renal disease, the risk to the living donor must be weighed against the risk of deterioration in the child's health if he/she is placed on dialysis pending transplant surgery. The child's family must often discuss this issue with the medical and psychosocial teams, with consideration of the individual family situation when making a decision. The extent to which the child will tolerate dialysis therapy must also be factored into the decision-making process.

Since the average waiting list for children is considerably shorter than the adult waiting list given the priority provided to children, many parents want to wait until their child is over 16 and then consider any substantial increases in terms of waiting time at this point if transplant surgery is still required. However, it should be noted that because of age-related morbidity, the parents may no longer be eligible to act as donors. Furthermore, a deceased donor's kidney may have been damaged in the past, e.g., due to the deceased donor's previous condition such as hypertension and atherosclerosis, which may also account in part for the previously mentioned longer survival of living donor vs. deceased donor kidney transplants. A study in 2015 examined which donor order was preferred for a child if only one living donor was available, i.e., living then deceased or deceased then living. The authors concluded that the only condition under which it was favorable for a child to receive a deceased donor kidney first was when the child was highly sensitized [44]. Overall, a healthy kidney from a living donor is a remarkable treatment option during a crucial phase of development.

In conclusion, the transplant evaluation process is comprehensive and multi-disciplinary with the intent of ensuring the safety, efficacy, and long-term success of the graft and benefits in duration and quality of life to the child. Referral for transplantation should occur early, as soon as a child reaches advanced stages of chronic kidney disease, and ideally before the initiation of dialysis. Appropriately executed, the transplant evaluation affords the opportunity for the transplant team to optimally prepare a child and their caregivers medically, surgically, and psychosocially for favorable short- and long-term outcomes (Table 49.2).

Table 49.2 Examinations needed for listing for transplantation

Evaluations for anatomic conditions
Ultrasound of jugular, subclavian veins, and arteries
Ultrasound of abdominal vessels (aorta, V. cava, iliac veins)
History of abdominal surgery
Urologic situation and need of pre-transplant interventions (UTIs, bladder emptying problems, megacystis, uretheral valves, neurogenic bladder)
MCUG
Cystoscopy (in individual patients)
Cystomamonetry (in individual patients)
Indications for nephrectomy (i.e., Denys-Drash syndrome, non-treatable arterial hypertension, nephrotic syndrome with persisting gross albuminuria, UTIs, dilatation of kidneys, ureter)
Laboratory, imaging, and other studies
WBC, RBC, GOT, GPT, yGT, Potassium, Sodium, Chloride, Calcium, Glucose, Creatinine, Urea
Virology: Hepatitis A, B, C, CMV IgG/IgM; EBV IgG/IgM, HIV, Measles IgG, Mumps IgG, Rubella IgG, Varicella IgG, Herpes Simplex Virus IgG, RPR
Quantiferon test
Urine: Dipstick Analysis – U-Protein, U-Glucose
Ophthalmologic exam
Echocardiogram, ECG
X-ray of chest and left hand
Vaccination history
Dental evaluation
Blood group, transfusion history
HLA-identification
HLA-antibodies/Panel-reactive antigens
Other considerations
Cystatin C, CK, LDH
Endocrinology: fT4, TSH, PTH, 25-OH Vitamin D3, Testosterone, Oestradiole, FSH, LH, HbA1c
Coagulation: INR, PTT, Thrombin Time, Fibrinogen, AT II, Protein C, S, APC, Factor II and V Mutation, MTHFR Mutation, Antiphopholipid-Antibodies, LP(a)
24-h Urine for Creatinine-Clearance and Calciuria, U-alpha-1 Microglobulin, U-Creatinine, U-Albumin
Ultrasound abdomen
Pulmonary function test
24-h Blood Pressure
Audiometry, ENT-Evaluation
Gynecologic evaluation (girls after menarche)

References

1. https://transplantliving.org/living-donation/history/.
2. Van Arendonk KJ, Boyarsky BJ, Orandi BJ, et al. National trends over 25 years in pediatric kidney transplant outcomes. Pediatrics. 2014;133(4):594–601. https://doi.org/10.1542/peds.2013-2775.
3. Amaral S, Sayed BA, Kutner N, Patzer RE. Preemptive kidney transplantation is associated with survival benefits among pediatric patients with end-stage renal disease. Kidney Int. 2016;90(5):1100–8. https://doi.org/10.1016/j.kint.2016.07.028.
4. McDonald SP, Craig JC, Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62. https://doi.org/10.1056/NEJMoa031643 PMID: 16287913.
5. Kanzelmeyer NK, Pape L. State of pediatric kidney transplantation in 2011. Minerva Pediatr. 2012;64:205.
6. Francis A, Didsbury MS, van Zwieten A, et al. Quality of life of children and adolescents with chronic kidney disease: a cross-sectional study. Arch Dis Child. 2019;104(2):134–40. https://doi.org/10.1136/archdischild-2018-314934.
7. Winterberg PD, Garro R. Long-term outcomes of kidney transplantation in children. Pediatr Clin N Am. 2019;66(1):269–80. https://doi.org/10.1016/j.pcl.2018.09.008.
8. Yaffe HC, Friedmann P, Kayler LK. Very small pediatric donor kidney transplantation in pediatric recipients. Pediatr Transplant. 2017;21(5). https://doi.org/10.1111/petr.12924.
9. Chen A, Farney A, Russell GB, et al. Severe intellectual disability is not a contraindication to kidney transplantation in children. Pediatr Transplant. 2017;21(3). https://doi.org/10.1111/petr.12887.
10. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children [published correction appears in Pediatr Nephrol. 2012 Mar;27(3):507]. Pediatr Nephrol. 2012;27(3):363–73. https://doi.org/10.1007/s00467-011-1939-1.
11. Palmer B, Kropp B. Urologic evaluation and management of pediatric kidney transplant patients. Urol Clin North Am. 2018;45(4):561–9. https://doi.org/10.1016/j.ucl.2018.06.004.
12. Verghese P, Minja E, Kirchner V, Chavers B, Matas A, Chinnakotla S. Successful renal transplantation in small children with a completely thrombosed inferior vena cava. Am J Transplant. 2017;17(6):1670–3. https://doi.org/10.1111/ajt.14213.
13. Salvatierra O Jr, Concepcion W, Sarwal MM. Renal transplantation in children with thrombosis of the inferior vena cava requires careful assessment and planning. Pediatr Nephrol. 2008;23(12):2107–9. https://doi.org/10.1007/s00467-008-0951-6.
14. Shahbazov R, Talanian M, Alejo JL, Azari F, Agarwal A, Brayman KL. Surgical management of encapsulating peritoneal sclerosis: a case report in kidney transplant patient. Case Rep Surg. 2018;2018:4965459. Published 21 Feb 2018. https://doi.org/10.1155/2018/4965459.
15. Woodrow G, Fan SL, Reid C, Denning J, Pyrah AN. Renal Association Clinical Practice Guideline on peritoneal dialysis in adults and children. BMC Nephrol. 2017;18(1):333. Published 16 Nov 2017. https://doi.org/10.1186/s12882-017-0687-2.
16. Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32 Suppl 2(Suppl 2):S32–86. https://doi.org/10.3747/pdi.2011.00091.
17. Melek E, Baskın E, Gülleroğlu KS, Kırnap M, Moray G, Haberal M. Timing for removal of peritoneal dialysis catheters in pediatric renal transplant patients. Exp Clin Transplant. 2016;14(Suppl 3):74–7.
18. Amaral S, McCulloch CE, Black E, Winnicki E, Lee B, Roll G, Grimes B, Ku E. Trends in living donation by race and ethnicity among children with end-stage renal disease in the United States, 1995–2015. Transplant Direct. 2020;6(7):e570.
19. Flechner SM, Thomas AG, Ronin M, et al. The first 9 years of kidney paired donation through the National Kidney Registry: characteristics of donors and recipients compared with National Live Donor Transplant Registries. Am J Transplant. 2018;18(11):2730–8.
20. Sypek MP, Alexander SI, Cantwell L, et al. Optimizing outcomes in pediatric renal transplantation through the Australian Paired Kidney Exchange Program. Am J Transplant. 2017;17(2):534–41. https://doi.org/10.1111/ajt.14041.
21. Hotter A. The physiology and clinical implications of wound healing. Part I. Wound healing physiology. Plast Surg Nurs. 1984;4(1):4–13. https://doi.org/10.1097/00006527-198400410-00002.
22. Okumi M, Kakuta Y, Unagami K, et al. Current protocols and outcomes of ABO-incompatible kidney transplantation based on a single-center experience. Transl Androl Urol. 2019;8(2):126–33. https://doi.org/10.21037/tau.2019.03.05.
23. Nelson PW, Landreneau MD, Luger AM, et al. Ten-year experience in transplantation of A2 kidneys into B and O recipients. Transplantation. 1998;65(2):256–60. https://doi.org/10.1097/00007890-199801270-00020.
24. Pelletier JH, Kumar KR, Engen R, et al. Recurrence of nephrotic syndrome following kidney transplantation is associated with initial native kidney biopsy findings [published correction appears in Pediatr Nephrol. 2019 Mar;34(3):539]. Pediatr Nephrol. 2018;33(10):1773–80. https://doi.org/10.1007/s00467-018-3994-3.
25. Li Y, Greenbaum LA, Warady BA, Furth SL, Ng DK. Short stature in advanced pediatric CKD is associated with faster time to reduced kidney function after transplant. Pediatr Nephrol. 2019;34(5):897–905. https://doi.org/10.1007/s00467-018-4165-2.

26. Francis A, Johnson DW, Melk A, et al. Survival after kidney transplantation during childhood and adolescence. Clin J Am Soc Nephrol. 2020;15(3):392–400. https://doi.org/10.2215/CJN.07070619.
27. Nelson DR, Neu AM, Abraham A, Amaral S, Batisky D, Fadrowski JJ. Immunogenicity of human papillomavirus recombinant vaccine in children with CKD. Clin J Am Soc Nephrol. 2016;11(5):776–84. https://doi.org/10.2215/CJN.09690915.
28. Nelson DR, Fadrowski J, Neu A. Immunogenicity of the meningococcal polysaccharide conjugate vaccine in pediatric kidney transplant patients. Pediatr Nephrol. 2018;33(6):1037–43. https://doi.org/10.1007/s00467-017-3878-y.
29. Kaur K, Jun D, Grodstein E, et al. Outcomes of underweight, overweight, and obese pediatric kidney transplant recipients. Pediatr Nephrol. 2018;33(12):2353–62. https://doi.org/10.1007/s00467-018-4038-8.
30. Winnicki E, Dharmar M, Tancredi DJ, Nguyen S, Butani L. Effect of BMI on allograft function and survival in pediatric renal transplant recipients. Pediatr Nephrol. 2018;33(8):1429–35. https://doi.org/10.1007/s00467-018-3942-2.
31. He S, Le NA, Frediani JK, et al. Cardiometabolic risks vary by weight status in pediatric kidney and liver transplant recipients: a cross-sectional, single-center study in the USA. Pediatr Transplant. 2017;21(6). https://doi.org/10.1111/petr.12984.
32. Maldonado AQ, Tichy EM, Rogers CC, et al. Assessing pharmacologic and nonpharmacologic risks in candidates for kidney transplantation. Am J Health Syst Pharm. 2015;72(10):781–93. https://doi.org/10.2146/ajhp140476.
33. Lefkowitz DS, Fitzgerald CJ, Zelikovsky N, Barlow K, Wray J. Best practices in the pediatric pretransplant psychosocial evaluation. Pediatr Transplant. 2014;18(4):327–35. https://doi.org/10.1111/petr.12260.
34. Dobbels F, Decorte A, Roskams A, Van Damme-Lombaerts R. Health-related quality of life, treatment adherence, symptom experience and depression in adolescent renal transplant patients. Pediatr Transplant. 2010;14(2):216–23. https://doi.org/10.1111/j.1399-3046.2009.01197.x.
35. Guilfoyle SM, Goebel JW, Pai AL. Efficacy and flexibility impact perceived adherence barriers in pediatric kidney post-transplantation. Fam Syst Health. 2011;29(1):44–54. https://doi.org/10.1037/a0023024.
36. Reese PP, Hwang H, Potluri V, Abt PL, Shults J, Amaral S. Geographic determinants of access to pediatric deceased donor kidney transplantation. J Am Soc Nephrol. 2014;25(4):827–35. https://doi.org/10.1681/ASN.2013070684.
37. Otukesh H, Hoseini R, Rahimzadeh N, et al. Outcome of renal transplantation in children: a multi-center national report from Iran. Pediatr Transplant. 2011;15(5):533–8. https://doi.org/10.1111/j.1399-3046.2011.01507.x.
38. Liu L, Zhang H, Fu Q, et al. Current status of pediatric kidney transplantation in China: data analysis of Chinese Scientific Registry of Kidney Transplantation. Chin Med J. 2014;127(3):506–10.
39. Gupta M, Wood A, Mitra N, Furth SL, Abt PL, Levine MH. Repeat kidney transplantation after failed first transplant in childhood: past performance informs future performance. Transplantation. 2015;99(8):1700–8. https://doi.org/10.1097/TP.0000000000000686.
40. Butani L, Troppmann C, Perez RV. Outcomes of children receiving en bloc renal transplants from small pediatric donors. Pediatr Transplant. 2013;17(1):55–8. https://doi.org/10.1111/petr.12021.
41. Matas AJ, Hays RE, Ibrahim HN. Long-term non-end-stage renal disease risks after living kidney donation. Am J Transplant. 2017;17(4):893–900. https://doi.org/10.1111/ajt.14011.
42. https://unos.org/news/living-donor-committee-offers-multiple-resources-for-improving-data-quality/.
43. De Pasquale C, Veroux M, Indelicato L, et al. Psychopathological aspects of kidney transplantation: efficacy of a multidisciplinary team. World J Transplant. 2014;4(4):267–75. https://doi.org/10.5500/wjt.v4.i4.267.
44. Van Arendonk KJ, Chow EK, James NT, et al. Choosing the order of deceased donor and living donor kidney transplantation in pediatric recipients: a Markov decision process model. Transplantation. 2015;99(2):360–6. https://doi.org/10.1097/TP.0000000000000588.

50 The Spectrum of Patient and Caregiver Experiences

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Introduction

Children and adolescents with end-stage kidney disease (ESKD) have severely impaired quality of life and poor psychosocial outcomes compared with the general population [1–6]. Quality of life is worse in children on dialysis compared with kidney transplant recipients or those with chronic kidney disease (CKD) not yet requiring kidney replacement therapy [2, 4, 5, 7, 8]. Children on dialysis report substantial decrements in the domains of pain, emotion, physical function, and peer and family interaction [2, 7, 8].

Dialysis is highly burdensome, painful, and invasive. Children on dialysis report a higher burden attributed to kidney disease and treatment compared with other stages of CKD [7, 9].

Children on dialysis and their caregivers are required to manage multiple medications and adhere to dietary and lifestyle restrictions. They have high rates of hospitalization, including for surgical procedures and complications such as infection and hypertension [10–12], which can disrupt their daily activities at home, and social and school participation. All these challenges are particularly difficult as children and adolescents are at the same time negotiating development tasks, milestones, and transition to adulthood.

In a recent study, children with CKD identified and prioritized the outcomes of survival, ability to participate in sports, fatigue, lifestyle restrictions, growth, kidney function, hospitalization, social functioning, medication burden, and infection, to be of highest importance, with lifestyle restriction indicated to be of greater importance in children on dialysis compared to other stages of CKD [13]. Caregivers of children with CKD gave high priority to the outcomes of kidney function, survival, infection, anemia, growth, financial impact, cardiovascular disease, graft survival, impact on family, and blood pressure; reflecting concerns about their child's prognosis and development [13]. This reiterates the severe and broad-ranging impacts that dialysis can have on children and their caregivers.

This chapter will describe the spectrum of the lived experience of children on dialysis and their caregivers based on evidence from qualitative studies. Qualitative studies can provide detailed and in-depth insights on the experiences, beliefs, and values of children on dialysis expressed in their own terms, which may often remain unspoken and underrecognized in clinical settings [14]. The domains of the patient experience covered in

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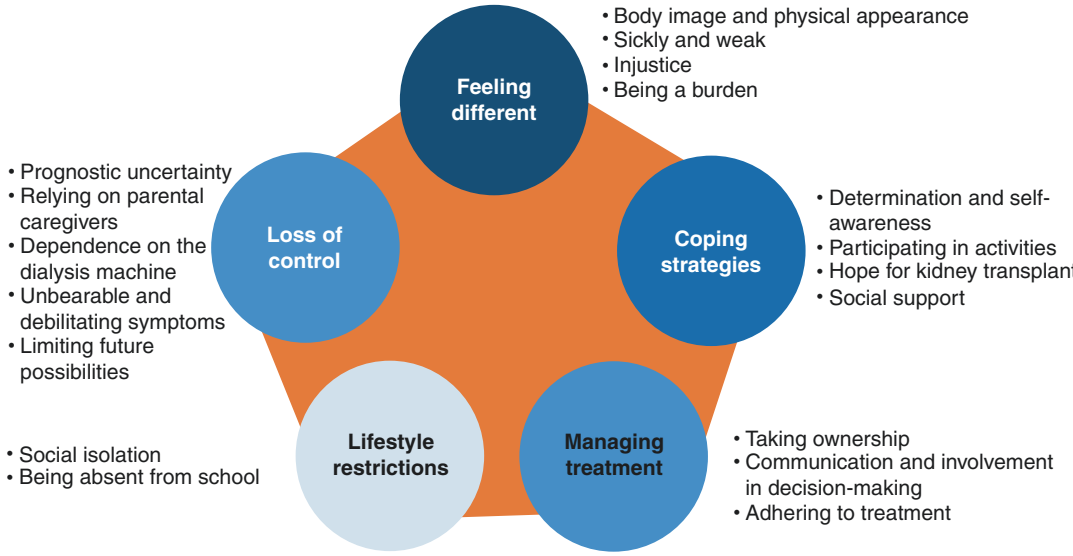

Fig. 50.1 Children's experiences of living with dialysis

this chapter will include: feeling different, loss of control, lifestyle restrictions, managing treatment, and coping strategies (Fig. 50.1). Parental experiences will also be summarized based on the existing studies [15, 16] and conveyed through real-life accounts from parents sharing their stories of caring for their child on dialysis (Boxes 50.1, 50.2, 50.3, 50.4, 50.5, and 50.6). Insights into the patient and caregiver experience can inform strategies to improve service delivery and policy for better outcomes in children and adolescents requiring dialysis, and their caregivers.

Box 50.1 Emotional Turmoil and Uncertainty

- ***Initial Diagnosis*:**

Lily's Mother: *My daughter, Lily, was 5 months old when she started hemodialysis. Hemodialysis is a very risky procedure for an infant but was the only way to treat her condition. I remember how shocked I was when we learned of Lily's diagnosis and her path for treatment. She would need dialysis and a g-tube to grow large enough to eventually receive a transplant. Not only did I worry about the very long and difficult days that lie ahead, but I also worried about the kind of life she would one day lead. I needed to know that there was a chance that she would be happy and "normal" one day.*

Jacob's Mother: *My son, Jacob, was a healthy kid, with no remarkable health problems to speak of. However, when he was 11, he seemed to be fighting a bug that he couldn't quite shake, so his doctor ordered labs. The labs revealed he was in renal failure, and he was rushed to the ER, taken straight to the ICU, and dialysis was started that very day. When the kidney biopsy result came in, we had to adjust quickly to our new normal. We would be going home with a kid that needed dialysis until he could eventually get a kidney transplant. I remember fighting tears the entire time we were there for that first HD outpatient session. I had to step out several times so that I didn't upset my son. Even though I had already witnessed him doing HD in the hospital, something about seeing the pro-*

cess happen in an outpatient setting really hit me hard.

Robert's Mother: *My son, Robert, was 12 years old when we were told that he needed to start dialysis. While Robert was in the ICU receiving his first rounds of hemodialysis, I was in shock. Kidney failure is seldom something you plan to go through. Even as a registered nurse, the words "renal failure" and "dialysis" were overwhelming. Organ failure of any kind is something I had heard about in the movies or read about in an article or a magazine. I had not known anyone who had personally gone through any kind of organ failure. How could it happen to my own son?*

Thomas's Mother: *We had no time to prepare, to make decisions, or to become properly educated. All of the sudden we were being asked to make decisions regarding our lifestyle and the type of dialysis we preferred. As the nurse was telling us about dialysis it was all I could do to hold myself together and not break down in tears as I thought, "What a terrible way for a kid to live." We managed to make it through the training, consent to have my son listed, consent to have the nurse set up appointments at two transplants centers, and get outside before I broke down into tears.*

- ***Uncertainty About the Future:***

Lily's Mother: *Lily was on dialysis for 10 months. When I see her scars now from her HD and PD catheters and her g-tube all of the memories come flooding back. Thankfully her scars don't bother her. I hope that one day she will feel as proud of all that she has endured as I am. I also hope that she will never have to do dialysis again.*

Robert's Mother: *I had so many questions and feelings that I didn't even know how to put into words. "How will this affect his future? Our family's future?" Our home was several states away from the hospital. "Would we have to relocate? Would he have to have a transplant? How would we get through this? Would we get through this?"*

Box 50.2 Loss of Control

- ***Loss of Childhood Memories***

Lily's Mother: *After enduring the previous 6 months of Lily's hemodialysis treatments, adding peritoneal dialysis as well put me over the edge emotionally. I resented that she needed to be dialyzed 14+ hours each day, and that she was being robbed of a normal childhood. Having two dialysis catheters meant that Lily could not get wet for risk of infection. This made bathing her very challenging. At home we gave her sponge baths and washed her hair in the sink. Still, Lily loved to watch her older sister take baths and I remember longing for the day when they would both be able to get into the tub together. Sundays were a very special day because Lily's dialysis nurse at the hospital would let her play in a bucket of water in her crib and get as wet as she wanted. During that year of dialysis I needed a sense of normalcy during an otherwise abnormal situation. I took many photos and usually not of Lily in the hospital. I needed proof that in addition to all of the time she spent in the hospital she was also growing up like every other baby. When I look back at those photos now, I know that hidden underneath her clothes are catheters and feeding tubes. It gives me comfort that she is smiling in the photos, and that she doesn't remember any of it.*

Thomas's Mother: *While on dialysis, my son was academically falling behind and not reaching his benchmarks. I wanted*

the school and his teachers to do everything possible to make sure he was learning, but, as a mom I could see how challenging it was for him to stay on task and focus on his learning. In the end, his health was the priority and that became our focus. Years later, after he had another transplant, we had academic testing done because he was beginning to struggle with reading fluency and comprehension. What we discovered was that the gaps and deficiencies in his academic skills correlated with this time period prior to his first transplant and the time he was on dialysis.

- ***Trust in the Clinician and Care Team***

Lily's Mother: *We were blissfully unaware of all of the things that could potentially go wrong during hemodialysis. We put our faith in the care provided by our dialysis nurses. We did have two frightening incidents when dialysis did not go as planned. Both times, the nurses responded to the situation right away and called in the doctor. We felt reassured that the matter was handled correctly and efficiently. The incidents, however, also reminded us of how challenging and dangerous it was each time we dialyzed our infant daughter. Sensing my feelings toward all of this dialysis, our doctor said something very wise to me back then: "This is short-term pain for long-term gain." He was completely right and we have entrusted him with her care for 13 years now.*

Robert's Mother: *We met so many wonderful doctors and medical professionals but when I saw "our" nephrologist I felt like everything was going to be okay. He knew everything about my son, more about our family than anyone else there, and he knew about all the questions I was afraid to ask. I felt so alone, and I valued his visit and his wisdom.*

Box 50.3 Change in Family Dynamics

- ***Strain on Marriage and Relationships***

Thomas's Mother: *We rarely left my son to the care of anyone else. The one event we did allow him to do was his annual trip to camp with my parents. My mom was one of two people we would leave him with. She was such an important part of our plan. Since she had flexible hours/days at work, she would take him to dialysis if we were not available. In preparation for the trip to camp we had her go through a mini-training with the director of the dialysis center. The nurse was more than happy to train my mom in what to do while my son was in her care. Everyone thought that the night away would be great for my partner and me, but it was just the opposite. We were anxious the entire time and worried about everything that could go wrong. We decided that we preferred to have my parents come to our house to relieve us for an hour or two.*

Jacob's Mother: *I can see where some marriages would also be strained by this experience, but for us, this didn't happen. We approach it very much as a team. In fact, we often marvel at the fact that our mental and emotional breakdowns never happen at the same time – so, when I finally breakdown, my husband is the one to be strong, and* vice versa.

Anna's Mother: *I recall that Anna's illness really pulled us together as a family. We were working together to focus on saving her life. My husband and I took over different aspects of her care. I specifically focused on more day-to-day things and he looked at the long-term strategic planning. Honestly, she became our entire lives and focus. There was very little time for anything else. There was lots of stress, anxiety and worry. I knew other families that broke up or had one partner tune out, but that*

didn't happen to us. I don't think either of us were thinking of ourselves then. It was more of how do we get this done and make sure she survives AND thrives.

- ***Sibling Inattention and Neglect***

Lily's Mother: *Our older daughter, Ashley, was 3 years old when Lily was diagnosed and her life really changed. Instead of attending morning preschool, Ashley needed to go to all-day preschool, 5 days a week. One of us would take her to school early in the morning, then head to the hospital for dialysis, then someone (usually a grandparent) would pick Ashley up from school and whoever would be with Lily at the hospital would finally see Ashley in the late afternoon. For a long time Ashley thought all siblings had medical problems. We were very concerned that Ashley would feel left out by all of the attention Lily was getting, so we made an extra effort to spend time one-on-one with her and to make sure she had plenty of grandparent attention. We also included Ashley in small but important PD steps at home, like turning the machine on and carrying the bag of fluid to the machine so it could warm up.*

Robert's Mother: *I am a single mom with three high-needs kids. I tried to plan activities for the times that Robert would be going on and off dialysis so that the other kids would be safe and so that I wouldn't be interrupted but I was not always successful. My other two kids were very understanding and tried to help when they could. I will never forget the day that the man who delivers the dialysis supplies called to see if he could come earlier than scheduled. It was a snowy day and it was our responsibility to have the path clear for the handcart. My daughter offered to go shovel a path through the snow.*

Jacob's Mother: *Going through something like this as a family has ultimately made us closer, but it certainly has challenges. We have an older son who was 13 at the time his brother got sick, and he had a period of time – especially those first few months – where he basically raised himself. We have always thought of him as an old soul, mature beyond his years, so he handled it like he handles everything in life – he just handled his business. Still, it is hard to realize how much of our attention he had to do without.*

- ***Need for Support***

Lily's Mother: *We had a great support system. My parents each volunteered to take Lily to dialysis one day each week, and my husband took her on Saturdays. My parents also graciously offered to take Lily to dialysis together on Sundays, to allow my husband, our older daughter and me some family time. I kept a blog going about Lily's medical situation so that I wouldn't have to constantly answer phone calls and emails from everyone. Reading comments was a great way for us to feel supported by our family and friends.*

Robert's Mother: *I remember feeling overwhelmed and alone so much of the time even though we were surrounded by people who were caring and supportive. I wished that the dialysis nurse would call to check on us more often, not because we were having any problems, but just because I needed reassurance and to talk with someone who understood.*

Thomas's Mother: *Our family was able to cope with the time my son was on dialysis because we had a strong support group. On nights he was dialyzed, friends would make us meals from the dialysis cookbook. Family members would show up at our house to clean it for us. My sister-in-law did our grocery shopping. Neighbors mowed our lawn, raked the leaves and plowed the driveway when it was needed.*

We did not need these things to be done for us, but graciously accepted the help because we understood this was their way of helping us and showing they cared about our family. My son being on dialysis was an extremely humbling time. We had to accept help when we didn't request it and show graciousness when we just wanted to be left alone. We learned to go outside our comfort zone and let people into our lives because they cared about us. We needed the support or our family, friends, neighbors, coworkers, dialysis staff, and community. Without all of their support we could not have managed the emotional and lifestyle challenges we faced.

Box 50.4 Lifestyle Restrictions

Lily's Mother: *We didn't go anywhere out of town with Lily during the first 16 months of her life. Our lives consisted of driving between the hospital and our home every day. Once she was listed for transplant, we couldn't go more than 30 minutes from our home in case we got "the call." We parents were going stir crazy. Each night, we needed to be home before 8 pm when Lily would be hooked up to the PD machine for the next 10 hours. Usually we read books together and she would drift off to sleep and be laid in her crib while the machine started to do its work. The majority of evenings, however, there were alarms or vomiting or some other reason that the nighttime would not be restful. Ten kilograms (or 22 pounds) of weight was the magic number the surgeons wanted Lily to reach to list her for transplant. Each day was a battle because she was so nauseous. We needed to feed her enough fortified milk to help her grow, but not so much that she would vomit it back up. Lily vomited about 10 times each day – in her crib, all over our house, in her car seat on the way to the hospital,* etc. *I was constantly cleaning up after her and worrying that she would not grow large enough for her transplant.*

Thomas's Mother: *The dietician met with us to give us meal plans and guidelines to follow regarding diet and hydration. All of the healthy lifestyle choices we had been living by the past 6 years we disregarded and replaced with a dialysis-friendly lifestyle. I researched and found great suggestions and recipes. All information I found was geared toward adult patients, so I cleared all the information with our pediatric dialysis staff. It wasn't long after returning home from my son's nephrectomy that we cleaned out our cupboards. We decided that it was better for us to get rid of food than it was to have it in the house and create temptation. We were committed to the family eating only the foods that Thomas could eat.*

Anna's Mother: *We were brave enough to manage a trip to Disneyland during this time. It took weeks of coordination with the dialysis supply company, the hotel, and the dialysis nurses at our children's hospital. We had to ensure there was a hospital nearby that could handle pediatric dialysis in case of emergency. We had to contact the hotel to make sure they would accept medical supplies mailed prior to our visit and would ship to a place that was not our home address. We had to time our visits so that we would be back at the hotel every evening in time to hook her up. We had to stay awake most nights, scared that she was going to roll out of the bed and pull her tube out. But it was worth it – 100%. She had an amazing time and got to be an everyday kid enjoying Disneyland with her cousins.*

Jacob's Mother: *We were able to travel, first by taking a road trip and then later, when we were braver, by plane. It was through our travel experience that we developed our spine, so to speak. Travel on*

PD forces you to assess how you want to approach life, in general – do you want to play it safe all the time, taking very little risk? Or, are you willing to take some calculated risks? The road trip went smoothly, but we were on edge, scared that we would forget some critical supply or that he would end up getting sick now that he stepped outside our little house bubble. He didn't and we had a great trip. Yay, us! The plane ride took two attempts. On our first attempt, Jacob threw up on the way to the airport. We worried, of course, but with no other symptoms, we chalked it up to being car-sick and decided to keep going. Jacob fainted 20 minutes later when we were in the security line. We were taken by ambulance to our local children's hospital ER, where he very promptly recovered, once he had IV fluids. The doctors concluded he was dehydrated, adjusted his dialysis prescription for that night, and gave us their blessing to go on our trip. Our little bravery we had earned from the road trip had vanished and we were shook up. We were so tempted to play it safe and just cancel the trip. That was when we made a critical decision, and we still use it to guide all of our decisions – we decided that we needed to teach our son how to live safe, but not live scared. If we cancelled our trip, we were teaching him to live scared. So, we went. The trip went fairly smoothly and we have great family memories from it, but it was so much more than a trip – I felt like my son learned a little about the art of taking calculated risks, that I hope he carries that with him.

Thomas's Mother: *I recall this time in our lives being so emotional that I avoided going out in our community to do day-to-day tasks such as: going to the drug store, grocery shopping, going to community events. It was such an emotional challenge to "keep it together" in front of my son that avoiding situations was easier than facing them. People in our community are so kind and wanted us to know that they were supporting us. They always inquired how my son was doing and how we were doing. Another reason we avoided public events is that we didn't want his health situation to define our family. We wanted him to have as much normalcy as possible.*

Box 50.5 Caregiver Burden

- ***Hemodialysis***

Lily's Mother: *Lily's first hemodialysis treatment was very scary for us. Once she tolerated it well, she began receiving treatments a few times a week for 1 or 2 hours at first. The number of days at the hospital continued to increase until we were finally at the hospital every day, 7 days a week for 4-hour HD treatments each time. It took about 30 minutes to drive to the hospital, then another 30 minutes to prepare her to be put on the dialysis machine, then the 4-hour treatment, another 30 minutes post-treatment to take her off the machine, and then another 30 minutes to drive home. This meant we spent at least 6 hours each day doing hemodialysis for our daughter. This one simple treatment was very time consuming, but so very important until she could receive her transplant. When Lily first started receiving dialysis, she would take frequent naps. We could read a few books and then she would soon be dosing off to sleep. As she grew, however, her awake time got longer and longer. And the dialysis tubing seemed to be getting shorter and shorter. We only had about 2–3 feet of extra tubing to work with. Soon, she was pulling up on the edge of her hospital crib, then she was trying to walk across the crib and away from the machine. We were always nervous that she would accidentally*

pull out her catheter, which would mean another procedure to place it all over again. Lily took her very first steps to her dialysis nurse while being hooked up to the machine. Eventually, she was not taking any naps while on the machine. This proved to be a very big challenge to entertain her for 4 full hours of treatment each day. We enlisted the help of every person who was willing to assist us. Lily was too young to watch videos so we sang songs, blew bubbles, and found new and interesting things for her play with. Thankfully, the hospital allowed us to leave many boxes of books, music, and toys near her crib to rotate through each day. All in all, we did daily hemodialysis for 10 months each and every day except on Thanksgiving, Christmas, and New Year's Day. On those 3 days, I remember feeling a wave of relief that she didn't have to go to the hospital, but also dread that she was not being dialyzed.

Jacob's Mother: *Life on hemodialysis was no picnic. It dominated our day, once you factored in the time to drive there, the time to get set up, do the treatment, get taken off, and then drive home. It was scary, with all the beeping, alarms, and blood. It was mind-numbingly boring. I also hated the time in between HD, when I was painfully aware that his body was building up all of the waste products that he needed to get rid of – the weekends being the hardest for that one, since this is when he went for a longer chunk of time without dialysis.*

Anna's Mother: *When Anna was 18 months old she went on hemodialysis. We were at the dialysis center 5 days a week for 4–5 hours at a time, plus an hour's drive time to get to and from. Keeping a toddler entertained in the dialysis center was quite a task. It's hard to entertain an 18 month old when you can only sit still on the bed. We had a storage box that was filled with games that she could play with while sitting up. Simple things, like Tupperware containers full of rice with measuring cups and spoons and funnels. We had games with magnets. We had endless books of stickers so that she could put stickers all over the storage bin.*

- ***Peritoneal Dialysis***

Lily's Mother: *All of the equipment and many boxes of supplies were delivered to our home. Her bedroom no longer looked like a little baby's nursery, but instead it resembled a hospital room. I would check on her repeatedly during PD to make sure she hadn't rolled over and kinked her tubing or pulled out her catheter or g-tube. I was on mental alert 24 hours a day. After a few weeks of not sleeping due to worrying all night long, we brought in home health nurses to monitor her PD at night so that we both could get some sleep.*

Jacob's Mother: *Choosing to do PD was a clear advantage – being able to do the dialysis at home, while he slept, was so much better than going into the clinic three times a week. He did have to do HD for about a month after he was discharged, while we were trained to do the PD and his catheter healed. When we passed our PD training, stocked up on supplies (So. Many. Supplies.), and were given the green light to start, life got much easier. PD is a tremendous blessing in so many ways. For one, he just seemed healthier, receiving dialysis every day. It did not take much time out of his schedule, since it happened at night. His diet was liberalized, and we even got to push potassium-rich foods sometimes.*

Anna's Mother: *When Anna was 2 years old she went on peritoneal dialysis. While this allowed us to do her dialysis at home, it was a life-altering event again. My daughter could finally return to day care and eventually preschool. She was ecstatic to be around kids again. But the*

schools were less than happy to have her because of the medical complications she posed. We had to give very detailed lessons to the staff at day care about what to do if her tube became infected or came out. Her preschool teacher refused to be responsible for medical emergencies, so we had to train another person from the administration. At home, we had to keep her in a crib and diapers for much longer than she would have normally because we were afraid of her getting up at night and pulling out her tube. Most nights we were woken by alarms because she had rolled over in her sleep and the tube was kinked. Because she was also tube fed, four out of seven nights a week she would be throwing up. My husband and I would team up with one of us holding her over the soiled bed, still hooked to the PD machine, while the other one changed the sheets. We bought bed sheets in bulk because we went through them so quickly. I don't think anyone in the family had a full night's sleep for the entire year that she was on PD before her transplant. We devoted a room just for the supplies – so many boxes! They stretched to the ceiling! The amount of care we needed to take to ensure that our child didn't get infected – from the masks, the washing, to the 'not opening the door while you're hooking her up.' It was nerve-racking. But it was a relief to know that PD was eliminating more waste from her system than the hemodialysis.

Robert's Mother: *Our decision to do peritoneal dialysis was an easy one. I had so many questions about what the best thing for Robert would be but it all boiled down to one thing. We lived in a very rural state that is often snowy in the winter. The only way we could go home would be if we learned to do PD on our own and flew back for appointments every month. Learning to do PD was not quick or easy. Robert had to heal after having the PD tube inserted before PD could be started. I would go to PD school while Robert was receiving hemodialysis. It looks easier in the books and diagrams than it is in real life when you are tired and the machine is beeping and you are trying to figure out why and how to fix it. The sterile technique required was also very challenging. Everything about dialysis was hard. There was so much to worry about. I remember packing dialysis supplies into plastic bags to load into the back of the truck so that we could make the drive home from the Ronald McDonald House. My parents spent hours at our home rearranging bedrooms so that there would be a room for my son and all of his supplies, and so that he could start dialysis as soon as we got home. I remember cutting a hole in our bathroom wall so that we could drain into the septic system instead of the kitchen sink. I remember trying to time dialysis so that my son could go to church, schools, and activities with friends. I remember being told yet again that his phosphorus level was too high, and we needed to work even harder at managing his diet. I remember trying to keep track of the supplies and order them during the "order window" for our delivery.*

Box 50.6 Financial Burden

Lily's Mother: *We relocated to a different state for 3 years so that our daughter could receive the very best nephrology care, and so that our older daughter could be cared for by her grandparents. We also enrolled our older daughter in a full-time preschool while I was at the hospital with Lily. During those 3 years, my husband flew back and forth regularly to his job in a different state. Thankfully, we were able to afford the curveball that life had thrown at us.*

Anna's Mother: *Dialysis was a life saver, yet was incredibly disruptive to our*

lives. My husband is an entrepreneur and he had to close his business to take a job that had insurance. I had to go on family leave to spend my time taking Anna to and from dialysis appointments. Eventually I returned to work part-time, but was unable to work full-time because of her medical needs.

Robert's Mother: *Flying to the hospital every month was a challenge both financially and physically. It takes a lot of planning to make sure that you take the right supplies for the trip. I often had to repack our bags because the dialysate bags weighed more than what the airline would allow in a suitcase. It is hard to take a PD machine through an airport security checkpoint.*

The Patient Experience

Feeling Different

> Look, we're like Frankenstein. It's having all these tubes stuck into us. They're trying to make us like zombies. [17]

Body Image and Physical Appearance Some children and adolescents feel self-conscious about the appearance of the catheters, fistulas, and cannulas required for dialysis access and the surgical scars – "*It can make you a bit like self-conscious if you have the tube. You worry that people can see it through your clothes or the scars, like all the scars, when you go to the beach or something you worry that people are looking at your scars. I suffer with people looking at my scars, I don't really like them looking at my scars*" [12]. Some attempt to conceal their catheter under their clothing. They describe themselves as being a "*freak*" [18] or "*weird*," believing that they look like "*Frankenstein…and zombies*" [17]; and being teased by friends – "*when my friends see my fistula they jeer me by saying 'what is this, you are like an engine, where is your power socket?' And I avoid them*" [19]. Some worry about being shorter and smaller than their peers – "*I'm a teenager but get treated like a dumb kid because I'm so small. I hate it when people say, 'Oh, what a nice little girl!'*" [18]. They feel inferior, and some boys in particular have concerns about being less "*masculine*" [12].

Sickly and Weak Compared with their well siblings and peers, children on dialysis perceive that they are weaker and less able to participate in activities. They are unable to keep up with others because of their ill-health, fatigue, and lack of energy – "*They are healthier than me, but I'm weak. Because of my disease, I feel different. They can do whatever they want. But I can't. I have to come to a dialysis centre three times a week*" [19]. Some feel ashamed about being the "kidney patient" and choose not to disclose their diagnosis to others. They lose their once-held notion of youthful invincibility and instead feel vulnerable.

Injustice Some question why they have CKD and feel that it is unfair to have to live with the disease and have to do dialysis, particularly because the disease was not their fault. They describe dialysis as having "robbed" them of the lifestyle they wanted.

Being a Burden Some children on dialysis believe that they are a burden on their families – "*I feel as if I'm a burden on my family members' shoulder*" [19]. They harbor guilt for having to depend on their parents and siblings for medical care and support, daily tasks, and for depriving their families of the freedom to do what they wanted such as travelling. Some feel at fault for being a financial burden on their family – "*It affected both economics and morale. My father worried a lot, my mother had stomach problems. It is difficult economically to travel to the hemodialysis centre*" [19]. Some regard themselves as a disappointment to their parents because they cannot achieve or meet their expectations in the areas of academics or sports. "*I'm like I'm sorry for being born, I'm sorry for doing dialysis, you don't know how it feels. [My parents] say stuff like I'm not doing anything with my life*" [12].

Loss of Control

A prisoner to the machine. [20]

Prognostic Uncertainty Some children and adolescents on dialysis worry about hospitalization and the need for surgical procedures – "*going from living a normal life, from what I knew, to being in hospital most of the time, and having surgery done every now and then, I don't like it*" [12]. Some have fears about their own mortality – "*I'm home alone, then I'd probably die on the couch. I fear that. Just pass out and don't wake up. That's what I fear*" [12] and "*I have to constantly lie down. This makes me feel I'm going to die*" [19]. The uncertainty about their chances of receiving a kidney transplant can cause angst and distress, while at the same time they fear the pain and complications that may occur after transplant including graft loss and having to return to dialysis – "*I'm thinking oh I'm not going to get a transplant so I'm not going to bother with going through that effort just to know that everything's just gonna go downhill again*" [12]; as well as death – "*I don't like how I am at risk of it dying again and then I am going to have to go into surgery and then what are we going to do – so … that's what I don't like really. I don't like being at risk of dying*" [21]. Some children worry about their potential living kidney donor – "*I'm still worried about the transplant, worried about the possibility of something happening to [my brother]. I don't want to lose my only brother*" [12].

Relying on Parental Caregivers Children depend on their parents to help with dialysis, medications, and attending clinical appointments – "*My parents are very involved in caring for me and my kidney disease; I depend on them a lot*" [22]. However, some are frustrated and feel like a "*baby*" [22] when they believe their parents are "*super protective*" [23] and did not trust them to manage or make choices about their own treatment.

Dependence on the Dialysis Machine Being forced to undergo the constant, grueling, and "*relentless*" [20] regimen of dialysis for survival caused some children and adolescents to feel frustrated and helpless. Some refer to themselves as "*puppets pulled by strings, forever managed by hoses and tubes*" [17]. They lose a sense of bodily integrity and "*intactness*" [17] in having a body "*full of holes*" [20] and controlled by medical interventions.

Unbearable and Debilitating Symptoms Dialysis-related symptoms such as headache, fatigue, and itch can be intolerable – "*The machine is too bad. I have a headache after dialysis sessions. My blood pressure sometimes drops. I feel exhausted and I can't walk*" [19].

Limiting Future Possibilities Particularly for adolescents, they feel anxious that dialysis can threaten their ability to work or pursue their career goals – "*It's always been a military career for me and nothing else, and the thing is that this kidney puts that whole dream and that whole lifestyle at risk…that's like the only career I've ever wanted, I can't think of myself doing anything else. This [dialysis] seems to have taken a lot of things away*" [12]. They have concerns about being able to establish a relationship with a partner and how dialysis impacts fertility – "*With my future, I'm mostly worried about relationships. Will I ever meet a guy who'll be there for me no matter what? Will he care if I'm still doing dialysis*?" [12].

Lifestyle Restrictions

I would have wished to be normal and see how my life would have been if I didn't get [kidney disease]. I'd be a better student, a straight-A student. [24]

Social Isolation Children and adolescents on dialysis can feel socially isolated as a consequence of being ill, having to do dialysis, attend clinical appointments, and being frequently hospitalized for complications. They are often absent from school and cannot participate in extracurricular or recreational activities with peers – "*you feel tired every day, you can't do anything, and*

you're so distanced from your friends, like they're off enjoying being eighteen, going to parties and everything, and I'm here stuck doing dialysis" [12]. They feel excluded from what their friends are able to do – "*I do dialysis every night so I can't go to sleepovers, camp, or anything…[I feel] left out! … You just feel like you can't do anything and [can't] go out by yourself*" [24]. For those doing in-center hemodialysis, they feel trapped and stuck – "*When I came here to the hospital, I felt like I was trapped in a prison and I can't do anything about it. I hate it and I'm sick of the same place. Over and over again doing the same thing, same place, etc*." [12]. Also, some are frustrated in having to be cautious, such as avoiding swimming with a PD catheter, because they would be excluded from joining in activities with their friends.

Being Absent from School As a consequence of the fatigue from doing dialysis, some children and adolescents struggle to attend school and engage in study. Some feel ashamed about their poor results and fear other children teasing or "*laughing*" [25] at them for being behind in their studies. Some encounter a lack of understanding and pressure in the school environment – "*I hate how people are always on my back at school. When I tell them the reason why I can't do full time, they just say I use dialysis as an excuse*" [12]. Some younger children worried about their ability to continue schooling – "*I can't sleep at nights. I always think what would I do if I can't recover and I can't go to the high school*" [19].

Managing Treatment

> It's my dialysis and nobody else's. [26]

Taking Ownership Some adolescents want ownership of their dialysis and to be more independent in managing their treatment; and to be able to integrate and minimize the disruption of dialysis in their daily lives. They believe it is important to be given the flexibility and be empowered with technical confidence through training and support to manage dialysis, and to be able to adjust the treatment based on their symptoms and lifestyle. Particularly for those on home hemodialysis, they can "*base my dialysis times around my lifestyle*" [12].

Communication and Involvement in Decision-Making Some want opportunities for more involvement in decision-making about their treatment, including dialysis, medications, diet, surgical procedures, and kidney transplantation. Some feel they often have no choice and just accept the necessity of having "*needles, growth hormone, or surgery*" [23]. They feel intimidated because they expect they may be ignored, judged, or reprimanded by clinicians and parents if they voice their preferences – "*I don't talk to doctors a lot. I just sit there and let mum talk*" [23].

Adhering to Treatment Some resent and struggle to adhere to the dietary and fluid restrictions because it interferes with their lives – "*The main thing is that you can't drink as much as you like. It was hard to play football this year because dialysis interfered with my practice time*" [24]. They feel frustrated, particularly if they are reprimanded by their parents or clinicians for not adhering to their diet and fluid recommendations. Regarding medications, some find it difficult to remember to take medications, to swallow the medications, and bear the side effects – "*some medications make me have vertigo and nausea*" [19]. Certain medications can be difficult to take as they make children feel sick – "*I didn't take my tablets because they made me sick. Oh they are disgusting! I took a sip and I threw up. They said if I didn't drink it I wouldn't be able to eat. I still ate*" [23]. Some children and adolescents are embarrassed about taking medications in front of others. Some find it patronizing and frustrating if their doctors doubt that they are taking medications.

Coping Strategies

> [It's hard], but you persevere through it and you learn. You gain from the experience and you grow through it. It's very much a growing experience. I

> just try to live my life to the fullest as possible every day. I know kids in the hospital for whom this is so bad. They say if they hadn't gotten sick or if they had done this or that, they wouldn't have gotten kidney failure. But I don't think about what I could have done. I think about what I can do now. [22]

Determination and Self-Awareness Some children and adolescents refuse to allow dialysis to dictate and constrain their lives by trying to live as normally as they could – "*if there's something that I want to do, I go ahead and do it; I don't let my kidney disease stop me*" [22]. Some regard dialysis as a job – "*I kind of think of it as a job. I feel I'm going to work, because it is like working, because I'm setting up my machine, taking myself off and leaving*" [26]. Over time, they gain awareness about their own resilience, maturity, and strength they had developed whilst on dialysis – "*I didn't mind going back to dialysis very much because I did get to mature a lot more as a person within a quick vicinity of time*" [12].

Participating in Activities To overcome the constraints and stress of dialysis, some make efforts to engage in various activities including walking, talking with others, and listening to music – "*I listen to music sometimes just to get my frustration out. I might go out … to volunteer to get away from the atmosphere I'm always surrounded by. I might talk to one of my close friends, maybe even a family member*" [24]. For some who had to give up activities prior to commencing dialysis (e.g., swimming and contact sports), they chose different sports or activities they were able to do.

Hope for Kidney Transplant Whilst on dialysis, some wait in hope for a kidney transplant, which would allow them to regain independence and live a normal life – "*It would make me feel better, like make me feel stronger*" [21].

Social Support Children on dialysis value the social, emotional, and practical support from family members and friends, who provided them reassurance, comfort, and encouragement. Some appreciate that their siblings and friends regarded them as "*normal*" [22].

The Caregiver Experience

Parents of children on dialysis can experience emotional turmoil, uncertainty about their child's prognosis, and loss of control in having to relinquish aspects of their child's care to clinicians [15, 27–29]. They also contend with changes in family dynamics, including spousal relationships, and lifestyle restrictions [15]. From the parental perspective, the burden of caregiving encompasses having to meet the demands of medical care, overcoming challenges of providing adequate nutrition while adhering to diet and fluid restrictions, organizing logistics including transportation and accommodation, comprehending overwhelming and complex information, managing the psychosocial and educational needs of their child, and dealing with financial hardship [15, 16, 27–32].

The domains of the caregiver experience covered in this chapter will include: emotional turmoil and uncertainty, loss of control, change in family dynamics, lifestyle restrictions, caregiver burden, financial burden, and personal growth. The stories of five mothers caring for a child on dialysis illustrate each of these domains (Boxes 50.1, 50.2, 50.3, 50.4, 50.5, and 50.6). The names of the children on dialysis, Lily, Robert, Thomas, Anna and Jacob, have been changed to protect their identities.

Emotional Turmoil and Uncertainty

Initial Diagnosis Parents of children on dialysis face many different emotions, particularly shock, at the time of diagnosis [32]. They are often thrown into the caregiver role without warning and feel expected to understand complex medical information very quickly [28, 32] – "*You don't remember at the time because you are shocked and you are, like, in a shadow; you can't think at that moment because it's just bombarded with all this bad information"* [32]. Parents ask themselves questions such as "*Why is this happening to my child?*" and "*How long will my child be on dialysis?*" They wonder about their child's future and if everything will eventually be

okay. Selected excerpts from real life parental stories that illustrate the range of emotions faced by caregivers upon initial diagnosis are provided in Box 50.1.

Uncertainty About the Future Caregivers can feel overwhelmed about the future of their child on dialysis. They wonder if a transplant will be possible [32]. It can be devastating for parents if their child has to remain on or return to dialysis. They may also worry about morbidity and mortality of their child on dialysis [32] (Box 50.1).

Loss of Control

Loss of Childhood Milestones Parents mourn the loss of a "normal" childhood for their child on dialysis. Developmental milestones including eating, walking, talking, bathing, and growing are often delayed during dialysis. Parents are also concerned about the long-term consequences of dialysis on the child's future health, academic development, and relationships [13, 23] (Box 50.2).

Trust in the Clinician and Care Team Parents need to feel comfortable with their child's care team [31], particularly as they need to relinquish control of their child to clinicians [15]. The relationships forged with the doctors, nurses, and other support staff are incredibly important. "*I've been living with this for 3 years; I know what I'm talking about. It sort of reached a point with me that I thought, we're losing control over our own child … I made the decision that I'm calling the shots … we really had to sort of push our way to the front*" [29]. They appreciated clinicians who provided clear and comprehensive information [32]. Some parents travel or relocate to access quality care for their child (Box 50.2).

Change in Family Dynamics

Having a child on dialysis imposes stress on relationships within the family. Some parents experience strain in their marriage, and may feel unable to devote adequate attention to their other children because of the medical and healthcare needs of their child on dialysis [28].

Strain on Marriage and Relationships Some caregivers struggle with disagreements with their partner in providing care for their child on dialysis. They are aware of the need to take "time outs" with partners to maintain healthy relationships but find it difficult to find the time to do so [33]. Some rely on support from extended family to share caregiving responsibilities (Box 50.3).

Sibling Inattention and Neglect Having to explain dialysis to siblings is a challenge for caregivers. Some feel they must justify the extra time, attention, and resources needed to care for their child on dialysis. Some worry about sibling resentment and neglect [15] and look for ways to incorporate siblings into daily life, and to ensure that they spend one-on-one time with their other children (Box 50.3).

Need for Support Despite being overwhelmed by their child being on dialysis, some caregivers find it difficult to ask for or accept help from family and friends. Caregivers can feel isolated because of the lack of understanding from others about the medical challenges the family is facing [15, 28]. Some turn to social media to communicate updates and to convey the most important information regarding their child's medical situation (Box 50.3).

Lifestyle Restrictions

The grueling dialysis regimen and complex fluid and dietary requirements restricts freedom to travel, participate in social activities, and pursue career goals [15, 32]. The multiple challenges of managing fluid and dietary requirements include feeding through the NG or G-tube, which can cause discomfort; and adhering to dietary and fluid restrictions, whilst at the same time ensuring that their child is receiving adequate nutrition [28]. Parents also need to obtain supplies for dial-

ysis and ensure they have strategies to prepare for the risks of health complications. Some avoid social situations or public events because it is emotionally difficult and they do not want their health situation to define the family. Some parents may feel they are no longer able to pursue their own educational or career goals [32] (Box 50.4).

Caregiver Burden

In prioritizing the health and medical needs of their child on dialysis, some caregivers struggle to maintain their own well-being [31]. The ongoing, time-consuming, and highly intense regimen of dialysis, and having to subsume the multiple roles of being a parent, caregiver and advocate, can take a toll on the physical, emotional, and spiritual health of caregivers [28, 32] – "*It's a hard, tiring job because it's an everyday process…It's a workout job. It's a job that you really have to focus on, put your mind, heart into it. … It's a job that you have to give up just about your everyday life by focusing in on this. … It's very hard. It's tiresome*" [32]. Parental accounts of the specific burdens related to hemodialysis and peritoneal dialysis are provided in Box 50.5.

Financial Burden

Caring for children on dialysis requires resources to be directed toward meeting their complex needs. Some parents are unable to sustain employment, and face difficulties in navigating the complex processes to access financial assistance [15, 16, 32] (Box 50.6).

Personal Growth

Over time, some parents develop coping strategies to care for themselves, and believe they gain unique insight and learnings from their experience to enable them to cope in the longer-term [32]. They may feel they gain a new perspective in appreciating the "*little things, and undertake a more holistic approach to life and caregiving*" [32].

Implications for Practice

The insights gained from the experiences and perspectives of children and adolescents on dialysis, and their caregivers, have implications for practice, particularly in terms of strengthening shared decision-making, improving symptom management, increasing attention to psychosocial needs, providing school and community advocacy, and supporting the role and responsibilities of caregiving.

There is a need to empower children and adolescents on dialysis to be involved in decision-making about their health and treatment – dialysis, medications, diet and fluid management, surgery, transplantation. Interventions to support shared decision-making may include age and developmentally appropriate decision coaching, decision-aids, and psycho-educational programs [23, 34, 35]. Providing access to supportive care, which includes symptom management [36], may help to alleviate the distressing, severe, and debilitating symptoms such as fatigue and pain in children on dialysis. Multidisciplinary care should involve psychiatrists, psychologists, and social workers, as children and adolescents on dialysis suffer unresolved anxiety, guilt, fear, low self-esteem, stress, and disappointment.

Caregivers also need resources to manage the uncertainty, anxiety, and fears, as these can impact their wellbeing and capacity to provide care for their child [15, 37]. We suggest that clinicians address with caregivers their concerns about losing control of children on dialysis, and to establish a clinician-parent partnership approach in providing care for the child on dialysis. Advocacy efforts in school and community settings may promote understanding among their teachers and peers, which may in turn support motivation and ability in children on dialysis to engage in school and community activities and reduce their sense of social isolation. Concerns about career opportunities also suggest the need for vocational counselling. Training, education, and access to support (including practical and financial support) for caregivers can help to strengthen their ability to provide care for their child on dialysis, and respite programs could also provide some relief for caregivers [16, 31, 37].

Conclusion

Dialysis profoundly impacts the lives of children and caregivers. Children and adolescents on dialysis contend with a sense of being different from others because dialysis and its related treatment have severe consequences on their body image and appearance, wellbeing, and cause them to feel guilt and a burden on their family. They lose many aspects of control because of the uncertainties about their deteriorating health and treatment options, having to depend on their families for healthcare and daily tasks, the constant need to do dialysis, debilitating symptoms, and fearing that dialysis will jeopardize opportunities in the areas of relationships, family, and career. Children and adolescents feel constrained and restricted in their daily living, which they attribute to the dialysis regimen, having to attend clinical appointments, being hospitalized, being vulnerable to infections and complications, and feeling too unwell to participate in activities; and are frustrated as they cannot attend school and participate in social activities with their peers. In terms of managing treatment, some want to take more ownership over their dialysis and to be empowered to be involved in decision-making about their health and treatment. Children and adolescents struggle to take medications and adhere to dietary and fluid restrictions because it conflicts with their goal of being "normal," interferes with lifestyle, or is unpleasant to take and they cannot tolerate the side effects.

Despite these challenges, some develop determination, resilience, and forge meaning in their circumstances. They refuse to allow dialysis to constrain them and make the effort to preoccupy themselves with activities. They also value the emotional and practical support from their family and friends. Caregivers of children on dialysis must also cope with uncertainty, loss of control, additional responsibilities in providing ongoing medical care and advocacy for their child and manage the social and financial challenges. Addressing these broader needs is needed to improve the experience of children and adolescents on dialysis, and their caregivers, for better overall wellbeing and outcomes in this population.

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References

1. Hamilton AJ, Caskey FJ, Casula A, Ben-Shlomo Y, Inward CD. Psychosocial health and lifestyle behaviors in young adults receiving renal replacement therapy compared to the general population: findings from the SPEAK study. Am J Kidney Dis. 2019;73(2):194–205. https://doi.org/10.1053/j.ajkd.2018.08.006.
2. Francis A, Didsbury MS, van Zwieten A, Chen K, James LJ, Kim S, et al. Quality of life of children and adolescents with chronic kidney disease: a cross-sectional study. Arch Dis Child. 2018;104(2):134–40. https://doi.org/10.1136/archdischild-2018-314934.
3. Splinter A, Tjaden LA, Haverman L, Adams B, Collard L, Cransberg K, et al. Children on dialysis as well as renal transplanted children report severely impaired health-related quality of life. Qual Life Res. 2018;27(6):1445–54.
4. Tjaden LA, Grootenhuis MA, Noordzij M, Groothoff JW. Health-related quality of life in patients with pediatric onset of end-stage renal disease: state of the art and recommendations for clinical practice. Pediatr Nephrol. 2016;31(120):1579–91.
5. Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW. Health-related quality of life in pediatric patients with ESRD. Pediatr Nephrol. 2006;21(6):846–50.
6. Medyńska A, Zwolińska D, Grenda R, Miklaszewska M, Szczepańska M, Urzykowska A, et al. Psychosocial aspects of children and families treated with hemodialysis. Hemodial Int. 2017;21(4):557–65.
7. Tong A, Wong G, McTaggart S, Henning P, Mackie F, Carroll RP, et al. Quality of life of young adults and adolescents with chronic kidney disease. J Pediatr. 2013;163(4):1179–85.
8. Goldstein SL, Rosburg NM, Warady BA, Seikaly M, McDonald R, Limbers C, et al. Pediatric end stage renal disease health-related quality of life differs by modality: a PedsQL ESRD analysis. Pediatr Nephrol. 2009;24(8):1553–60.
9. Tjaden L, Tong A, Henning P, Groothoff J, Craig JC. Children's experiences of dialysis: a systematic review of qualitative studies. Arch Dis Child. 2012;97:395–402.
10. Springel T, Laskin B, Shults J, Keren R, Furth S. Longer interdialytic interval and cause-specific hospitalization in children receiving chronic dialysis. Nephrol Dial Transplant. 2013;28(10):2628–36.

11. Springel T, Laskin B, Furth S. Readmission within 30 days of hospital discharge among children receiving chronic dialysis. Clin J Am Soc Nephrol. 2014;9(3):536–42.
12. Tong A, Henning P, Wong G, McTaggart S, Mackie F, Carroll RP, et al. Experiences and perspectives of adolescents and young adults with advanced CKD. Am J Kidney Dis. 2013;61(3):375–84.
13. Hanson CS, Gutman T, Craig JC, Bernays S, Raman G, Zhang Y, et al. Identifying important outcomes for young people with chronic kidney disease and their caregivers: a nominal group technique study. Am J Kidney Dis. 2019;74(1):82–94. https://doi.org/10.1053/j.ajkd.2018.12.040.
14. Hanson CS, Craig JC, Tong A. In their own words: the value of qualitative research to improve the care of children with chronic kidney disease. Pediatr Nephrol. 2017;32(9):1501–7.
15. Tong A, Lowe A, Sainsbury P, Craig JC. Experiences of parents who have children with chronic kidney disease: a systematic review of qualitative studies. Pediatrics. 2008;121(2):349–60.
16. Medway M, Tong A, Craig JC, Kim S, Mackie F, McTaggart S, et al. Parental perspectives on the financial impact of caring for a child with CKD. Am J Kidney Dis. 2015;65(3):384–93.
17. Neff EJ. Nursing the child undergoing dialysis. Issues Compr Pediatr Nurs. 1987;10(3):173–85.
18. Neff JA. Autonomy concerns of a child on dialysis. Matern Child Nurs J. 1975;4(2):101–8.
19. Başkale H, Başer G. Living with haemodialysis: the experience of adolescents in Turkey. Int J Nurs Pract. 2011;17(4):419–27.
20. Waters LA. An ethnography of a children's renal unit: experiences of children and young people with long-term renal illness. J Clin Nurs. 2008;17(23):3103–14.
21. Walker RC, Naicker D, Kara T, Palmer SC. Children's experiences and expectations of kidney transplantation: a qualitative interview study. Nephrology (Carlton). 2019;24(6):647–53. https://doi.org/10.1111/nep.13405.
22. Snethen JA, Broome ME, Bartels J, Warady BA. Adolescents' perception of living with end stage renal disease. Pediatr Nurs. 2001;27(2):159–61.
23. Gutman T, Hanson CS, Bernays S, Craig JC, Sinha A, Dart A, et al. Child and parental perspectives on communication and decision making in pediatric CKD: a focus group study. Am J Kidney Dis. 2018;72(4):547–59.
24. Nicholas DB, Picone G, Selkirk EK. The lived experiences of children and adolescents with end-stage renal disease. Qual Health Res. 2011;21(2):162–73.
25. Lansing L. Back to school for the child on long-term hemodialysis. J Am Assoc Nephrol Nurses Tech. 1981;8(5):13–5.
26. Braj B, Picone G, Children HF, Cross N, Pearlman L. The lived experience of adolescents who transfer from a pediatric to an adult hemodialysis Centre. CANNT J. 1999;9(4):41–6.
27. Pourghaznein T, Heydari A, Manzari Z, ValizadehZare N. "Immersion in an ocean of psychological tension:" the voices of mothers with children undergoing hemodialysis. Iran J Nurs Midwifery Res. 2018;23(4):253–60.
28. Tong A, Lowe A, Sainsbury P, Craig JC. Parental perspectives on caring for a child with chronic kidney disease: an in-depth interview study. Child Care Health Dev. 2010;36(4):549–57.
29. MacDonald H. Chronic renal disease: the mother's experience. Pediatr Nurs. 1995;21(6):503–37.
30. Mieto FS, Bousso RS. The mothers' experiences in the pediatrics hemodialysis unit. J Bras Nefrol. 2014;36(4):460–8.
31. Geense WW, van Gaal BGI, Knoll JL, Cornelissen EAM, van Achterberg T. The support needs of parents having a child with a chronic kidney disease: a focus group study. Child Care Health Dev. 2017;43(6):831–8.
32. Wightman A, Zimmerman CT, Neul S, Lepere K, Cedars K, Opel D. Caregiver experience in pediatric dialysis. Pediatrics. 2019;143(2):e20182102. https://doi.org/10.1542/peds.2018-2102.
33. Heaton J, Noyes J, Sloper P, Shah R. Families' experiences of caring for technology-dependent children: a temporal perspective. Health Soc Care Community. 2005;13(5):441–50.
34. Feenstra B, Boland L, Lawson ML, Harrison D, Kryworuchko J, Leblanc M, et al. Interventions to support children's engagement in health-related decisions: a systematic erview. BMC Pediatr. 2014;14:109.
35. Adams RC, Levy SE. Shared decision-making and children with disabiliies pathways to consensus. Pediatrics. 2017;139(6):e20170956.
36. Thumfart J, Reindl T, Rheinlaender C, Müller D. Supportive palliative care should be integrated into routine care for paediatric patients with life-limiting kidney disease. Acta Paediatr. 2018;107(3):403–7.
37. Watson AR. Strategies to support families of children with end-stage renal failure. Pediatr Nephrol. 1995;9(5):628–31.

Index

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