Bradley A. Warady
Franz Schaefer
Steven R. Alexander
Editors

Pediatric Dialysis

Second Edition

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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 manner in which the pediatric patient is affected by renal insufficiency. It was based on this philosophy that the inaugural edition of *Pediatric Dialysis* was published in 2004. Since that time, advances have taken place in dialysis-related care with the creation of a wealth of new knowledge, outpacing much of the content that occupied a prominent place in the original text. In response, we believe that even in this age of the electronic transmission of information, the availability of a contemporary, comprehensive, and authoritative source of information such as *Pediatric Dialysis* cannot only help facilitate the provision of superb patient care by seasoned clinicians, but it also can 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.

We are, in turn, fortunate to have been able to enlist the collaboration of over 70 colleagues from North America, Europe, and Asia to thoroughly update this text, which remains the most comprehensive source of state-of-the-art information on the dialysis of infants, children, and adolescents currently available. To them, we are eternally grateful for their commitment to this project. The inclusion of a host of new authors from "both sides of the pond" with their unique and fresh perspectives, combined with many authors from the first edition and all with recognized expertise on the topic chosen for their review, has resulted in a text that is clinically relevant and that will someday hopefully duplicate the appearance of one of the initial editions, owned by a dialysis nurse and characterized as being "full of worn pages as a result of almost daily use." The addition of several new chapters, including *Conservation of Residual Renal Function in Children Reaching End-Stage Renal Disease, Intensified Hemodialysis in Children,* and *Transitioning the Adolescent Dialysis Patient to Adult Care*, should contribute to that end.

As clinicians ourselves who have spent many hours over the past three 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 undoubtedly the product of the hard work 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 second 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
Heidelberg, Germany — Franz Schaefer
Stanford, CA, USA — Steven R. Alexander

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Part I

Essential Primers

Notes on the History of Dialysis Therapy in Children

1

Steven R. Alexander and Pierre Cochat

Key Words
Dialysis therapy • Children • History

Introduction

In his authoritative and entertaining monograph on the history of dialysis, Stewart Cameron calls attention to the important role played by the development of dialysis technology in the founding of nephrology as a medical specialty [1]. Prior to the 1950s and 1960s, the study and management of disorders of the kidney was the province of general physicians. Along with the introduction of the renal biopsy and its interpretation [2], 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]. When long-term dialysis became possible in the 1960s, hundreds of units sprang up in North America and Europe spawning a new breed of physicians who "…trained frantically to run them…" These physicians adopted a culture that was more "active" than the traditional contemplative approach of medicine specialties, 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, with whom physicians in general found it difficult to relate…" [1].

In contrast, the discipline of pediatric nephrology emerged in response to different drivers. Based on 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 some 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

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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 therapies, attempting to ease the progression to end-stage renal disease (ESRD). When ESRD was reached, older children and adolescents often had to look to adult ESRD programs for access to chronic dialysis and transplantation; infants and younger children were frequently offered only palliative care [5].

During the past five 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 ESRD has come to occupy a prominent if not dominant place in pediatric 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, sustained, and demanded 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. We have left to the chapters that follow a detailed description of these innovations. Our goal is to place them in historical context, acknowledging the debt owed to those pioneering pediatric nephrologists, nurses, engineers, dieticians, and social workers and their young patients whose efforts have helped make a complex and life-sustaining therapy a part of routine medical management for children throughout the world.

Dialysis: The Founding Fathers

The term *dialysis* has both Latin and Greek roots and refers to a separation or dissolution: (from *dialyein* – to separate; *dia* – apart; *lyein* – to loose) [6]. The modern understanding of the term is the result of the work of a Scottish physical chemist, Thomas Graham (1805–1869) who redefined *dialysis* to reflect his newfound understanding of the ability of a semipermeable membrane (Graham's own concept) to separate solutions containing a crystalloid from a colloid [7]. Using sheets of vegetable parchment impregnated with starch as the membrane, Graham observed that some substances (e.g., sugars) crossed the membrane and would crystallize on drying, while larger molecules like gum arabic would remain in the original solution. Based on his own discovery of the laws governing diffusion of gasses, Graham realized that the crystalloid molecules moved by the force of diffusion across the membrane which prevented the movement of larger molecules. For this work, Graham is known as the "father of modern dialysis" [8].

Earlier work by a Frenchman, Rene' Dutrochet (1776–1847) introduced the term *osmosis* to describe the movement of water down concentration gradients of salts across membranes that retard the movement of solutes. Dutrochet's *osmotic pressure* forms the basis of osmotic-induced ultrafiltration and has earned him the sobriquet, "grandfather of dialysis" [9].

Application of these principles led scientists in the late nineteenth century to explore the use of semipermeable membranes in the laboratory to investigate the properties of many substances. Animal membranes were popular, including the peritoneal membrane (of calves), but the concept was limited to separation and purification of substances. Beginning with the animal experiments of John Jacob Abel (1857–1938) and his team in Baltimore, the early twentieth century saw much progress in the ability to perform dialysis in living animals. In 1913, Abel's team built an apparatus using hollow collodion tubes encased in a glass cylinder that foretold the design of modern hollow fiber dialyzers. They called the process

"vividiffusion" and were the first to conceive of dialysis as a means of removing "…substances from the blood whose accumulation is detrimental to life…" [10]. However, clinical application of these techniques would be delayed until mid-century when both hemodialysis (HD) and peritoneal dialysis gained traction as treatments for renal failure in humans.

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 [11]. At that time, dehydrated infants too small or dehydrated to permit intravenous access, were treated by injecting fluids into the subcutaneous tissues ("clysis"), a method Blackfan and Maxcy noted 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…" [11]. These same characteristic features, simplicity, practicality, and safety, have made peritoneal dialysis particularly well suited for use in children for the past 60 years.

The first reports of the use of the peritoneum to treat children with renal failure appeared in 1948 [12] and 1949 [13] at a time when worldwide reported clinical experience with PD totaled only 100 patients [14]. These first pediatric acute PD reports are of interest in part because they describe in arresting detail many of the problems that have continued to complicate the use of PD in children.

Writing in the premier issue of the journal Pediatrics, a pediatrician, Allan Bloxsum, and his urologist colleague at Houston's St. Joseph's Hospital, Norborne Powell, described the treatment of an oliguric 10-year-old boy who suffered acute glomerulonephritis complicating scarlet fever. Severely hypertensive, fluid overloaded, and becoming increasingly cyanotic, "…it appeared that the boy was going to die…" [12]. Modeling their technique on methods first described in adults in 1946 [15], Bloxsum and Powell had #30 Fr. mushroom catheters surgically placed into the right and left lower quadrants to serve as irrigating tubes. The irrigating solution was mammalian Tyrode's solution, then in common use as a surgical irrigant. It contained sodium, potassium, chloride, magnesium, phosphate, bicarbonate, and dextrose in near-physiologic concentrations, along with penicillin (only 5,000 units/L), sulfadiazine, and heparin. Fluid from 1-L autoclaved flasks was dripped continuously at 10 mL/min into one catheter while being drained by gravity from the other. Peritoneal lavage was continued for 4 days, during which the patient's azotemia worsened, but enough ultrafiltration occurred to improve blood pressure from 186/130 to 148/105. Fortunately, a spontaneous diuresis began almost immediately, and by the third day of treatment, the boy had begun to recover. During lavage, the drainage catheter often became obstructed requiring reversal of flow through the two catheters and eventual application of suction to the drainage line. By the fourth day, the system would no longer drain at all, with fluid leaking freely around both catheters. Peritoneal fluid cultures were positive for three organisms, which may have been contaminants, as the boy did not display signs of clinical peritonitis. Although Bloxsum and Powell entitled their paper: "The treatment of acute temporary dysfunction of the kidneys by peritoneal irrigation: Successful treatment of a 10-year old male child," the contribution of peritoneal irrigation to the child's successful recovery is questionable.

The 1949 experience of Henry Swan and Harry H. Gordon was more promising [13]. 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 L/day) of sterile, physiologic

Tyrode's solution to flow by gravity from 20-L 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 lightbulbs 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 [13]. 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 renal failure 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 [17]. These methods were adapted for use in children in the early 1960s by teams in Indianapolis and Memphis [18, 19] 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 [20, 21]. Subsequent reports established PD as the most frequently employed renal replacement therapy (RRT) for AKI in pediatric patients [22–28]. 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 end-stage renal disease (ESRD). The need to reinsert the dialysis catheter for each treatment made prolonged use of PD in young 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. 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 hemodialysis, and three remained on IPD; no child had been successfully transplanted [29].

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 [30] and later refined by Tenckhoff and Schechter in 1968 [31], the permanent PD catheter revolutionized chronic PD for adults and children in the same way the Scribner shunt transformed chronic hemodialysis, making long-term renal replacement 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 [32, 33]. In the early 1970s, this work culminated in Seattle in the establishment of the first pediatric chronic home PD program [34]. The success of the Seattle program throughout the 1970s showed that chronic IPD could be a practical option for some children with ESRD [35].

Additional limited experience with chronic IPD was reported from several other pediatric centers [36–39], 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 one great advantage of HD: efficiency. Moreover, it became clear from efforts

to maintain adult ESRD patients on chronic IPD that long-term technique survival was not often achieved [40]. Inadequate dialysis 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 RRT for children, especially infants. In fact, 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 …" [41], and with Reinhart: "…we may find the price the child pays for life too great…" [42]. During a period in which advances in ESRD therapy pushed the upper age limits for successful therapy well into the seventh and eighth decades, the youngest ESRD patients remained therapeutic orphans, considered by many to have severely limited chances for survival [43, 44].

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 ESRD in children [44]. As originally described, 2 L of dialysate were infused into an adult and retained for 4–5 h, then drained and repeated a total of five times per day while the patient went about regular daily activities [45]. 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 transplantable age and size.

The first child to receive CAPD was a 3-year-old girl in Toronto in 1978 [46, 47]. Although a number of pediatric dialysis programs in North America [48–51] and Europe [52, 53] quickly followed suit, enthusiasm in many areas was tempered by the availability of dialysis fluid only in 2,000-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 much of the rest of the world [54].

During the 1980s, the popularity of CAPD for children spread worldwide [55]. 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 [56]. Pediatric nephrologists in developing countries soon realized that CAPD was relatively affordable, which meant that ESRD was no longer an inexorably lethal condition for children from families with limited resources [57–59]. And throughout the world, the survival of so many more children with ESRD increased the 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 h 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 that could afford it. 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 [60, 61]. 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 [61]. Soon CCPD became extremely popular among pediatric dialysis programs in developed countries worldwide [62–66].

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 [62]. The ready availability of potent vitamin D analogues, ESRD-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. 22, 23, 25, and 27) gave pediatric nephrologists a powerful armamentarium with which to bring the child on chronic dialysis safely to transplantation in optimal condition – well nourished, normally grown, with minimal renal anemia and bone disease. Attention could then be turned to quality of life issues, scholastic and emotional development, and child and family psychosocial adjustment to the rigors of ESRD and chronic dialysis (see Chaps. 29, 30, and 33).

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 [63–67]. 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 [68], 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 [69]. 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 [70]. 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, but 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 [71]. 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 3½-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 [72]. 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. [72]

Merrill's pediatric patient received a single 4-h dialysis treatment and was said to have had "…modest improvement, but of short duration…" [72].

In 1955, FM Mateer, L. Greenman, and T.S. 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)…" [73]. Their equipment was built by the Westinghouse Company based on an Alwall coil kidney design [74]. 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 m of $1\frac{1}{8}$ in. cellophane tubing wound on stainless steel screens submerged in a warmed 32 L bath of dialysate. An in-line roller pump propelled heparinized blood through the tubing from radial artery through the cellophane coils to return via the saphenous vein. Dialysate consisted of Pittsburgh tap water to which were added sodium, calcium, chloride, bicarbonate, glucose, and variable amounts of potassium; a fresh batch was mixed every 200 min, and with every bath change an antibiotic (usually oxytetracycline) was injected into the tubing leading to the artificial kidney [73].

For these severely uremic children, dialysis was clearly a heroic treatment that was surprisingly effective, if only temporarily. After treatments lasting 2–13 h, 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…" [73].

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 hemodialysis treatments in five children (2–14 years of age) using an improved disposable Alwall twin coil kidney that could be modified for children <20 kg by using only one of the two coils, thereby reducing priming volume from 750 to 400 mL [75]. 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 [75].

Four of the five children survived, including a 2-year-old boy with probable acute 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…" [75].

Unlike the concise and constricted prose demanded by modern journal editors, the papers by Mateer and Carter published 50 years ago are wonderfully detailed, conveying the intensity and drama that must have attended these early hemodialysis 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… [73]

Intoxications with salicylates or barbiturates represented another potential use for hemodialysis in children [76], but while potentially lifesaving in cases of reversible AKI or intoxications, the role of periodic hemodialysis 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 [77]. The Scribner shunt consisted of silastic-teflon 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 [78], and by the mid-1960s the availability of repeated vascular access via these shunts made chronic hemodialysis in children a reality.

Using a pumpless system developed for pediatric patients by Robert Hickman and Belding Scribner in Seattle in the early 1960s [79], the first large pediatric chronic hemodialysis programs were established in Seattle [80], San Francisco [81], Los Angeles [82], Minneapolis [83], London [84], and Paris [85].

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 hemodialysis 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 hemodialysis of 14 children 2–16 years of age weighing 10–52 kg [81]. 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 hemodialysis when the scarcity of this resource forced painful decisions into the hands of so-called "Life and Death Committees" [86]. 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…" [81].

Using the Seattle pumpless method [79], 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 [87], consisted of two grooved polypropylene plates separated by a sheet of cellophane clamped tightly together. 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 arteriovenous shunts originating in 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/min, and because of this low clearance, five of the children were dialyzed 18–27 h/week. Dialysis prescriptions were adjusted according to pre-dialysis BUN, which averaged 70–86 mg/dL [81].

There were many complications, including hemodynamic decompensation due to the a-v shunt, 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 successful kidney transplants [81]. Looking back on his early experience, Potter recently recalled that although hemodialysis in 1970 appeared to be a potentially successful therapy for 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 problem of ultrafiltration monitoring in infants, at once the most critical due to their small body size and narrow blood volume safety limits, was solved ingeniously by another pioneering pediatric hemodialysis 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 [88]. 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 hemodialysis in North America in the early 1970s [89].

Developments in Europe paralleled those in North America. In 1975, the second edition of the famous French textbook of pediatric nephrology was coedited by Pierre Royer, Renée Habib, Michel Broyer, and Chantal Loirat. There were six pages about hemodialysis (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" [90]. According to these authors, there were three major contraindications to chronic dialysis in children: (1) systemic disease such as lupus, (2) mental retardation, and (3) 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 hemodialysis sessions. Morbidity mainly included arterial hypertension, renal osteodystrophy, anemia, undernutrition, and poor growth velocity. However, actuarial patient survival was reported to be 90% after 3 years on chronic hemodialysis [90].

By the early 1970s, it became clear among pediatric nephrologists in North America and Europe that the care of children with ESRD required separate facilities from those in which adult patients were dialyzed. The concept of specialized pediatric dialysis centers was pioneered in Europe by Broyer, Scharer, Chantler, Donkerwolke, Rizzoni, and others who stressed the importance of concentrating pediatric ESRD patients in multidisciplinary pediatric centers specially equipped by experience and expertise to care for children on dialysis and for their families [91]. 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 RRT 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 [92]. The 1971 report presented data on 296 patients aged less than 15 years at the start of RRT who were receiving treatment at 122 centers, only five of which had treated three 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, school facilities, along with a separate children's ward in which therapy was provided away from adult patients [93]. 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 ESRD. By 1989, nearly 80% of all children receiving dialysis in the countries of the EDTA were cared for in specialized pediatric centers [94].

The most recent report on pediatric dialysis in Europe appeared in 2010 summarizing data on 483 incident and 2,512 prevalent pediatric dialysis patients (age <15 years) from 28 countries [95]. In comparison to the last demographic report of the former EDTA registry 14 years ago, the authors found in 2007 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 [95].

In North America, the success of the EDTA pediatric registry prompted over 60 pediatric ESRD programs to band together in 1987 to form what is now called the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [96]. 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). In a recent report from 2008, the NAPRTCS presented data on 6,491 children treated with dialysis in North American centers since 1992, approximately one-third of whom had received hemodialysis (http://web.emmes.com/study/peds). A complete listing of the more than 130 publications based on NAPRTCS data that have appeared since 1990 is available on the NAPRTCS web site, as are all of its most recent Annual Data Reports (http://web.emmes.com/study/peds).

Both the EDTA and the NAPRTCS 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 three decades, HD in children has dramatically improved, with the near disappearance of many of the complications that once plagued pediatric hemodialysis: disequilibrium syndrome, need for blood transfusions, disabling bone disease and uremic dwarfism, aluminum encephalopathy, pyrogenic reactions and symptoms of bioincompatibility, malnutrition, intradialytic symptomatic hypovolemia, seizures and developmental delay, just to name a few.

Indeed the history of maintenance HD in children has been strongly modified by the introduction of more efficient and biocompatible synthetic membranes, by erythropoietin treatment, by growth hormone therapy, by the development of new therapeutic approaches to bone disease and calcium-phosphate disorders, by advances in vascular accesses (microsurgery for arteriovenous fistulas, new materials for cuffed tunneled venous catheters), by introducing pediatric data for dialysis adequacy measurement (Kt/V, urea reduction ratio), by novel dialysis strategies (high-flux dialysis, hemodiafiltration), by optimizing the use of anticoagulation (low molecular weight heparins, regional trisodium citrate), by improving dialysis water quality and bacterial safety (ultrapure dialysate), by noninvasive investigation of vascular access blood flow, by using urokinase or tPA for the management of the thrombosed hemodialysis catheter, by improving nutritional assessment and support, by using new machines with precise control of ultrafiltration by volumetric assessment and continuous blood volume monitoring during dialysis sessions, by the availability of specific small size dialyzers and tubing for infants, and by the use of sodium modeling [97–102]. In the mean time, HD practice has benefited from specific medical and staff training, including courses, fellowship programs, and congresses. Specific regulations have been established for HD practice in children, according to local health-care organization, public health, resources, and law. During this period, patient morbidity and mortality have significantly decreased. Worldwide experience has resulted in large databases and general practical guidelines [103–105]. However this only includes developed countries since the cost of HD is rather high, and such a technique is not available/accessible in many developing countries.

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

- Daily online hemodiafiltration allows better nutrition, reduces blood pressure, improves

left ventricular size and function, improves calcium x phosphate control, better controls chronic microinflammation, and promotes catch-up growth in children [98, 106].
- The lowest age limit for starting HD in children has dropped, including neonates thanks to specific devices and improvement in general care of such patients [107].
- Various high-tech pediatric permanent HD catheters have been developed.
- There is a better worldwide knowledge and investigation of cardiovascular risk factors leading to better long-term control and prevention of cardiovascular disease [107].
- The use of several online 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 online inlet and outlet dialysate conductivity measurements), estimation of sodium concentration derived from conductivity, intra-HD urea kinetics and delivered dialysis dose from online urea monitors, dialysate temperature modulation according to blood temperature monitoring [108].

All these improvements have led to better quality of life, better nutritional status, better neurological development, better psychosocial outcome, and better patient survival, and all have their origins in the work of pioneering medical teams, patients, and families beginning more than 60 years ago. The following chapters 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 Jr CM. 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. Webster's New Twentieth Century Dictionary. Collins World Publishing, 1978. p. 503.
7. Graham T. Liquid diffusion applied to analysis. Philos Trans R Soc Lond B Biol Sci. 1862;151:183–224. Cited in Reference 1, p. 27.
8. Negoi D, Nolph KD. History of peritoneal dialysis. In: Khanna R, Krediet RT, editors. Nolph and Gokal's textbook of peritoneal dialysis. 3rd ed. New York: Springer; 2009. p. 1–2.
9. Negoi D, Nolph KD. History of peritoneal dialysis. In: Khanna R, Krediet RT, editors. Nolph and Gokal's textbook of peritoneal dialysis. 3rd ed. New York: Springer; 2009. p. 2.
10. Abel JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the blood of living animals by dialysis. J Pharmacol Exp Ther. 1913–1914; 5:275–316.
11. Blackfan KD, Maxcy KF. The intraperitoneal injection of saline solution. Am J Dis Child. 1918;15: 19–28.
12. Bloxsum A, Powell N. The treatment of acute temporary dysfunction of the kidneys by peritoneal irrigation. Pediatrics. 1948;1:52–7.
13. Swan H, Gordon HH. Peritoneal lavage in the treatment of anuria in children. Pediatrics. 1949;4: 586–95.
14. Odel HM, Ferris DO, Power MH. Peritoneal lavage as an effective means of extra-renal excretion. Am J Med. 1950;9:63–77.
15. Fine J, Frank HA, Seligman AM. The treatment of acute renal failure by peritoneal irrigation. Ann Surg. 1946;124:857–75.
16. Weston RE, Roberts M. Clinical use of a stylet catheter for peritoneal dialysis. Arch Intern Med. 1965; 15:659–62.
17. Maxwell MH, Rockney RB, Kleeman CR, Twiss MR. Peritoneal dialysis: technique and applications. JAMA. 1959;170:917–24.
18. Segar WE, Gibson RK, Rhamy R. Peritoneal dialysis in infants and small children. Pediatrics. 1961;27: 603–13.
19. Etteldorf JN, Dobbins WT, Sweeney MJ, Smith JD, Whittington GL, Sheffield JA, et al. Intermittent peritoneal dialysis in the management of acute renal failure in children. J Pediatr. 1962;60:327–39.
20. Segar WE. Peritoneal dialysis in treatment of boric acid poisoning. N Engl J Med. 1960;262:708–800.
21. 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.
22. 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.

23. Manley GL, Collipp PJ. Renal failure in the newborn: treatment with peritoneal dialysis. Am J Dis Child. 1968;115:107–10.
24. 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.
25. 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.
26. Wiggelinkhuizen J. Peritoneal dialysis in children. S Afr Med J. 1971;45:1047–54.
27. Day RE, White RHR. Peritoneal dialysis in children: review of 8 years' experience. Arch Dis Child. 1977;52:56–61.
28. Chan JCM. Peritoneal dialysis for renal failure in childhood. Clin Pediatr. 1978;17:349–54.
29. 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.
30. Palmer RA, Quinton WE, Gray J-F. Prolonged peritoneal dialysis for chronic renal failure. Lancet. 1964;1:700–2.
31. Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. ASAIO Trans. 1968;14: 181–7.
32. Boen ST, Mion CM, Curtis FK, Shilitar G. Periodic peritoneal dialysis using the repeated puncture technique and an automatic cycling machine. ASAIO Trans. 1964;10:409–14.
33. Tenckhoff H, Meston B, Shilipetar G. A simplified automatic peritoneal dialysis system. ASAIO Trans. 1972;18:436–40.
34. Counts S, Hickman R, Garbaccio A, Tenckhoff H. Chronic home peritoneal dialysis in children. ASAIO Trans. 1973;19:157–67.
35. Hickman RO. Nine years' experience with chronic peritoneal dialysis in childhood. Nephrol Dial Transplant. 1978;7:803.
36. Brouhard BH, Berger M, Cunningham RJ, Petrusik T, Allen W, Lynch RE, et al. Home peritoneal dialysis in children. ASAIO Trans. 1979;25:90–4.
37. 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.
38. Lorentz WB, Hamilton RW, Disher B. Home peritoneal dialysis during infancy. Clin Nephrol. 1981;15: 194–7.
39. 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.
40. Ahmad S, Gallagher N, Shen S. Intermittent peritoneal dialysis: status re-assessed. ASAIO Trans. 1979; 25:86–8.
41. Hurley JK. Kidney transplantation in infants (Letter). J Pediatr. 1978;93:538.
42. 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.
43. Dialysis and transplantation in young children (Editorial). Br Med J. 1979; No 6170, London, Saturday, 21 April; 2:1033–4.
44. Popovich RP, Moncrief JW, Dechard JF. The definition of a novel portable/wearable equilibrium dialysis technique (Abstract). ASAIO Trans. 1976; 5:64.
45. Moncrief JW, Popovich RP, Nolph KD. The history and current status of continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1990;16:579–84.
46. Oreopoulos DG, Katirtzoglou A, Arbus G, Cordy P. Dialysis and transplantation in young children (Letter). Br Med J. 1979;1:1628–9.
47. Balfe JW, Irwin MA. Continuous ambulatory peritoneal dialysis in pediatrics. In: Legain M, editor. Continuous ambulatory peritoneal dialysis. Amsterdam: Excerpta Medica; 1980. p. 131–6.
48. 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 Publishing; 1981. p. 195–209.
49. Kohaut EC. Continuous ambulatory peritoneal dialysis: a preliminary pediatric experience. Am J Dis Child. 1981;135:270–1.
50. Potter DE, McDaid TK, McHenry K, Mar H. Continuous ambulatory peritoneal dialysis (CAPD) in children. ASAIO Trans. 1981;27:64–7.
51. Salusky IB, Lucullo L, Nelson P, Fine RN. Continuous ambulatory peritoneal dialysis in children. Pediatr Clin North Am. 1982;29:1005–12.
52. 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.
53. Eastham EJ, Kirplani H, Francis D, Gokal R, Jackson RH. Pediatric continuous ambulatory peritoneal dialysis. Arch Dis Child. 1982;57:677–80.
54. Alexander SR. Pediatric CAPD update-1983. Perit Dial Bull. 1983;3(Suppl):S15–22.
55. Alexander SR, Honda M. Continuous ambulatory peritoneal dialysis for children: a decade of worldwide growth and development. Kidney Int. 1993;43(Suppl):S65–74.
56. 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.
57. 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.
58. Bakkaloglu SA, Ekim M, Sever L, et al. Chronic peritoneal dialysis in Turkish children: a multicenter study. Pediatr Nephrol. 2005;20:644–51.

59. Grunberg J, Verocay MC, Rebori A, et al. Twenty years' pediatric chronic peritoneal dialysis in Uruguay: patient and technique survival. Pediatr Nephrol. 2005;20:1315–19.
60. Diaz-Buxo JA, Farmer CD, Walker PJ, Chandler JT, Holt KL. Continuous cyclic peritoneal dialysis: a preliminary report. Artif Organs. 1981;5:157–61.
61. Price CG, Suki WN. Newer modifications of peritoneal dialysis: options in treatment of patients with renal failure. Am J Nephrol. 1981;1:97–104.
62. 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.
63. 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.
64. Edefonti A, Verrina E, Schaefer F, Fischbach M, Watson A. The European experience with CAPD/ CCPD in children. In: Fine RN, Alexander SR, Warady BA, editors. CAPD/CCPD in children. Boston: Kluwer Academic Publishers; 1998. p. 17–34.
65. 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.
66. 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.
67. Verrina E, Edefonti A, Gianglio B, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
68. 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 Med Scand. 1944;117: 121–34.
69. Kolff WJ. First clinical experience with the artificial kidney. Ann Intern Med. 1965;62:608–19.
70. MacLean J. The thromboplastic action of cephalin. Am J Physiol. 1916;41:250–7.
71. Andrus FC. Use of Visking sausage casing for ultrafiltration. Proc Soc Exp Biol Med. 1919;27:127–8.
72. Merrill JP, Smith III S, Callahan III EJ, Thorn GW. The use of an artificial kidney. II. Clinical experience. J Clin Invest. 1950;29:425–38.
73. Mateer FM, Greenman L, Danowski TS. Hemodialysis of the uremic child. Am J Dis Child. 1955;89:645–55.
74. Alwall N. Apparatus for dialysis of the blood in vivo. Acta Med Scand. 1947;128:317–35.
75. Carter FH, Aoyama S, Mercer RD, Kolff WJ. Hemodialysis in children: report of five cases. J Pediatr. 1957;51:125–36.
76. 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.
77. Quinton W, Dillard D, Scribner B. Cannulation of blood vessels for prolonged hemodialysis. ASAIO Trans. 1960;6:104.
78. Morse TS. Synthetic arteriovenous shunts for hemodialysis in children. J Pediatr Surg. 1970;5:23–31.
79. Hickman RO, Scribner BH. Application of the pumpless hemodialysis system to infants and children. ASAIO Trans. 1962;8:309–14.
80. Hutchings RH, Hickman R, Scribner BH. Chronic hemodialysis in a pre-adolescent. Pediatrics. 1966; 37:68–73.
81. Potter D, Larsen D, Leumann E, Perin D, Simmons J, Piel CF, et al. Treatment of chronic uremia in childhood. II. Hemodialysis. Pediatrics. 1970;46:678–89.
82. 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.
83. Mauer SM, Shideman JR, Buselmeier TJ, Kjellstrand CM. Long-term hemodialysis in the neonatal period. Am J Dis Child. 1973;125:269–72.
84. 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.
85. Broyer M, Loirat C, Kleinknecht C. Technical aspects and results of regular hemodialysis in children. Acta Paediatr Scand. 1972;61:677–84.
86. Obituary. Belding Scribner: inventor of shunt dialysis. BMJ. 2003;327(7407):167.
87. Cole JJ, Pollard TL, Murray JS. Studies on the modified polypropylene Kiil dialyser. ASAIO Trans. 1963;9:67–72.
88. Kjellstrand CM, Mauer SM, Shideman JR, Buselmeier TJ. Accurate weight monitoring during pediatric hemodialysis. Nephron. 1973;10:302–5.
89. Mauer SM, Lynch RE. Hemodialysis techniques for infants and children. Pediatr Clin North Am. 1976;23:843–56.
90. 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.
91. 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.
92. Scharer K, Brunner FP, Gurland HJ, Harlen H, Parsons FM. Combined report on regular dialysis and renal transplantation of children in Europe, 1971. Proc EDTA. 1972;9:191–200.
93. Chantler C, Donckerwolke RA, Brunner FP, Gurland H, Hathway RA, Jacobs C, et al. Combined report on

regular dialysis and renal transplantation of children in Europe, 1976. Proc EDTA. 1977;14:70–112.
94. Ehrich JHH, Rizzoni G, Brunner FP, Brynger H, Gerlings W, Fasbinder W, et al. Combined report on regular dialysis and transplantation of children in Europe, 1989. Nephrol Dial Transplant. 1991;6 Suppl 1:37–47.
95. Van Stralen KJ, Tizard EJ, Verrina E, Schaefer F, Jager KJ, and 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.
96. 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.
97. Shroff R, Ledermann S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2009;24:463–74.
98. Fischbach M, Terzic J, Laugel V, Dheu C, Menouer S, Helms P, et al. Daily on-line haemofiltration: a pilot trial in children. Nephrol Dial Transplant. 2004; 19:2360–7.
99. Goldstein SL, Allsteadt A. Ultrasound dilution evaluation of pediatric hemodialysis vascular access. Kidney Int. 2001;59:2357–60.
100. 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.
101. 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.
102. 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;16:1203–6.
103. Fischbach M, Edefonti A, Schröder C, Watson A, and the European Pediatric Dialysis Working Group. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20:1054–66.
104. KDOQI http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines.cfm
105. NAPRTCS https://web.emmes.com/study/ped/
106. 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.
107. 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.
108. 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.

The Biology of Dialysis

2

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Keywords
Diffusion • Convection • Membrane • Hemodialysis • Hemofiltration

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 molecular weight (MW). After a frame of reference is established with a discussion of toxin elimination mechanisms for the native kidney, the dialytic solute removal mechanisms (diffusion, convection, and adsorption) broadly applicable to all renal replacement therapies are reviewed. The relative importance of these mechanisms in the different therapies used in both the ESRD and AKI settings will then be discussed. 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. 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

Classification of Uremic Toxins

In the properly functioning human kidney, plasma water and blood solutes are removed by ultrafiltration and convection, respectively. Solutes of MW

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Table 2.1 Uremic toxin classes and dialytic removal mechanisms

Solute category	Primary removal mechanism
Small solutes (mw <300 D)	Diffusion
Middle molecules (mw 500–5,000 D)	Diffusion Convection
LMW proteins (mw 5,000–50,000 D)	Convection Diffusion Adsorption
Large proteins (mw >50,000 D)	Convection

mw molecular weight, *D* daltons, *LMW* low molecular weight

less than approximately 40,000 daltons have essentially unrestrained passage through the glomerulus, the kidney's filtration unit [1]. Therefore, the rate of clearance at the level of the glomerulus for such molecules very closely approximates renal plasma flow rate. Most molecules subsequently undergo some degree of modification in distal portions of the nephron, such that urinary clearance ultimately is modified quite significantly, relative to the clearance by the glomerulus. By definition, ESRD and AKI are associated with absent or minimal native kidney function. As a result, blood solutes normally removed by the above filtration mechanism are retained in the bloodstream with a resultant increase in their plasma concentrations.

The classification of uremic solutes is typically based on MW [2] and four reasonably well-accepted classes currently exist (Table 2.1), although a more sophisticated classification scheme has been proposed by Vanholder and colleagues comprising the Uremic Toxicity Working Group [3]. In the traditional scheme, one category, simply called "small solutes," is comprised predominantly of nitrogenous compounds of MW less than 300 daltons. Prototypical solutes in this category are by-products of protein metabolism and include the compounds urea (MW, 60 daltons) and creatinine (MW, 113 daltons), which are commonly measured in clinical medicine to estimate kidney function. The second category, referred to as "middle molecules," consists of a diverse group of molecules in the 500–5,000 dalton range [4]. Although this class has been widely studied from an experimental perspective, a representative solute, which is clinically measurable, has not yet been identified. Low-molecular-weight (LMW) peptides and proteins (MW, 5,000–50,000 daltons) are the most recently identified class of uremic toxins [5]. The plasma concentrations of these compounds are typically increased 10–100-fold in ESRD. A specific toxin in this class, β2-microglobulin (β2M: MW, 11,800 daltons), has been identified as a causative factor in the development of dialysis-related amyloidosis, a deposition disorder specific to the ESRD population [6]. For major therapeutic approaches [intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT)] used in acute and chronic dialysis, Table 2.1 also indicates the predominant solute removal mechanisms (see below) for these solute classes.

Renal Mechanisms for Toxin Removal

Although creatinine and, particularly, urea are felt to be surrogates for the entire small solute class in patients with renal failure, these compounds do not inherently have significant toxicity. In addition, the renal handling of compounds in this class is quite dissimilar. Although glomerular filtration is the initial elimination step for both urea and creatinine, subsequent handling of these two molecules in distal portions of the nephron is quite disparate. Whereas urea undergoes significant reabsorption in the proximal tubule [7], the final concentration of creatinine in the urine is influenced heavily by the extent of its tubular secretion [8]. This latter feature is especially important in advanced stages of chronic kidney disease, during which tubular creatinine secretion can account for a substantial percentage of total renal elimination [9].

Previous work suggests reabsorption followed by cellular catabolism in the proximal tubule is another important elimination mechanism for many uremic toxins, especially the LMW protein class of compounds. In addition to β2M (see above), complement Factor D (MW, 23.5 kDa) [10] is also a representative molecule in this category. Factor D acts as an up-regulator of the alternative complement pathway and activation of the alternative pathway by blood–membrane interaction (with resultant C3a generation) is enhanced

in the presence of the high serum concentrations of Factor D found in uremic patients. In an elegant study, Pascual et al. [10] characterized Factor D metabolism in patients with normal renal function and varying degrees of renal insufficiency. A significant direct correlation was observed between serum Factor D concentration and serum creatinine while the relationship between serum Factor D concentration and creatinine clearance was very similar to that between serum creatinine and creatinine clearance. Serum Factor D concentrations in patients with ESRD were 10–20-fold higher than those with normal kidney function. Using radiolabeled Factor D, these investigators also characterized its metabolism in patients with normal renal function. The glomerular sieving coefficient of Factor D was estimated to be 0.36. After glomerular filtration, essentially complete reabsorption was suggested by an absence of radioactivity in the final urine. On the other hand, in patients with proximal tubular disorders, such as that produced by long-term gentamicin administration, significant urinary radioactivity was quantified. Similar findings have been reported for β2M.

Another uremic toxin for which renal removal is highly dependent on proximal tubule function is the advanced glycation end product (AGE) pentosidine [11–14] (MW, 379 daltons), which circulates both in a protein-bound and free form. Miyata et al. [13] characterized free pentosidine metabolism in rats with normal renal function. Following exogenous administration of radiolabeled pentosidine, radioactivity was measured in urine, feces, and expired air over a 72 h period. Urinary elimination accounted for over 80% of the total pentosidine excretion during this period. However, chromatographic analysis of the 72 h urine collection indicated the primary peaks were not intact pentosidine but rather lower-molecular-weight compounds. This finding, coupled with the immediate but transient appearance of radioactivity in proximal tubule cells after pentosidine administration, suggested initial metabolism of intact pentosidine in the proximal tubule with subsequent excretion of lower-molecular-weight metabolites primarily also via a renal mechanism.

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 [15], 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 [16]. Solute diffusion within a membrane is influenced by both membrane thickness (diffusion path length) and membrane diffusivity [17], 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 [18]. 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 [19] (Fig. 2.1):

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

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 [20]. Minimizing the thickness of these unstirred layers is primarily dependent on achieving relatively

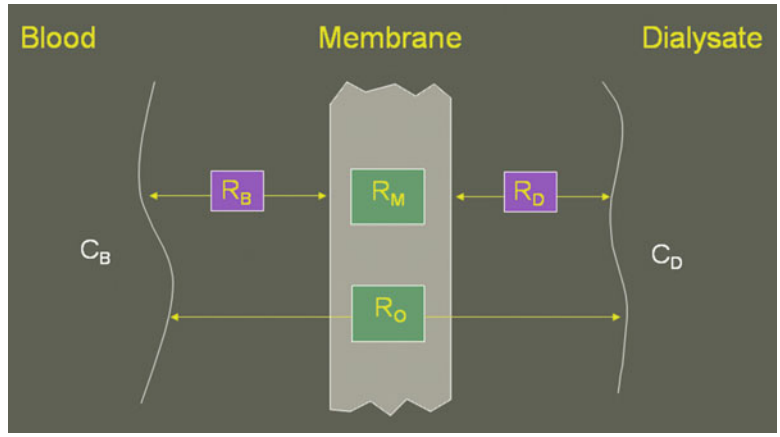

Fig. 2.1 Diffusive mass transfer resistances in a hemodialyzer (Source: Reprinted with permission from Ref. [18])

high shear rates, particularly in the blood compartment [21]. 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 is that due to the membrane itself.

Another approach to quantifying diffusive mass transfer specifically through an extracorporeal membrane is by use of Fick's law of diffusion [22]:

$$N = D\left(dC / dx\right) \tag{2.4}$$

In this equation, N is mass flux (mass removal rate normalized to membrane surface area). In addition, D is membrane diffusivity, an intrinsic membrane property for the particular solute being assessed, and dC/dx is the change in solute concentration with respect to distance. This equation also can be expressed in a more applicable, integrated form:

$$N = D(\Delta C / \Delta x) \tag{2.5}$$

Thus, for a given concentration gradient across a membrane, the rate of diffusive solute removal is directly proportional to 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 [23]:

$$\varphi = \lambda D \rho \Delta C / t \tag{2.6}$$

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:

$$\rho = N\pi r^2 \tag{2.7}$$

Equations 2.6 and 2.7 suggest diffusive transport is relatively favorable for 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 2.6 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,

cellulose triacetate) 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 1,000 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.

Solute Removal by Convection

Convective solute removal is primarily determined by the sieving properties of the membrane used and the ultrafiltration rate [24]. 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.

Because the flux (water permeability) and sieving properties of a membrane are tied closely to one another, a clear understanding of the determinants of flux is necessary. Several approaches have been used to characterize and quantify the flux properties of extracorporeal membranes, including that defined by Equation 2.6. The Hagen–Poiseuille equation [25], which describes fluid flow through a cylinder, can be used as the basis for developing the relationship between ultrafiltrate flux and mean pore size (r_p) in such a model. Using this equation as the foundation, Handley et al. recently [26] proposed the following expression for membrane hydraulic permeability (K_f):

$$K_f = n\pi r^4 / \tau \mu \Delta x \qquad (2.8)$$

In this equation, n is the number of pores per unit area (i.e., pore density), r is the pore radius, τ is a factor accounting for pore tortuosity, μ is the viscosity of the ultrafiltrate, and Δx is the membrane wall thickness. Since the rate of ultrafiltrate flow is directly related to the fourth power of the pore radius, the membrane characteristic that most directly influences water permeability is mean pore size. Note that this fourth-power dependence differs from the second-power dependence of diffusive solute transport on pore size described in Equation 2.6. Thus, the membrane's diffusive properties can be dissociated to some degree from its water permeability.

Both the water and solute permeability of a membrane used for therapies which involve relatively high ultrafiltration rates are influenced by the phenomena of secondary membrane formation [27] and concentration polarization [28] (Fig. 2.2). The exposure of an artificial surface to plasma results in the nonspecific, instantaneous adsorption of a layer of proteins, the composition of which generally reflects that of the plasma itself. Therefore, plasma proteins such as albumin, fibrinogen, and immunoglobulins form the bulk of this 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 [29]. 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.

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

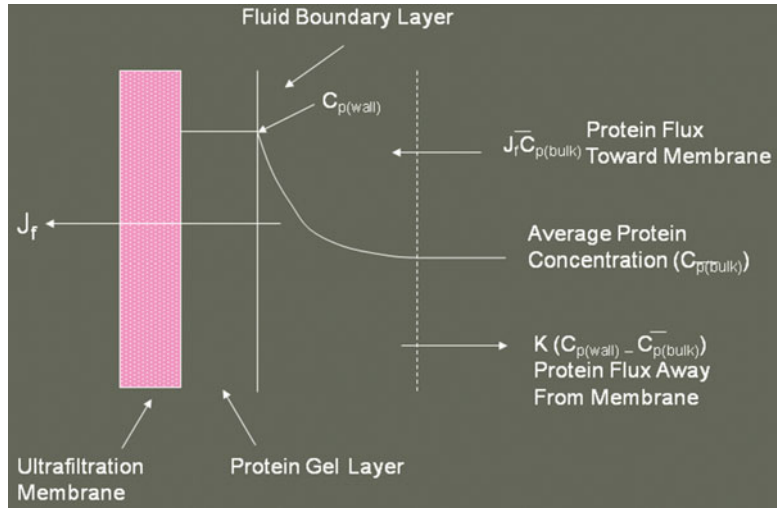

Fig. 2.2 Secondary membrane and concentration polarization phenomena in convective therapies (Source: Reprinted with permission from Ref. [24])

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) concentration 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) [30]. 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). Likewise, concentration polarization may play a significant role in continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF), and the specific operating conditions used in these therapies influence the polarization process.

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 an individual 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, proinflammatory cytokines in AKI 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 [28]. At this point, maintenance of a certain ultrafiltration rate is only achieved by a

concomitant increase in TMP. At sufficiently high TMP, fouling 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.

Convective solute removal can be quantified in the following manner [31]:

$$N = (1-\sigma)J_v\ C_m \qquad (2.9)$$

In this equation, N is the convective flux (mass removal rate per unit membrane area), J_v is the ultrafiltrate flux (ultrafiltration rate normalized to membrane area), C_m is the mean intramembrane solute concentration, and σ is the reflection coefficient, a measure of solute rejection. As Werynski and Waniewski have explained [31], the parameter (1−σ) can be viewed as the membrane resistance to convective solute flow. If σ equals 1, no convective transport occurs while a value of 0 implies no resistance to convective flow. Of note, the appropriate blood compartment concentration used to determine C_m is the submembranous concentration rather than the bulk phase concentration. Therefore, this parameter is significantly influenced by the effects of concentration polarization.

It is useful to assess individually the parameters on the right-hand side of the above equation and the manner in which changes in these parameters may affect the rate of convective solute transport. During a convective therapy, changes in the permeability properties of the hemofilter membrane or in the operating conditions may alter these parameters. However, a complex interplay exists between these parameters and the net effect of changes in hemofilter membrane permeability or treatment operating conditions may be difficult to predict. To illustrate this point, the effect of a progressive decrease in membrane permeability as a membrane becomes fouled with proteins can be assessed. As fouling occurs, the resistance to convective solute flow (σ) increases such that the parameter (1−σ) decreases. In addition, fouling may result in a decrease in ultrafiltrate flux (J_v) despite attempted increases in TMP. However, when the membrane becomes irreversibly fouled (i.e., gel formation occurs), its ultrafiltration capacity markedly declines. Finally, polarization of solute at the membrane surface due to the fouling causes an increase in the submembranous blood compartment concentration but a decrease in the filtrate concentration. The net effect on C_m, which essentially is a mean of the submembranous and filtrate concentrations, is difficult to predict and depends on the specific solute in question.

Solute Removal by Internal Filtration

Another convection-based mechanism by which solute removal occurs during HD is internal filtration. This phenomenon is understood best by drawing the distinction between dialyzers of low and high water permeability, from the perspective of the directionality of transmembrane fluid flow. In clinical HD, an individual patient's weight loss requirement dictates the rate of plasma water ultrafiltration and a specified ultrafiltration profile is achieved by providing prescriptive information (weight loss, treatment time, etc) to the HD machine. However, it is important to recognize that this prescriptive ultrafiltration rate represents a *net* value and may or may not be equivalent to the *absolute* ultrafiltration rate in specific segments of the dialyzer [32].

Under typical HD conditions (i.e., net ultrafiltration rate of 10–15 mL/min), the absolute ultrafiltration rate in the proximal (arterial) end of a high-flux dialyzer is considerably higher than the above net value. In the proximal (arterial) end of the dialyzer, because the blood compartment pressure is higher than the dialysate compartment pressure, ultrafiltrate leaves the blood compartment rapidly. However, the hydraulic characteristics of a high-flux dialyzer result in a significant axial (end-to-end) pressure drop and, at some point along the length of the hollow fibers, the blood compartment pressure becomes less than that in the dialysate compartment. This dialysate-to-blood pressure gradient results in a reversed ultrafiltrate flow (i.e., "backfiltration") from this

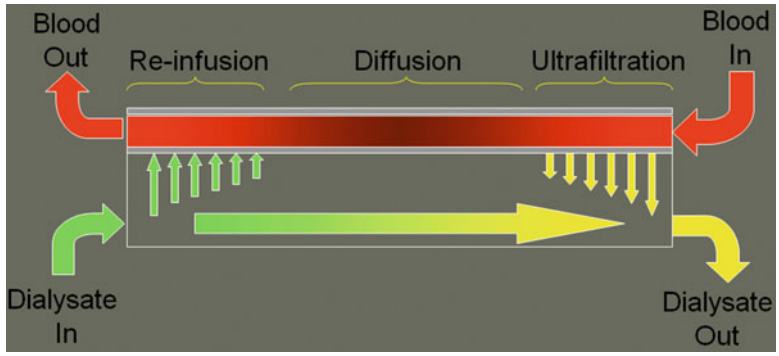

Fig. 2.3 Phenomenon of backfiltration in a high-flux hemodialyzer

point to the distal (venous) end of the dialyzer (Fig. 2.3). Under most HD scenarios in which a low K_{UF} dialyzer (<20 mL/h/mm Hg) is used, the high proximal ultrafiltration rate described above is not observed. Consequently, axial pressure drop is less pronounced and a reversed pressure gradient does not develop. As such, backfiltration is not a significant issue for dialyzers of relatively low water permeability.

Although concerning from the perspective that it may result in the transfer of bioactive dialysate contaminants to the bloodstream [33], this internal filtration mechanism is actually beneficial with respect to the removal of relatively large-sized uremic compounds by the following mechanism [34–36]. In the arterial end of the dialyzer, convective solute removal occurs in association with the ultrafiltered plasma water. Because the rate of flow of oncoming dialysate is much greater than the ultrafiltration rate, the concentrations of solutes convected from the blood in this portion of the dialyzer are greatly reduced. This dilution effect greatly attenuates solute "reentry" in the distal (backfiltration) portion of the dialyzer because convective transport back into the blood compartment depends directly on the dialysate concentration at this point. In this manner, the "silent clearance" provided by internal filtration contributes significantly to the total removal of compounds poorly removed by diffusion during high-flux HD.

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 and proteins) are removed [37–39]. 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 [40]. 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, attributable to the relative hydrophobicity of these membranes [41].

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 [42].

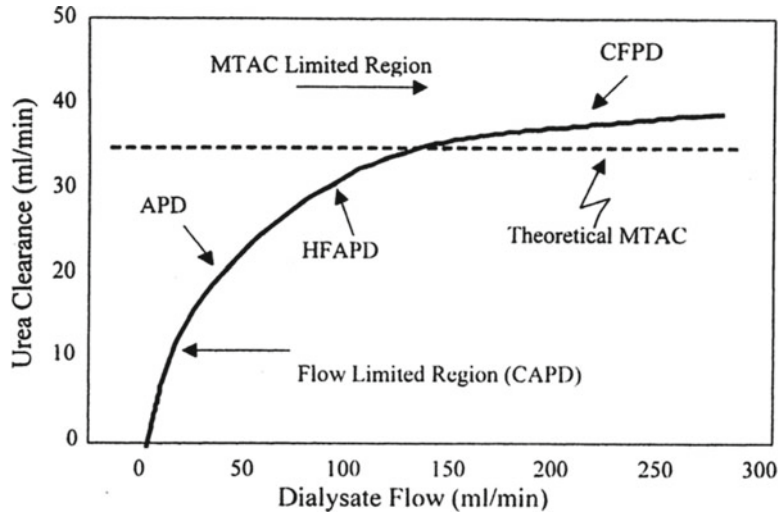

Fig. 2.4 Plot of urea clearance vs. dialysate flow rate in peritoneal dialysis (Source: Reprinted with permission from Ref. [16])

Factors Affecting Solute Transport

The dialysate compartment: In Fig. 2.4, 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 3–5 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 6–10 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.

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. 2.4 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 [43] and theoretical mathematical models based on mass transfer-area coefficient (MTC) calculations [44]. 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 above mentioned 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 [45]. 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. [46]. 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 [47]. Experimental work has in fact suggested that peritoneal ultrafiltration and solute clearances might be blood flow limited at least in some conditions [48].

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 [49], while other studies have suggested much lower values of effective blood flow [50]. 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 [51].

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 [50, 52, 53].

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 [48]. 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 [54]. 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" [55].

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 [56], solute clearance (K) is the ratio of mass removal rate (N) to blood solute concentration (C_B):

$$K = N / C_B \tag{2.10}$$

From this relatively simple expression, it is clear that a defined relationship between clearance 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. [57], 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. 2.5a). 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. 2.5b), instantaneous clearance progressively falls during the course of an exchange concomitant with a decreasing

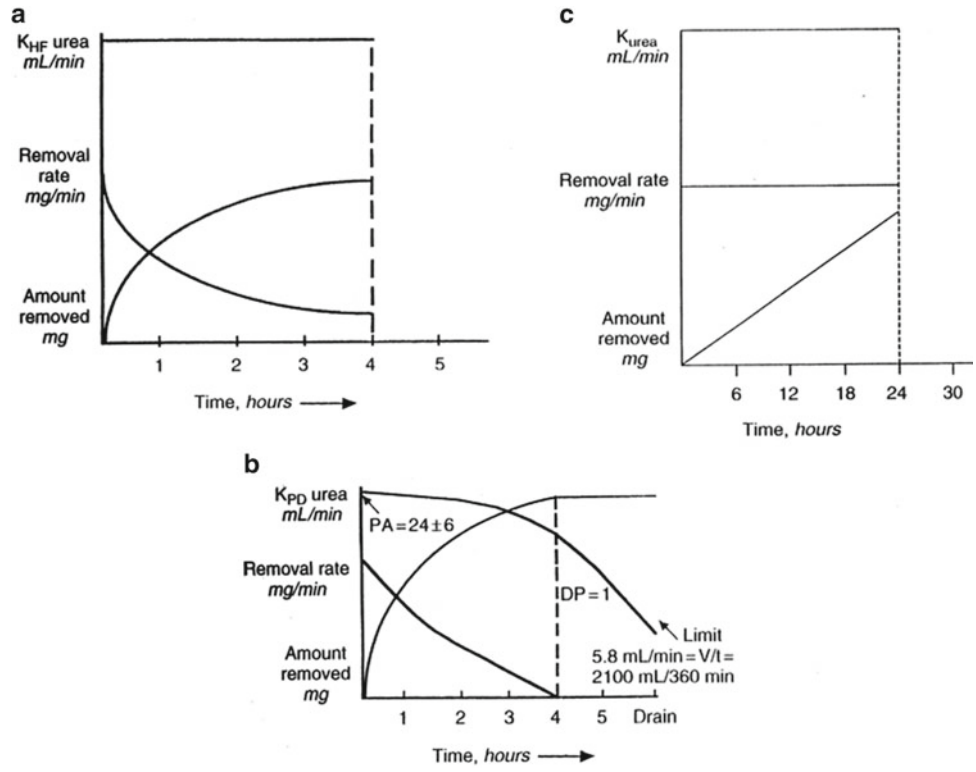

Fig. 2.5 Relationship between clearance and mass removal rate for intermittent hemodialysis (**a**), peritoneal dialysis (**b**), and continuous renal replacement therapy (**c**) (Source: Reprinted with permission from Ref. [58])

transmembrane concentration gradient. Therefore, both mass removal rate and clearance, derived by measuring solute mass in the effluent dialysate collected over 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. 2.5c, this relationship for CRRT operated at steady state with respect to BUN (in a patient with a constant protein catabolic rate) is shown [58]. 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 [59]:

$$K_B = \left[\left(Q_{Bi} * C_{Bi}\right) - \left(Q_{Bo} * C_{Bo}\right)\right] / C_{Bi} + Q_F * \left(C_{Bo} / C_{Bi}\right) \tag{2.11}$$

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 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 [60]:

$$K_T = K_D + Q_F * T_r \qquad (2.12)$$

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:

$$T_r = S\left(1 - K_D / Q_B\right) \qquad (2.13)$$

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 [61–63]. 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, results 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 intra-dialyzer solute distribution volume [64]:

$$Q_{BW} = 0.93 * Q_B[1 - Hct + K(1 - e^{-\alpha t})Hct] \qquad (2.14)$$

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. [65].

(The factor 0.93 in Equation 2.14 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 Equation 2.11.

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 Equation 2.14 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. 2.10, 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:

$$K_D = Q_{Do} * C_{Do} / C_{Bi} \qquad (2.15)$$

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 [64]. 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 [66]. 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 "intra-corporeal" 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 [67]. 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 [68]. 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 [66].

Quantification of Solute Removal by Disparate Therapies

Peak Concentration Hypothesis

Keshaviah and Nolph reasoned that issues related to small solute removal and azotemia control could explain the similar clinical outcomes reported for patients treated with chronic HD and CAPD. Consequently, they offered the peak concentration hypothesis [69], which suggests the success of CAPD is related to its steady, continuous nature as opposed to the "peak and trough" phenomenon associated with intermittent HD. Specifically, borrowing from clinical knowledge gained in therapeutic drug monitoring, they proposed that uremic toxicity is more related to peak solute concentrations than to time-averaged solute concentrations. Thus, the appropriate comparison is the peak BUN in intermittent HD and the steady-state BUN in CAPD. Based on this comparison, a urea Kt/V of 1.0 delivered per treatment in thrice-weekly HD (3.0 per week) is equivalent to a weekly urea Kt/V of 1.7–1.8 in CAPD. At the time this hypothesis was formulated, these values were generally considered to represent adequate therapy for both HD [70] and CAPD [71]. Of note, a fundamental assumption in the peak concentration hypothesis is that delivery of an equivalent urea Kt/V in CAPD and HD results necessarily in equivalent steady-state and time-averaged BUN values, respectively. However, subsequent kinetic analyses [66, 72] have challenged this assumption (see below).

Solute Removal Index (SRI)

Recognizing the difficulties inherent to clearance-based measurements of dialysis dose, Keshaviah and Star proposed the SRI as an alternative [73]. Specifically, this parameter was introduced to avoid the need to use scaling factors when comparing intermittent and continuous therapies. Qualitatively, SRI is the ratio of net solute removal to pre-dialysis body content of solute and is expressed quantitatively as:

$$SRI = [(BUN_i \cdot V_i - BUN_f \cdot V_f - G \cdot t) / BUN_i \cdot V_i] \cdot 100\% \quad (2.16)$$

In this equation, the subscripts "i" and "f" denote pre-dialysis and post-dialysis, respectively. Proponents of the SRI point to several attributes that make it a simpler and more accurate measurement of dialysis dose than other quantification techniques. First, absolute urea removal is dependent on accurate measurement of V, which is not provided by many of the two-BUN methodologies, such as URR and the Daugirdas equation [68]. Second, absolute urea removal is influenced by the pre-dialysis BUN while the SRI is not. Finally, double-pool effects, access recirculation, and cardiopulmonary recirculation do not affect SRI determinations but may adversely impact the accuracy of other methods [74, 75].

Equivalent Renal Clearance (EKR)

In developing the equivalent renal clearance (EKR) concept, Casino and Lopez recognized the difficulty of incorporating solute clearance provided continuously by residual renal function (RRF) into that provided by intermittent HD [76].

These investigators defined EKR as the ratio of net solute generation to time-averaged solute concentration (for an intermittent therapy) or steady-state solute concentration (for a continuous therapy):

$$\mathrm{EKR}\ (\mathrm{mL/min}) = \mathrm{G}(\mathrm{mg/min}) / \mathrm{C}(\mathrm{mg/mL}) \tag{2.17}$$

In essence, this parameter is a time-averaged, continuous-equivalent product of clearance and time (i.e., K*t) that accounts for the differing relationship between clearance and actual solute removal among different therapies. For the purpose of standardization, Casino and Lopez suggested that EKR be normalized to urea volume and then multiplied by a "standard" urea volume of 40 L to obtain a corrected EKR (EKR_c):

$$EKR_c = (EKR / V) * 40 \tag{2.18}$$

Based on this approach, EKR_c curves as a function of number of HD treatments per week, single-pool Kt/V per treatment, and residual urea clearance were generated. For an anephric patient dialyzed thrice weekly, EKR_c values of 11 mL/min (corresponding to a single-pool Kt/V of 1.0 per treatment) and 9 mL/min (corresponding to a single-pool Kt/V of approximately 0.72) were considered adequate and inadequate therapy, respectively.

Standard Urea Clearance

Gotch also proposed a model designed to measure and compare dialysis doses provided by any combination of intermittent and continuous dialysis therapy. The model employs urea as a generic LMW uremic toxin and a normal renal clearance reference standard. Based on an average urine flow rate of 1.5 mL/min and a glomerular filtration rate of 100 mL/min, a "normal" urea clearance is 45 mL/min [7, 77]. Gotch suggested that this value be used as a renal function standard ("reference") to which dialysis dose in various forms of RRT could be referenced. The above reference urea clearance, normalized to a body water (urea distribution volume) of 35 L, equates to a Kt/V of 12.96 on a weekly basis.

In the standard Kt/V model, urea clearance provided by an intermittent RRT is converted to a continuous-equivalent clearance, which can then be added to any clearance provided continuously (i.e., from RRF or a continuous PD modality). Specifically, the model determines a continuous-equivalent clearance for an intermittent therapy that results in a steady-state BUN equivalent to the pre-dialysis BUN for that intermittent regimen (assuming a symmetric intermittent schedule). As such, the foundation of the model is very similar to that of the peak concentration hypothesis. In the model development, pre-dialysis BUN for an intermittent therapy is expressed as a function of several parameters, including single-pool and equilibrated Kt/V values per treatment, urea volume, treatment duration (t), and any continuous urea clearance present. Equilibrated Kt/V is derived from the rate of dialysis, K/V, which in turn is derived by dividing the single-pool Kt/V by t [74]. Standard (i.e., continuous-equivalent) Kt/V is then determined from pre-HD BUN (as derived above), normalized PCR, and urea volume. As discussed in greater detail by Gotch [78, 79], this analysis permits quantitative comparison of HD regimens of varying duration and frequency to CAPD, with inclusion of the contribution made by RRF.

References

1. Deen W, Bridges C, Brenner B, Myers B. Heteroporous model of glomerular size selectivity: application to normal and nephrotic humans. Am J Physiol. 1985; 249:F374–89.
2. Clark WR, Ronco C. Renal replacement therapy in acute renal failure: solute removal mechanisms and dose quantification. Kidney Int. 1998;53(Suppl 66): S133–7.
3. Vanholder R, Argiles A, Baurmeister U, Brunet P, Clark WR, Cohen G, De Deyn P, Deppisch R,

Descamps-Latscha B, Henle T, Jorres A, Massy Z, Rodriguez M, Stegmayr B, Wratten ML. Uremic toxicity: present state of the art. Int J Artif Organs. 2001;24:695–725.
4. Anderstam B, Mamoun A, Sodersten P, Bergstrom J. Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit ingestive behavior in the rat. J Am Soc Nephrol. 1996;7: 2453–60.
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. Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitumo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, Cohen A, Schmid K. A new form of amyloid protein associated with chronic hemodialysis was identified as $beta_2$-microglobulin. Biochem Biophys Res Commun. 1985;129:701–6.
7. Chassis H, Smith HW. The excretion of urea in normal man and in subjects with glomerulonephritis. J Clin Invest. 1938;17:347–55.
8. Clark WR, Mueller BA, Kraus MA, Macias WL. Quantification of creatinine kinetic parameters in patients with acute renal failure. Kidney Int. 1998;54: 554–60.
9. Mitch WE, Walser M. A proposed mechanism of reduced creatinine excretion in severe chronic renal failure. Nephron. 1978;21:248–54.
10. Pascual M, Steiger G, Estreicher J, Macon K, Volanakis J, Schifferli J. Metabolism of complement factor D in renal failure. Kidney Int. 1988;34: 529–36.
11. Friedlander M, Wu Y, Elgawish A, Monnier V. Early and advanced glycosylation end products. J Clin Invest. 1996;97:728–35.
12. Miyata T, Ueda Y, Yoshida A, Sugiyama S, Ida Y, Jadoul M, Maeda K, Kurokawa K, van Ypersele C. Clearance of pentosidine, an advanced glycation end product, by different modalities of renal replacement therapy. Kidney Int. 1997;51:880–7.
13. Miyata T, Ueda Y, Horie K, Nangaku M, Tanaka S, van Ypersele C, Kurokawa K. Renal catabolism of advanced glycation end products: the fate of pentosidine. Kidney Int. 1998;53:416–22.
14. Jadoul M, Ueda Y, Yasuda Y, Saito A, Robert A, Ishida N, Kurokawa K, van Ypersele C, Miyata T. Influence of hemodialysis membrane type on pentosidine plasma level, a marker of "carbonyl stress". Kidney Int. 1999;55:2487–92.
15. Clark WR. Quantitative characterization of hemodialyzer solute and water transport. Semin Dial. 2001;14:32–6.
16. Ronco C, Clark WR. Factors affecting hemodialysis and peritoneal dialysis efficiency. Semin Dial. 2001;14:257–62.
17. Clark WR, Ronco C. Determinants of hemodialyzer performance and the effect on clinical outcome. Nephrol Dial Transplant. 2001;16(Suppl 3): 56–60.
18. Clark WR, Shinaberger JH. Effect of dialysate-side mass transfer resistance on small solute removal in hemodialysis. Blood Purif. 2000;18:260–3.
19. Clark WR, Hamburger RJ, Lysaght MJ. Effect of membrane composition and structure on performance and biocompatibility in hemodialysis. Kidney Int. 1999;56:2005–15.
20. 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.
21. 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: John Wiley and Sons; 1960. p. 34–70.
22. Clark WR, Kraus MA, Mueller BA. Problems of solute removal in continuous renal replacement therapy. In: Mehta RL, Lemaire N, editors. Complications of dialysis – recognition and management. 1st ed. New York: Marcel Dekker; 2000.
23. Lysaght MJ. Hemodialysis membranes in transition. Contrib Nephrol. 1988;61:1–17.
24. 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.
25. Whitaker S. Fluid statics and one-dimensional laminar flow. In: Whitaker S, editor. Introduction to fluid mechanics. 1st ed. Englewood Cliffs: Prentice-Hall; 1968. p. 61.
26. Handley HH, Gorsuch R, Levin NW, Ronco C. Intravenous catheter for intracorporeal plasma filtration. Blood Purif. 2002;20:61–9.
27. Rockel A, Hertel J, Fiegel P, Abdelhamid S, Panitz N, Walb D. Permeability and secondary membrane formation of a high flux polysulfone hemofilter. Kidney Int. 1986;30:429–32.
28. Kim S. Characteristics of protein removal in hemodiafiltration. Contrib Nephrol. 1994;108:23–37.
29. Ofsthun NJ, Zydney AL. Importance of convection in artificial kidney treatment. Contrib Nephrol. 1994;108: 53–70.
30. Henderson LW. Pre vs. post dilution hemofiltration. Clin Nephrol. 1979;11:120–4.
31. Werynski A, Waniewski J. Theoretical description of mass transport in medical membrane devices. Artif Organs. 1995;19:420–7.
32. Poh CK, Hardy PA, Liao Z, Huang Z, Moey K, Clark WR, Gao D. Use of magnetic resonance imaging to measure the local ultrafiltration rate in hemodialyzers. J Membrane Sci. 2002;204:195–205.
33. Lonnemann G, Koch KM. β2-microglobulin amyloidosis: effects of ultrapure dialysate and type of dialyzer membrane. J Am Soc Nephrol. 2002;13:S72–7.
34. Dellanna F, Wuepper A, Baldamus CA. Internal filtration – advantage in haemodialysis? Nephrol Dial Transplant. 1996;11(Suppl 2):83–6.
35. 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.

36. 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.
37. 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.
38. Jindal KK, McDougall J, Woods B, Nowakowski L, Goldstein MB. A study of the basic principles determining the performance of several high-flux dialyzers. Am J Kidney Dis. 1989;14:507–11.
39. 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.
40. Clark WR, Macias WL, Molitoris BA, Wang NHL. $ß_2$-microglobulin membrane adsorption: equilibrium and kinetic characterization. Kidney Int. 1994;46: 1140–6.
41. Clark WR, Macias WL, Molitoris BA, Wang NHL. Plasma protein adsorption to highly permeable hemodialysis membranes. Kidney Int. 1995;48:481–7.
42. Ronco C, Brendolan A, La Greca G. The peritoneal dialysis system. Nephrol Dial Transplant. 1998; 13(Suppl 6):94–9.
43. Amerling R, Ronco C, Levin NW. Continuous flow peritoneal dialysis. Perit Dial Int. 2000;20(Suppl 2): S178–82.
44. Ronco C. Limitations of peritoneal dialysis. Kidney Int. 1996;50(Suppl 56):S69–74.
45. Rippe B, Simonsen O, Stelin G. Clinical implications of a three pore model of peritoneal transport. Perit Dial Int. 1991;7:3–9.
46. Dedrick RL, Flessner MF, Collins JM, Schulz JS. Is the peritoneum a membrane? ASAIO J. 1982;5:1–8.
47. 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.
48. 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.
49. Aune S. Transperitoneal exchanges II: peritoneal blood flow estimated by hydrogen gas clearance. Scand J Gastroenterol. 1970;5:99–102.
50. 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.
51. Ronco C, Feriani M, Chiaramonte S, La Greca G. Pathophysiology of ultrafiltration in peritoneal dialysis. Perit Dial Int. 1990;10:119–26.
52. Waniewski J, Werynski A, Lindholm B. Effect of blood perfusion on diffusive transport in peritoneal dialysis. Kidney Int. 1999;56:707–13.
53. 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.
54. Kim M, Lofthouse J, Flessner MF. Blood flow limitations of solute transport across the visceral peritoneum. J Am Soc Nephrol. 1997;8:1946–50.
55. Ronco C. The nearest capillary hypothesis: a novel approach to peritoneal transport physiology. Perit Dial Int. 1996;16:121–5.
56. Henderson L. Why do we use clearance? Blood Purif. 1995;13:283–8.
57. Henderson L, Leypoldt JK, Lysaght M, Cheung A. Death on dialysis and the time/flux trade-off. Blood Purif. 1997;15:1–14.
58. Clark WR, Henderson LW. Renal vs. continuous vs. intermittent therapies for removal of uremic toxins. Kidney Int. 2001;59(Suppl 78):S298–303.
59. Clark WR, Shinaberger JH. Clinical evaluation of a new high-efficiency hemodialyzer: polysynthane (PSN™). ASAIO J. 2000;46:288–92.
60. Jaffrin MY. Convective mass transfer in hemodialysis. Artif Organs. 1995;19:1162–71.
61. Katz M, Hull A. Transcellular creatinine disequilibrium and its significance in hemodialysis. Nephron. 1974;12:171–7.
62. 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.
63. Schmidt B, Ward R. The impact of erythropoietin on hemodialyzer design and performance. Artif Organs. 1989;13:35–42.
64. Lim V, Flanigan M, Fangman J. Effect of hematocrit on solute removal during high efficiency hemodialysis. Kidney Int. 1990;37:1557–62.
65. Shinaberger J, Miller J, Gardner P. Erythropoietin alert: risks of high hematocrit hemodialysis. ASAIO Trans. 1988;34:179–84.
66. 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.
67. Clark WR, Rocco MV, Collins AJ. Quantification of hemodialysis: analysis of methods and relevance to clinical outcome. Blood Purif. 1997;15:92–111.
68. Daugirdas JT. Second-generation estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–13.
69. Keshaviah PR, Nolph KD. The peak concentration hypothesis: a urea kinetic approach to comparing the adequacy of continuous ambulatory peritoneal dialysis and hemodialysis. Perit Dial Int. 1989;9: 257–60.
70. Gotch F, Sargent J. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526–34.
71. Twardowski Z, Kolph KD. Peritoneal dialysis: how much is enough? Semin Dial. 1988;1:75–6.

72. Clark WR, Mueller BA, Kraus MA, Macias WL. Extracorporeal therapy requirements for patients with acute renal failure. J Am Soc Nephrol. 1997;8: 804–12.
73. Keshaviah PR, Star RA. A new approach to dialysis quantification: an adequacy index based on solute removal. Semin Dial. 1994;7:85–90.
74. Daugirdas JT, Schneditz D. Overestimation of hemodialysis dose (ΔKt/V) depends on dialysis efficiency (K/V) by regional blood flow but not by conventional two pool urea kinetic analysis. ASAIO J. 1995;41: M719–24.
75. Gotch F. Kinetic modeling in hemodialysis. In: Nissenson A, Fine R, Gentile D, editors. Clinical dialysis. 3rd ed. Norwalk: Appleton and Lange; 1995. p.166–8.
76. Casino FG, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis dose. Nephrol Dial Transplant. 1996;11:1574–91.
77. Dole VP. Back-diffusion of urea in the mammalian kidney. Am J Physiol. 1943;139:504–10.
78. Gotch FA, Sargent JA, Keen ML. Whither goest Kt/V? Kidney Int. 2000;58(Suppl 76):S3–18.
79. Gotch FA. Kt/V is the best dialysis dose parameter. Blood Purif. 2000;18:276–85.

The Demographics of Dialysis in Children

3

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Keywords
Dialysis • Demographic • Children • Dialysis incidence • Prevalence

Introduction

The use of chronic dialysis to sustain the lives of children with end-stage renal disease (ESRD) has been available in developed countries for more than 30 years [1, 2]. During the past few decades, advances in technology have made long-term dialysis a viable treatment option for pediatric ESRD patients of all ages, from newborns to adolescents [3]. While a successful kidney transplant remains the treatment of choice for all pediatric ESRD 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].

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The pediatric dialysis population is remarkably heterogeneous in many ways, as will be described in this chapter. Pediatric dialysis centers must be prepared to provide renal replacement therapy to patients whose size alone may differ by more than 2000%. 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 ESRD patient registries and a few recently published reviews [5, 7–24]. Our objective is not to attempt a precise accounting of these data, nor is it to systematically compare findings from one pediatric ESRD registry to another. While the methodology required for such rigorous cross-registry analyses exists, it would require access to data elements beyond the summaries

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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 first decade 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 demographics when compared to adult patients were first understood as a result of the pioneering efforts of the EDTA, which published an annual report containing pediatric summary data from a group of European countries for more than 15 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 ESRD 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 ERA-EDTA 2007 Report, available on the Internet at http://www.era-edta-reg.org/index.jsp, contains summary data from 28 European countries on patients of all ages in which information on children is largely reported in aggregate for the age group 0–19 years. More complete and age-specific pediatric data from a subset of 11 EDTA countries are also provided [25].

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 renal treatment centers in the United States, Canada, Mexico, and Costa Rica. Founded in 1987 to study renal transplantation, the NAPRTCS expanded in 1992 to include children receiving dialysis in participating NAPRTCS transplant centers. Details of the organizational structure and study methods used by the NAPRTCS have been published elsewhere [26]. It is important to point out that the 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 2008 Annual Data Report [5].

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 health-care 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 renal 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 2009 USRDS Annual Data Report is available on the Internet at http://www.usrds.org/adr.htm. [10].

The Japanese National Registry (JNR): In 2002, Hattori and associates reported the results of a nationwide survey of over 3,300 Japanese physicians who were members of national professional societies devoted to ESRD patient care or who were from pediatric departments in medical schools or colleges where children received renal replacement therapy [27]. The survey requested data on all children with ESRD who had not reached their 20th birthday by January 1, 1998, and represented the initial report from what was intended to become a national ESRD registry in Japan. A follow-up report has not yet been published.

Italian Registry of Pediatric Chronic Peritoneal Dialysis: This registry, which published its data in early 2004, has collected information from all hemodialysis (HD) and peritoneal dialysis (PD) patients less than 15 years of age who initiated renal replacement therapy between 1989 and 2000 [16]. The patients originated from all 23 active pediatric dialysis units in Italy and from

eight adult centers treating pediatric patients. The patients are followed until age 19 years.

Individual National Registries Accessible via Internet: Data compiled by national ESRD patient registries in several individual countries (including the NAPRTCS and USRDS) are available online. A convenient link to each of these individual reports has been provided by the ERA-EDTA at www.era-edta-reg.org/links.jsp. Of the 22 different countries covered by individual websites, only 12 countries provide reports in English (Australia/New Zealand, Brazil, Canada, Denmark, Finland, Italy, Norway, Scotland, Turkey, the United Kingdom, and the United States). Of these, Australia/New Zealand, Turkey, the United Kingdom, the USRDS, and the NAPRTCS contain specific pediatric data reports and analyses.

International Pediatric Peritoneal Dialysis Network (IPPN): The IPPN is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic PD. As of May 2010, 114 institutions from 42 countries participated in the network, and greater than 1,250 patients have been enrolled in the registry. Participating centers have access to a wide array of general, PD, clinical, laboratory, and medication statistics, and are able to compare their center's statistics to the international consortium. Additional information about the IPPN can be found at www.pedpd.org/index.php.

Incidence

ESRD is not a common pediatric disorder. The incidence of treated ESRD in children is only a small fraction of that seen in adults, as shown in Fig. 3.1 from the USRDS 2009 Annual Data Report. Note that the pediatric (age 0–19 years) ESRD incidence rates per million population, adjusted for age (i.e., adjusted to show incidence per million population of the same age) are much lower than all adult incidence rates and have remained essentially unchanged for more than two decades. Specifically, the incidence of ESRD in patients 0–19 years of age (adjusted for gender and race) was determined to be 15.1 per million

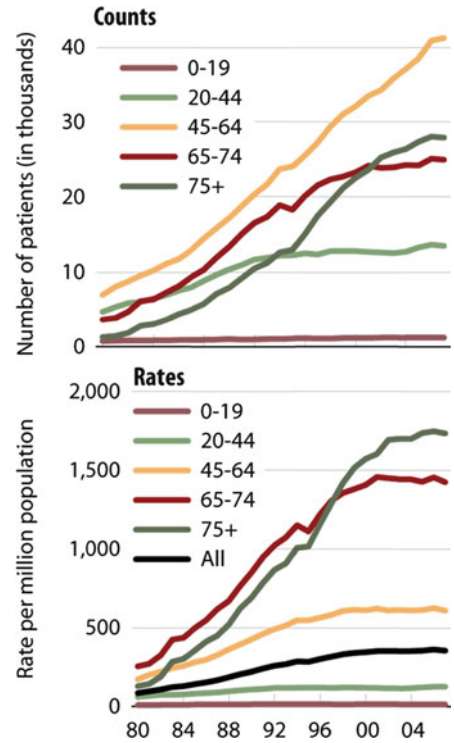

Fig. 3.1 Incident counts and adjusted rates, by age and year of analysis (Source: USRDS 2009 Annual Data Report) [10]

population per year in 2007, with a range of 14.6–15.2 per million population since 1990 (Fig. 3.1).

Differences in age conventions, referral practice, and the economic conditions within each country make direct comparisons of incidence data in different countries difficult. Nevertheless, the most recently reported incidence data for children aged 0–19 years ranged from less than two per million population in French-speaking Belgium to almost 24 per million in Iceland. In the majority of countries with reported data, the incidence of ESRD ranged from 7 to 15 per million population (Fig. 3.2). A recent study from Vietnam reported on the hospitalizations from 2001 through 2005 for children less than 19 years of age with chronic renal failure in Ho Chi Minh City, where all pediatric nephrologic care occurs for Southern Vietnam. Among the 310 patients examined, 85% already had ESRD, and 53 were from Ho Chi Minh City. Given that the mean population of Ho Chi Minh City younger than 19 years

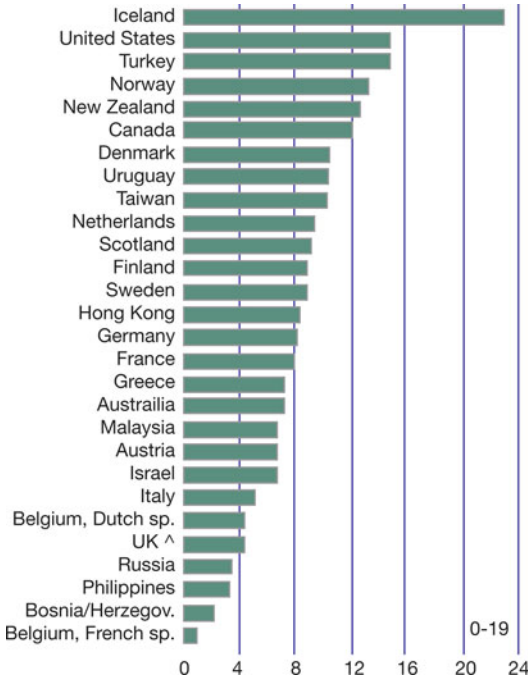

Fig. 3.2 Incidence of ESRD in 2005 per million population in children 0–19 years of age (Source: Reprinted with permission from the USRDS 2007 Annual Data Report, p. 348) [28]

is 2,200,845, a rough estimate of the incidence of ESRD in this population is 4.1 per million [20].

The USRDS registry has also provided incidence data, including preemptive transplantation, by age group within the pediatric population, as well as by race, gender, and primary diagnosis. The adjusted (for gender and race) pediatric ESRD rates for age are greatest in patients 15–19 years of age (27.3 per million population), with rates of 14.6 per million, 5.9 per million, and 10.4 per million population in the 10–14 year, 5–9 year, and 0–4 year age groups, respectively. There has been little change in this data over the past 20 years. The data generated from 2007 represent a total of only 1,304 patients <20 years of age. This is a slight increase from the total number of incident patients in 1990 (1,087 patients) and 1980 (756 patients) when the incidence rates were 14.4 per million population and 9.3 per million population, respectively (Fig. 3.1). Of the 1,304 pediatric patients with incident ESRD in 2007, 1,096 were on dialysis and 208 received preemptive transplantation [10].

The ESRD incidence rates are lowest in the White population of children, as is the case in adults. Based on data generated between 2005 and 2007, adjusted for gender, the incidence was 13 per million population in White patients <20 years of age compared to rates of 25, 22, and 21 per million for Native Americans, African Americans, and Asians, respectively. At the same time, the rates in males and females were 16 and 13 per million population, respectively [10]. It is noteworthy that the incidence of ESRD secondary to hypertension over the 4 year period from 1999 to 2002 in the United States was 2.3 per million population in African American children and only 0.3 per million population in White children. Similarly, the incidence of ESRD over the same time period secondary to glomerulonephritis was 8.1 per million population in African American children versus 5.4, 4.2, and 3.0 per million population for Native Americans, Asians, and Whites, respectively [29]. Finally, the 2009 USRDS Annual Data Reports highlights that since 2000, the rate of new pediatric ESRD cases caused by glomerulonephritis, adjusted for age, gender, and race, has fallen 12% (3.3 million per population) and the rate secondary to cystic/hereditary and congenital disease has risen by almost 16% (5.0 per million population) [10].

Prevalence

The prevalence of treated ESRD in children has shown a steady increase in recent years, although the rates of increase have been lower than what has been experienced in adults. In the United States between 1990 and 2007, prevalent pediatric ESRD patients increased only 36% compared to a 154% increase seen in patients 65–74 years of age [10]. In 2007, the adjusted prevalence rate, including children on dialysis or with a functioning transplant, was 84.5 per million population, compared to rates of 75.9 per million population in 1990 and 29.6 per million population in 1980. The 2007 data is representative of a total of 7,596 patients aged 0–19 years. Of these, 2,200 were on dialysis and 5,396 had a functioning transplant. As expected, the prevalence rate from data generated from 2005 to 2007 was greater in African Americans

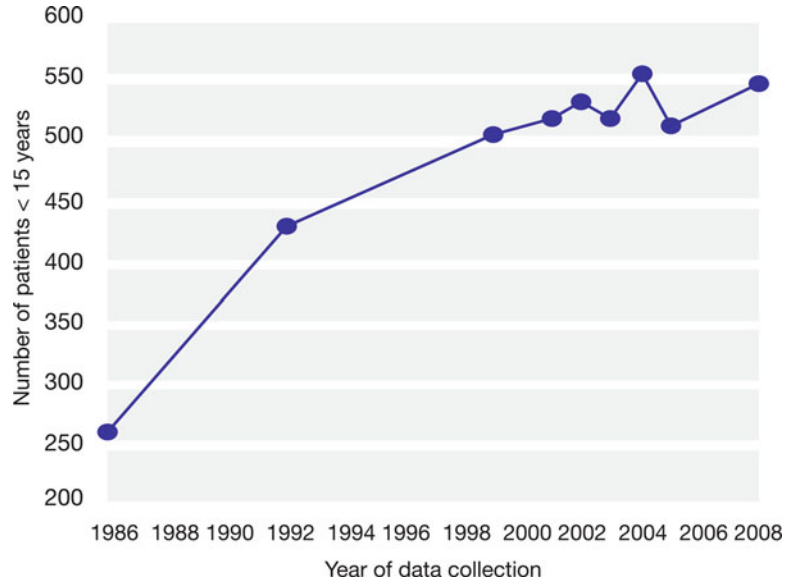

Fig. 3.3 Prevalent patients less than 15 years of age on renal replacement therapy (HD, PD, and transplant) in the United Kingdom (Source: Reprinted with permission from the Eleventh Annual Report (2008) of the UK Renal Registry, p. 258) [9]

(110 per million population) than Whites (80 per million population). The rates by age were 25, 48, 86, and 175 per million population for the 0–4, 5–9, 10–14, and 15–19 age groups, respectively.

Recently reported pediatric ESRD prevalence rates from other countries have been widely variable, although differences in the reported age range make direct comparisons between countries difficult. For example, a prevalence of 55.0 per million population, adjusted, was seen in the United Kingdom in children aged 0–15 years, whereas a prevalence of 110 per million was seen in Finland in children aged 0–19 years [8, 9]. Similar to trends observed in the United States, the most recent prevalence rate from the United Kingdom of 55 per million is substantially greater than the rate of 39 per million reported in 1992 (Fig. 3.3). In the United Kingdom, compared to White children, a higher prevalence rate among non-White children was observed in 2008 (Fig. 3.4). A study of Dutch children less than 16 years of age revealed a prevalence of 38.7 per million population in 2001 [23]. The 2006 ERA-EDTA Registry presented prevalence data collected from throughout Europe. The annual report, compiling pediatric data from Austria, Denmark, Finland, Greece, Iceland, Norway, Romania, Spain, Sweden, The Netherlands, and

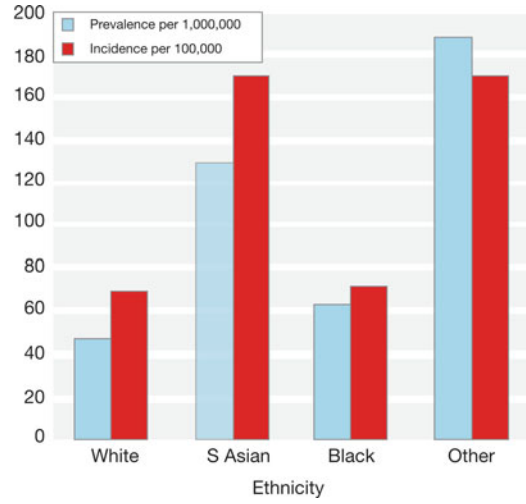

Fig. 3.4 Incidence and prevalence of renal replacement therapy in children less than 16 years of age in the United Kingdom, by ethnicity (Source: Reprinted with permission from the Eleventh Annual Report (2008) of the UK Renal Registry, p. 25) [9]

the United Kingdom/Scotland, showed an overall prevalence of 55 per million age-related population (0–19 year age group) [30]. In Jordan, as of 2005, the prevalence of ESRD was estimated to be 14.5 per million population (ages 0–13 years) [19]. Finland, Italy, and the United States have the largest pediatric ESRD populations (Fig. 3.5).

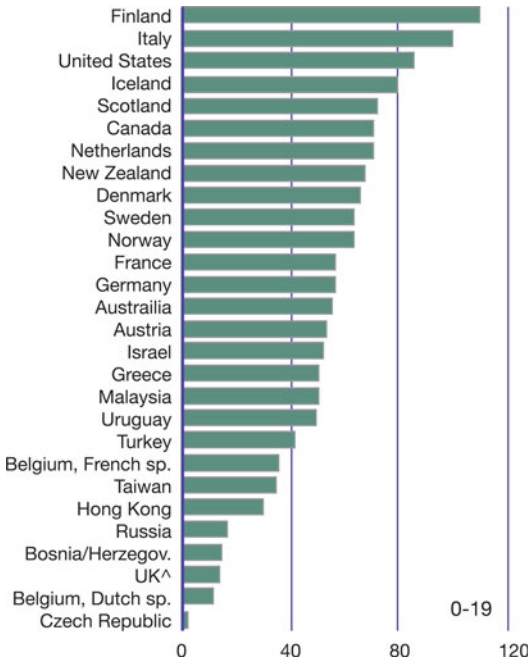

Fig. 3.5 Prevalence of ESRD in 2005 among children aged 0–19 years (Source: Reprinted with permission from the USRDS 2007 Annual Data Report, p. 348) [28]

Primary Renal Disease Diagnosis

Data from Chile, India, Italy, Japan, Kuwait, Nigeria, and the NAPRTCS (United States, Canada, Mexico, Costa Rica) on selected primary renal diagnoses are summarized in Table 3.1 [5, 13–17, 27]. Data from Chile, India, and Nigeria represent children with advanced chronic kidney disease and ESRD. The Kuwaiti, Italian, and NAPRTCS data describe the primary renal disorders of prevalent dialysis patients, whereas the data from Japan are from all ESRD patients. The Indian, Kuwaiti, and Nigerian data were obtained from a single center in each country, although in Kuwait at least, the center provides 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 renal 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.

The distribution of primary renal diagnoses is also different depending on the age at time of ESRD (or ERF) presentation, as shown in Fig. 3.6 from the United Kingdom's Renal Registry [31]. 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. It is interesting to note that ESRD due to reflux nephropathy presents at all ages (Fig. 3.6).

Age of Pediatric Dialysis Population

ESRD and the provision of dialysis occurs across the pediatric age range, but all registries reveal a direct correlation between age and percentage of the total dialysis population. Table 3.2 shows the ages of children who received dialysis treatment for ESRD in Japan (1998), the United Kingdom (2008), and the United States (2007) [9, 10, 27]. Figure 3.7 demonstrates the prevalence of renal replacement therapy (including preemptive kidney transplantation) in children by age group and time period, compiled from 12 European registries [22].

Choice of Dialysis Modality

Following the introduction of continuous PD techniques adapted to the needs of pediatric patients more than 25 years ago, PD quickly gained popularity among pediatric dialysis programs around the world. However, HD is also commonly used. USRDS data on percent distribution of incident patients (<20 years of age) by initial treatment modality in 2007 reveals that 50.6% (656 patients) received HD, 33.4% (433 patients) PD, and 16.0% (208) transplant [10]. Of the PD patients, only 10.9% were receiving continuous ambulatory peritoneal dialysis (CAPD). A compilation of 12 European pediatric ESRD registries shows almost identical statistics for the choice of renal replacement therapy among incident patients between 1995 and 2000: 48% received HD, 34% PD,

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

Diagnosis	Chile	India	Italy	Japan	Kuwait	Nigeria	United States
Aplasia/dysplasia/hypoplasia	20.7	4.9	23.8	28.9	18.7	–	14.0
Glomerulonephritis/FSGS	16.3	27.5	19.7	27.1	6.3	53.3	24.7
Obstructive uropathy/neurogenic bladder	22.0	36.3	13.8	1.7	16.6	28.9	12.9
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	3.0
Nephronophthisis	1.8	–	9.0	4.0	2.1	–	2.1
Reflux nephropathy	16.7	16.7	5.9	5.2	16.6	–	3.5

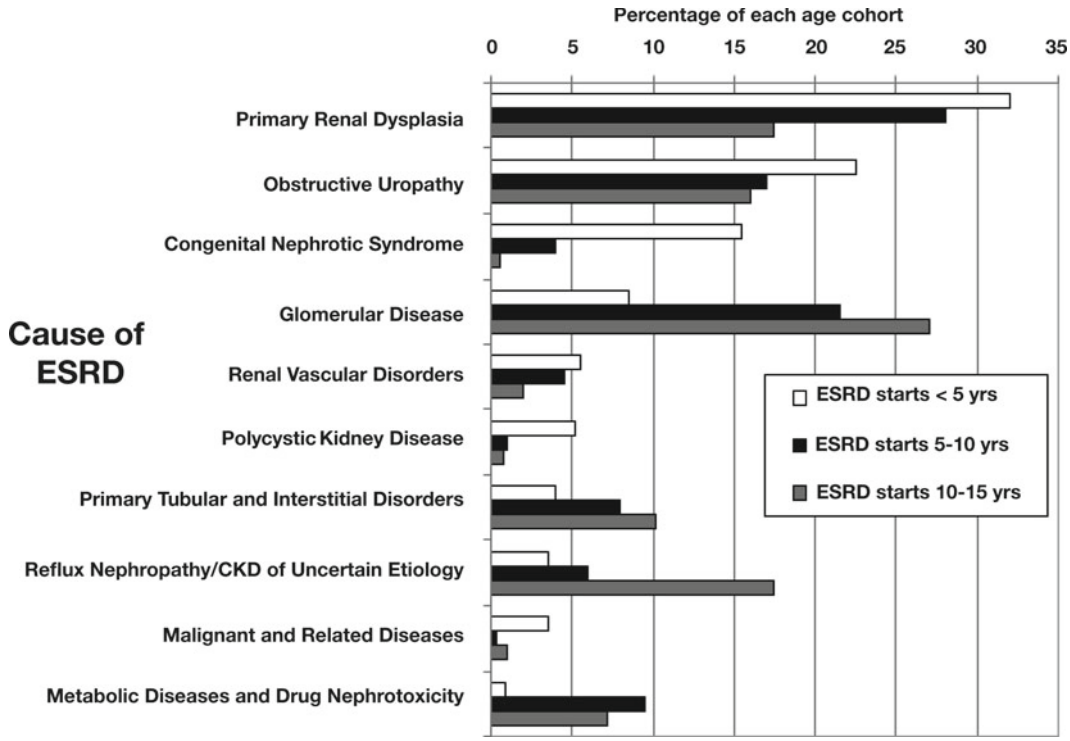

Fig. 3.6 Distribution of pediatric patients in the United Kingdom by diagnostic group and age at presentation of ESRD (Source: Reprinted with permission from the 2002 Report of the United Kingdom Renal Registry, p. 265) [31]

Table 3.2 Percent of prevalent pediatric dialysis patients by age group

Age group (years)	Japan		United Kingdom		United States	
	N	%	N	%	N	%
0–4	24	7	90	11	284	13
5–9	46	13	148	17	192	9
10–14	109	32	298	35	452	20
15–19	166	48	315	37	1,272	58
Total	345	100	851	100	2,200	100

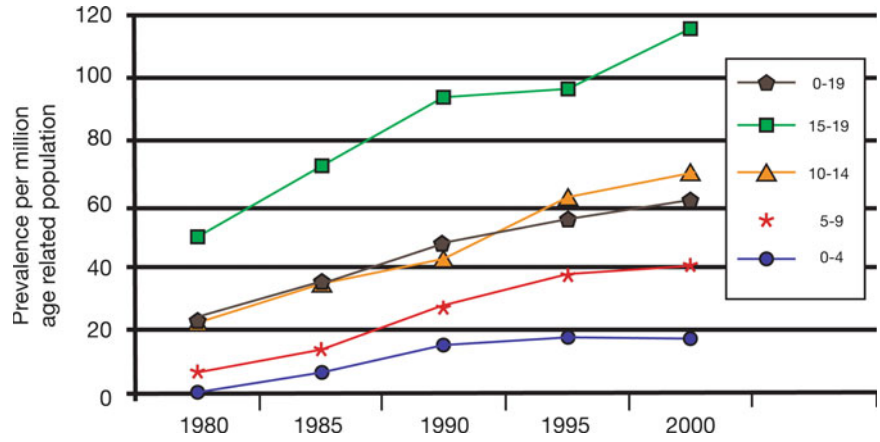

Fig. 3.7 Prevalence of renal replacement therapy (including preemptive kidney transplantation) by age and year in children, compiled from 12 European Registries (Source: Reprinted with permission from van der Heijden/Pediatric Nephrology) [22]

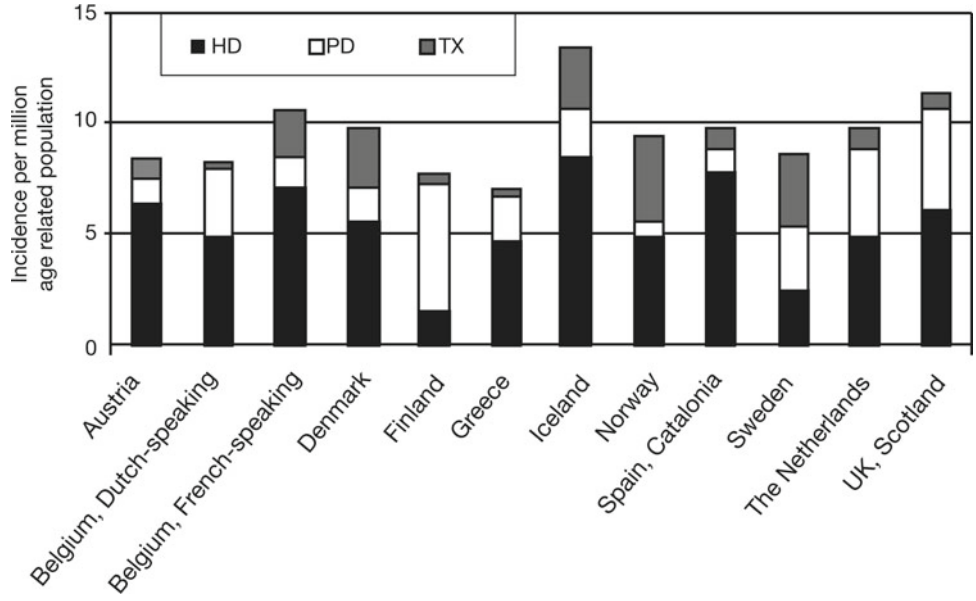

Fig. 3.8 First treatment modality among incident pediatric patients, by country, per million age-related population, for period 1980–2000 (Source: Reprinted with permission from van der Heijden/Pediatric Nephrology) [22]

and 18% received preemptive transplantation. Differences existed by registry, but HD tended to predominate, with the exception of some Scandinavian countries (Fig. 3.8) [22].

Recent data on modality choice in prevalent patients are summarized for three areas of the world in Table 3.3 [9, 10, 27]. United States' data are from the USRDS. Note that the majority of pediatric ESRD patients are being maintained with kidney transplants in the United States and the United Kingdom, but not in Japan. However, it should be noted that data from Japan is from 1998, and data from the United States and United Kingdom are from 2007 and 2008, respectively. The modality choices of pediatric ESRD patients in the United States and United Kingdom have remained stable over the past several years. The proportion of ESRD patients with a functioning

kidney transplant in the United States is also the highest in children when compared to all US age groups. The USRDS data represent 5,396 transplant recipients, 1,263 patients on HD, and 877 patients on PD (and 60 patients with unclear dialysis modality). Of the patients on HD, 1.4% were receiving it at home.

Modality choice for two pediatric age groups is shown in Table 3.4. PD predominates in the youngest dialysis patients across both registries, but the use of HD is more common in the United States versus Japan. Differences in renal replacement therapy by age were also observed in the United Kingdom in 2008 (Fig. 3.9).

Table 3.3 Modality choice as percent of total prevalent pediatric ESRD patients

Modality	United Kingdom	Japan	United States
Hemodialysis	10.9	17.4	16.6
Peritoneal dialysis	14.5	41.6	11.5
APD	12.4		10.4
CAPD	2.1		1.1
Transplant	74.3	40.7	71.0

Table 3.4 Modality choice for two pediatric age groups as percent of prevalent dialysis patients by age group

Modality	Japan	United States
Age 0–4 years		
Peritoneal dialysis	96	75
Hemodialysis	4	25
Age 10–20 years		
Peritoneal dialysis	51	33
Hemodialysis	49	67

Mortality Risk

Patient survival curves for a cohort of 2,867 North American pediatric dialysis patients are shown in Fig. 3.10. Data collection was initiated in 1992 [5]. Patient survival varies significantly by age, with the youngest patients having the lowest survival estimates.

The USRDS report has also revealed that the 5-year survival probability for children initiating dialysis therapy between 1998 and 2002 was lowest in the youngest patients, at 0.73 and 0.76 in HD and PD patients aged 0–9 years, respectively, compared to 0.82 and 0.85 in HD and PD patients aged 10 and older, respectively (Fig. 3.11) [10]. Little change in the probability of survival between 1993–1997 and 1998–2002 is also evident. The adjusted annual death rate for the US pediatric dialysis population based on 2007 data is reported to be 52.9 deaths per 1,000 patient years at risk. USRDS data also reveals that remarkably, the expected remaining lifetime in

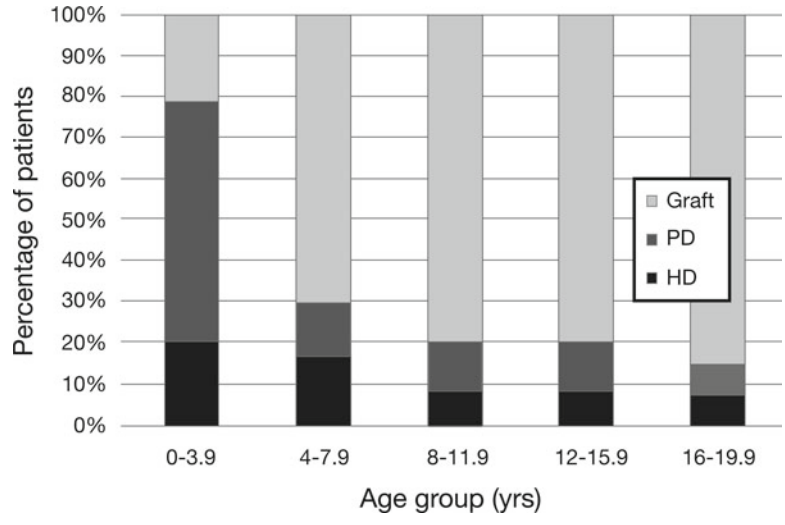

Fig. 3.9 Distribution of renal replacement modalities by age in the United Kingdom (Source: Reprinted with permission from the Eleventh Annual Report (2008) of the UK Renal Registry, p. 25) [9]

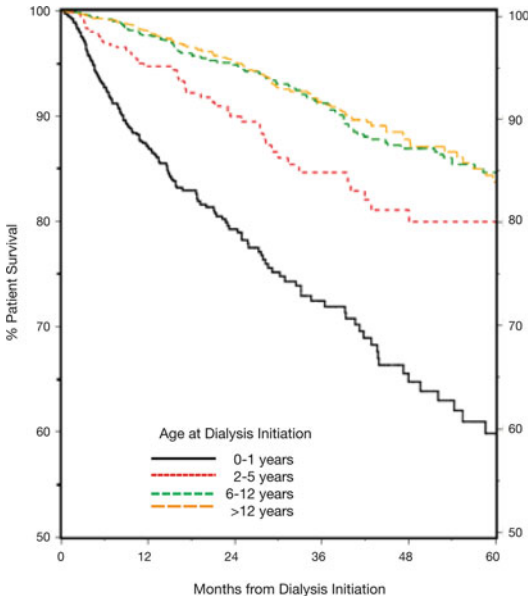

Fig. 3.10 Patient survival by age group. Patients were censored at time of transplantation and at last known follow-up (Source: Reprinted by permission from NAPRTCS 2008 Annual Report, Section 8-17) [5]

years of the prevalent pediatric dialysis population is exceedingly poor, especially when compared to the data of the general US population and prevalent transplant recipients (Fig. 3.12).

The most common causes of death (mortality rate per 1,000 patient years of risk) among prevalent pediatric dialysis patients listed in the USRDS include cardiac arrest (8.3), septicemia (3.3), cerebrovascular disease (1.5), withdrawal from dialysis (1.4), other infection (1.2), and acute myocardial infarction (1.1). Cardiac and infectious causes of death also predominated in European children with ESRD (Fig. 3.13) [22].

Fortunately, most children in the United States terminate a course of dialysis due to transplantation, not death (Table 3.5). Complications associated with a dialysis modality, and patient/family choice, lead to a switch in modality for almost 20% of pediatric dialysis patients.

Survival data for children on dialysis exists from many areas of the world. Figure 3.14 examines the survival of children on HD and PD treated in 23 dialysis centers participating in the Italian Registry of Pediatric Chronic Peritoneal Dialysis during the years 1989–2000 [16]. Figure 3.15 shows the survival of 59 chronic PD patients in Uruguay during the years 1983–2004. In Uruguay, one pediatric dialysis unit covers virtually the entire population, and access to renal replacement therapies is provided free of charge [24]. Chronic PD was first prescribed to children in Turkey in 1989. Twelve centers contributed data to a survey regarding PD care from 1989 to 2002 to the Turkish Pediatric Peritoneal Dialysis (TUPEPD) Study Group (Fig. 3.16) [18]. A 5-year survival range of 69–91% for pediatric patients receiving dialysis is observed in these studies, but differences in study design and data collection must be acknowledged.

Conclusion

We have briefly 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 ESRD patient data reporting and analysis is standardized.

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 ESRD and dialysis population small in the context of the global ESRD patient number, it is hoped that collaborative efforts among national registries will be encouraged and will in turn result in improved patient outcomes.

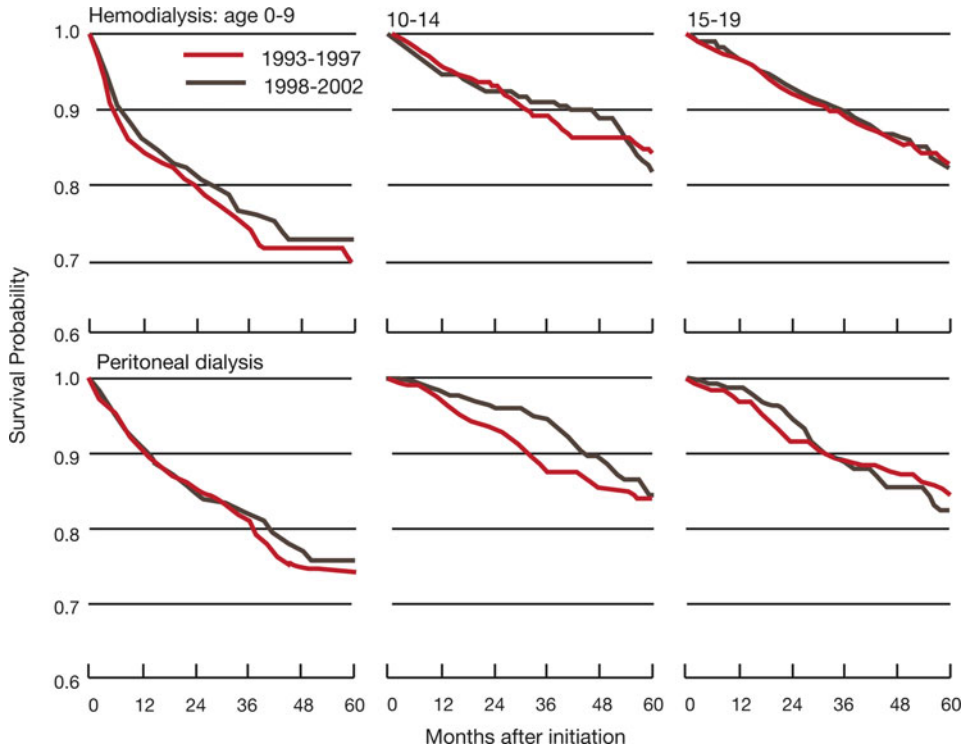

Fig. 3.11 Adjusted 5-year survival, by year, age, and dialysis modality. Dialysis patients who died or received a transplant in the first 90 days were excluded. Dialysis patients were followed from day 91 (after initiation of dialysis) until death, transplant, or the end of 2007. (Source: Reprinted with permission from the 2009 USRDS Annual Report) [10]

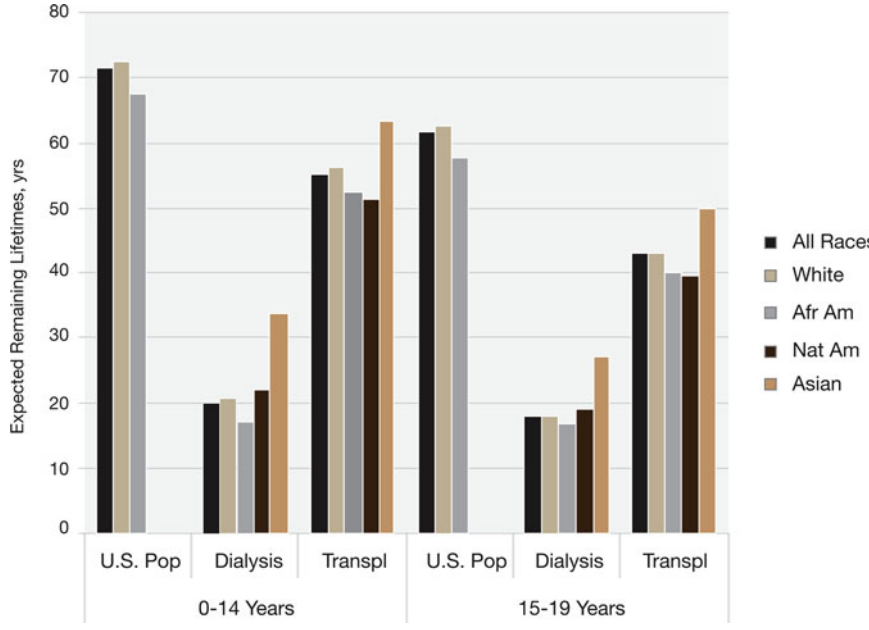

Fig. 3.12 Expected remaining lifetimes, in years, of the general US population (2004) and prevalent dialysis and transplant patients (2007), by age group [10]

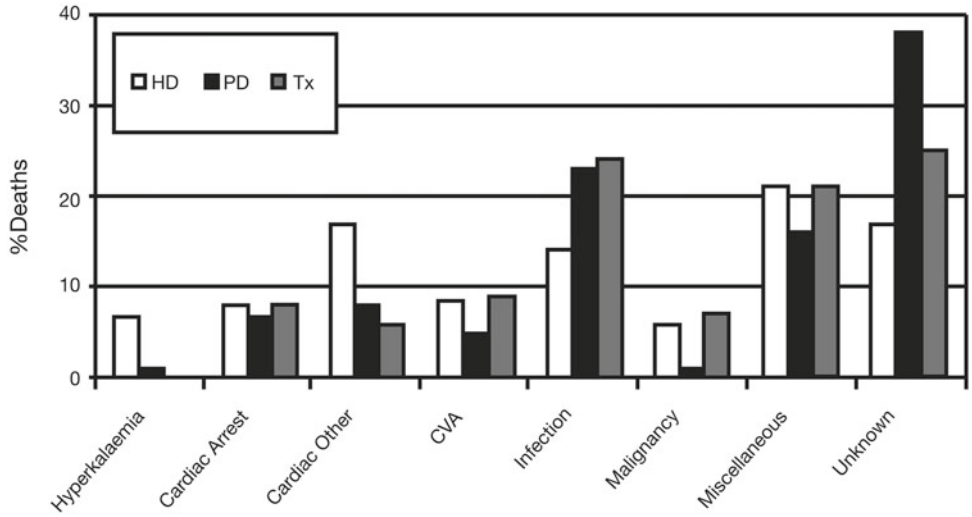

Fig. 3.13 Causes of death by treatment modality in children with ESRD from 12 European registries, 1980–2000 (Source: Reprinted with permission from van der Heijden/Pediatric Nephrology) [22]

Table 3.5 Reasons for termination of dialysis course and changing of dialysis modality in pediatric US ESRD patients since 1992

	All index courses		All courses	
	N	%	N	%
Terminated dialysis courses	4,407	100.0	5,612	100.0
Reason for termination				
Patient transplanted	3,028	68.7	3,689	65.7
Change of modality	819	18.6	1,194	21.3
Death	112	2.5	149	2.7
Kidney function returned	131	3.0	142	2.5
Other/unknown	317	7.2	438	7.8
Courses changing modality	819	100.0	1,194	100.0
Reason for modality change				
Excessive infection	251	30.6	336	28.1
Patient/family choice	167	20.4	275	23.0
Access failure	84	10.3	123	10.3
Inadequate ultrafiltration	45	5.5	62	5.2
Inadequate solute clearance	20	2.4	28	2.3
Excessive hospitalization (dialysis-related)	15	1.8	23	1.9
Other (medical)	108	13.1	171	14.4
Other (nonmedical)	32	3.9	39	3.3
Unknown	97	11.8	137	11.5

Source: Reprinted with permission from NAPRTCS 2008 Annual Report, Section 9-5

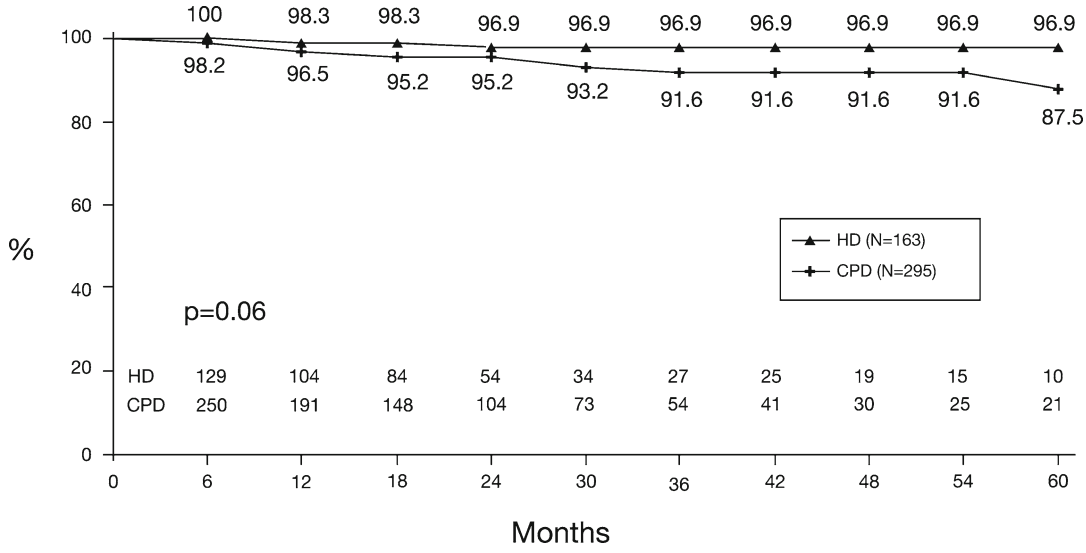

Fig. 3.14 Patient survival curves for chronic peritoneal dialysis patients, by age, participating in the Italian Registry of Pediatric Chronic Peritoneal Dialysis (CPD) from 1989 to 2000 (Source: Reprinted with permission from Verrina/Pediatric Nephrology) [16]

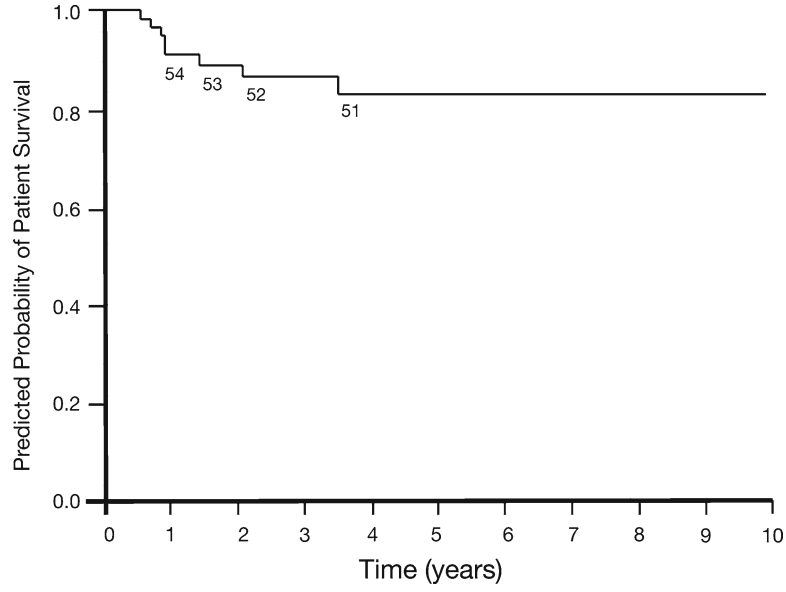

Fig. 3.15 Patient survival curve of 59 chronic peritoneal dialysis patients in Uruguay, 1983–2004 (Source: Reprinted with permission from Grünberg/Pediatric Nephrology) [24]

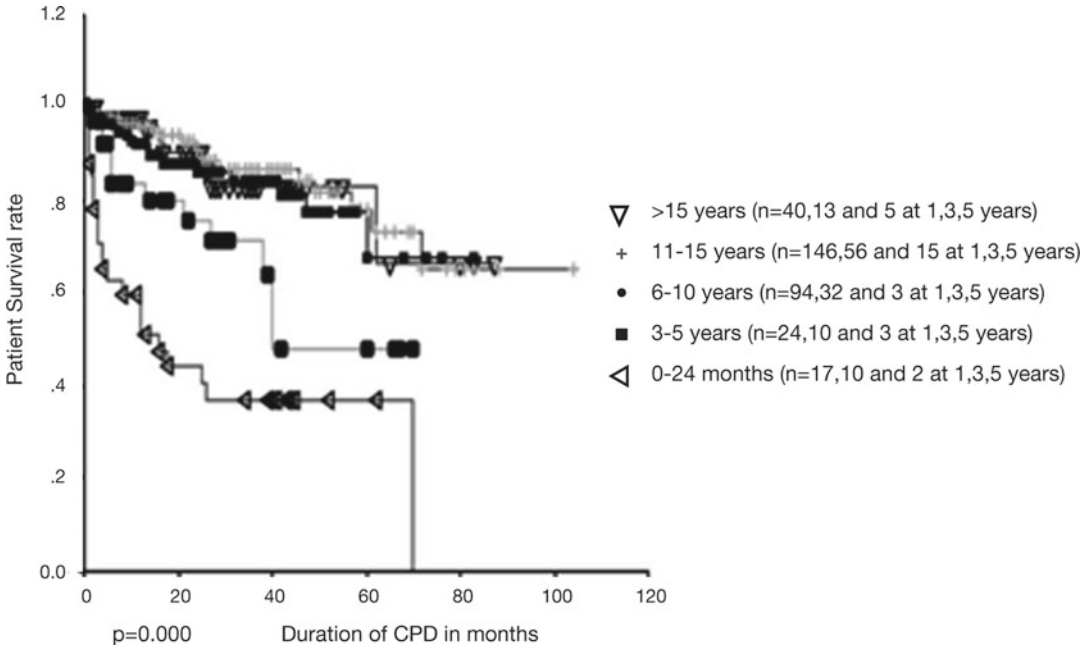

Fig. 3.16 Patient survival curve of 514 children on PD, by age, in Turkey, 1989–2002 (Source: Reprinted with permission from Bakkaloglu/Pediatric Nephrology) [18]

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. Fine RN. Peritoneal dialysis update. J Pediatr. 1982; 100:1–7.
2. Chesney RW. The development of pediatric nephrology. Pediatr Res. 2002;52:770–8.
3. Warady BA, Alexander SR, Watkins S, Kohaut E, et al. Optimal care of the pediatric end-stage renal disease patient on dialysis. Am J Kidney Dis. 1999;33:567–83.
4. Fadrowski JJ, Hwang W, Neu AM, Fivush BA, et al. Patterns of use of vascular catheters for hemodialysis in children in the United States. Am J Kidney Dis. 2009;53:91–8.
5. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2008 Annual Report. Online at: https://web.emmes.com/study/ped/annlrept/Annual%20Report%20-2008.pdf. Accessed 30 Dec 2009.
6. Smith JM, Stablein DM, Munoz R, Hebert D, et al. Contributions of the transplant registry: the 2006 annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). Pediatr Transplant. 2007;11:366–73.
7. Registry of Nephrology, Dialysis and Transplantation in Turkey. Registry 2007. Online at: http://www.tsn.org.tr/documents/registry/registry_2007_tr-en.pdf. Accessed 6 Jan 2010.
8. Finnish Registry for Kidney Diseases-Report 2007. Online at: http://www.musili.fi/fin/munuaistautirekisteri/finnish_registry_for_kidney_diseases/. Accessed 5 Jan 2010.
9. The Renal Association. UK renal registry. The eleventh annual report, 2008. Online at: http://www.renalreg.com/Reports/2008.html. Accessed 5 Jan 2010.
10. U.S. Renal Data System. USRDS 2009 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. 2009. Online at: http://www.usrds.org/adr.htm. Accessed 30 Dec 2009.
11. Fadrowski JJ, Frankenfield D, Amaral S, Brady T, et al. Children on long-term dialysis in the United States: findings from the 2005 ESRD clinical performance measures project. Am J Kidney Dis. 2007;50:958–66.
12. 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.

13. Hari P, Singla IK, Mantan M, Kanitkar M, et al. Chronic renal failure in children. Indian Pediatr. 2003;40:1035–42.
14. Lagomarsimo E, Valenzuela A, Cavagnaro F, Solar E. Chronic renal failure in pediatrics 1996. Chilean survey. Pediatr Nephrol. 1999;13:288–91.
15. Al-Eisa AA, Samhan M, Naseef M. End-stage renal disease in Kuwaiti children: an 8-year experience. Transplant Proc. 2004;36:1788–91.
16. Verrina E, Edefonti A, Gianoglio B, Rinaldi S, et al. A multicenter experience on patient and technique survival in children on chronic dialysis. Pediatr Nephrol. 2004;19:82–90.
17. Anochie I, Eke F. Chronic renal failure in children: a report from Port Harcourt, Nigeria (1985–2000). Pediatr Nephrol. 2003;18:692–5.
18. Bakkaloglu SA, Ekim M, Sever L, Noyan A, et al. Chronic peritoneal dialysis in Turkish children: a multicenter study. Pediatr Nephrol. 2005;20:644–51.
19. Sacca E, Hazza I. Pediatric end-stage renal disease: single center analysis. Saudi J Kidney Dis Transplant. 2006;17:581–5.
20. Mong Hiep TT, Janssen F, Ismaili K, Khai Minh D, et al. Etiology and outcome of chronic renal failure in hospitalized children in Ho Chi Minh City, Vietnam. Pediatr Nephrol. 2008;23:965–970.
21. Santa Cruz F, Cabrera W, Barreto S, Mayor MM, et al. Kidney disease in Paraguay. Kidney Int Suppl. 2005;97:S120–5.
22. van der Heijden BJ, van Dijk PC, Verrier-Jones K, Jager KJ, et al. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004;19:213–21.
23. Miklovicova D, Cornelissen M, Cransberg K, Groothoff JW, et al. Etiology and epidemiology of end-stage renal disease in Dutch children 1987–2001. Pediatr Nephrol. 2005;20:1136–42.
24. Grunberg J, Verocay MC, Rebori A, Ramela V, et al. Twenty years' pediatric chronic peritoneal dialysis in Uruguay: patient and technique survival. Pediatr Nephrol. 2005;20:1315–19.
25. ERA_EDTA Registry. ERA-EDTA registry annual report 2007. Academic Medical Center, Department of Medical Informatics, Amsterdam. 2009. Online at: http://www.era-edta-reg.org/index.jsp. Accessed 30 Dec 2009.
26. Neu AM, Ho PL, McDonald RA, Warady BA. Chronic dialysis in children and adolescents. The 2001 NAPRTCS Annual Report. Pediatr Nephrol. 2002;17:656–663.
27. Hattori S, Yosioka K, Honda M, Ito H. The 1998 report of the Japanese National Registry data on pediatric end-stage renal disease patients. Pediatr Nephrol. 2002;17:456–61.
28. U.S. Renal Data System. USRDS 2007 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, 2007. Online at: http://www.usrds.org/adr.htm. Accessed 5 Jan 2010.
29. US Renal Data System, USRDS 2004 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. 2004. Online at: http://wwwusrdsorg/adrhtm. Accessed 4 Jan 2009.
30. Stel VS, Kramer A, Zoccali C, Jager KJ. The 2006 ERA-EDTA Registry annual report: a precis. J Nephrol. 2009;22:1–12.
31. The Renal Association. UK renal registry. The fifth annual report, 2002. Online at: http://www.renalreg.com/Reports/2002.html. Accessed 6 Jan 2010.

Organization and Management of a Pediatric Dialysis Program

4

Linda Jones and Michael Aldridge

Keywords
Dialysis program • Pediatric • Management and organization

Introduction

The organization and management of pediatric dialysis facilities has undergone many changes over the past decade. We continue to be in a rapidly changing environment with continual technological and treatment advancements. At the same time, we are experiencing new challenges with staffing shortages and government/economical restraints. Despite our rapidly changing environment, the goal of meeting patient and family needs and promoting the quality of care necessary to maintain optimal patient outcomes remains unchallenged and universal. The development of a dialysis facility program must be carefully planned and organized to meet this goal. Essential program elements discussed in this chapter include facility culture and organization, physical design, materials management, and facility operations, which includes staffing concerns, patient care services, transition, and quality improvement.

Facility Culture and Organization

The operations of a dialysis facility are diverse and complex. A caring organizational culture and an innovative management philosophy related to personnel, material management, and information organization is necessary to foster the care and services that we provide today [1, 2]. Every organization has its own unique culture. The culture is, in turn, derived from the group's shared philosophical beliefs and values. Values direct our actions and convey what we feel is commitment to the organization. Historically, the workplace was viewed as an environment dedicated solely for work. Today we know that people are happier and more productive if they can also bring their souls to work, and the workplace is seen as a place where they can grow spiritually and emotionally as well as intellectually [3]. Therefore, it is important that we create a caring, open, and positive culture. Administration must not only support these values, but they must also exhibit, encourage, and enforce them. The simple value of treating all persons with respect and dignity is the basis for caring behaviors. This

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Table 4.1 CMS facility requirements for ESRD coverage

Governing standards/conditions
Appropriate state and local licensure
Participation with ESRD networks
Governing body and appropriate affiliation agreements
Responsibilities of the medical director
Appropriate personnel policies, job descriptions, and emergency coverage
Compliance with other regulatory agencies
Personnel qualifications and competencies
Medical director: board certified in internal medicine or pediatrics, completed training program in nephrology, and has 12 months experience providing care to dialysis patients
Nurse manager: full-time registered nurse with 12 months experience in patient care and 6 months experience in dialysis
Self-care and/or home dialysis training nurse: RN with 12 months experience in patient care and 3 months dialysis experience
Technician: complete a training program specific for patient care and/or water treatment and be certified by either a state or national certification program
Dietician: be registered with the Commission on Dietetic registration and have 12 months experience in clinical nutrition
Social worker: Master's degree with specialization in clinical practice. Twenty-four months experience with 12 months experience in dialysis or transplant or who has a consultative relationship with a social worker who qualifies
Patient care issues
Patient informed of services and medical condition
Patient involved in planning for his own care
Care provided by interdisciplinary team
Receives emergency preparedness training
Rights, responsibilities, and grievance procedure addressed
Medical records present an adequate picture of care
Adequate staffing provided to meet patient needs
Infection control
Standard/universal precautions practiced
Surveillance for infections and other adverse events
Appropriate monitoring for water treatment
Serological testing and vaccination for hepatitis B virus
Data collected to reflect performance regarding quality of care delivered and compliance with requirements
Home dialysis services are at least equivalent to those provided to in-center patients
Environment
Adequate space for safety of treatment
Appropriate toxic/hazardous material procedures and precautions
Procedures and staff preparedness for emergencies

approach not only fosters creativity and innovative ideas, but also allows for failures. Caring cultures encourage flexibility and support new ideas and change. This type of organizational culture is necessary to support and provide positive outcomes and satisfaction from patients and staff [1, 3].

Standards provide the foundation for all activities within the facility. They describe the philosophy and purpose of the facility, and define the services provided. In the United States, governing standards for each facility include the "Conditions of Coverage" as mandated by the Centers for Medicare and Medicaid Services (CMS), facility specific structure standards, and facility specific policies and procedures. The CMS requirements for end-stage renal disease (ESRD) coverage are quite detailed. Specific categories addressed are summarized in Table 4.1 [4].

Structure standards are the specific guidelines for each facility. Simply stated, they are the what, where, when, why, and who questions about the facility and the services that it provides. These provide more specific direction to the staff. As mentioned previously, standards should promote a positive approach to providing health care

Table 4.2 Components of facility structure standards

Facility description and purpose
Goals and objectives
Hours of operations
Patient care criteria
Admission, transfer, discharge criteria
Care plans
Home treatments and training guidelines
Guidelines for medical follow-up
Guidelines for habilitation/rehabilitation and transition
Utilization of staff
Responsibilities of staff
Orientation/competencies
Levels/skill mix
Staffing plans and call policies
Governing rules of the unit
Safety/disaster/emergency procedures
Infection control guidelines
Confidentiality/patient rights
Supplies/equipment/medication guidelines
Visitors policy
Methods of unit communication
Interfacility communication
Staff/family communication

services. For these to be useful, they must be concise and specific. In addition, they must also promote patient and staff collaboration while emphasizing mutual respect for all parties. Common issues that are included in facility standards are summarized in Table 4.2.

The American Nephrology Nurses Association (ANNA) has also developed Standards of Clinical Practice which provide guidelines to promote excellence in patient care [5]. These standards outline five basic care goals which should be incorporated into our basic care practice. Incorporating these care goals into policies and procedures would assure that the patient and family:

- Are knowledgeable about their disease and treatment
- Receive safe and effective care
- Are free of preventable complications
- Participate as much as possible in their own care
- Attain maximal habilitation/rehabilitation

While the governing and facility structure standards are important, specific procedures must also be developed to direct clinical practice. This can be accomplished through several formats. Treatment procedures outline step-by-step instructions necessary to complete a task. Critical pathways or algorithms dictate the course of action to take in response to specific clinical situations. Both procedures and critical pathways promote the caregiver's ability to provide effective, efficient, and safe care. There are available materials that will assist with this endeavor. The National Kidney Foundations sponsors a collaborative project known as the Kidney Dialysis Outcomes Quality Initiative (KDOQI). After an extensive literature review, this initiative has resulted in the development of guidelines related to the care of the chronic kidney disease (CKD) and ESRD populations that are based on scientific evidence and clinical expertise. The guidelines are quite comprehensive and address specific issues related to dialysis treatment adequacy, access management, anemia, bone care, and nutritional management. With these guidelines serving as background material, specific procedures or protocols can be developed.

Physical Design

The basic components of a dialysis unit are established through fairly standardized codes of construction and CMS recommendations. The facility must meet appropriate codes and standards for safety and infection control. Equally as important, the physical design of the facility must allow for space that will meet current and future needs of the facility. Flexibility and efficiency are two key elements that will help accomplish this goal [6].

An effective facility design must meet the needs of the staff, as well as the patient and family. Therefore, it is important to design flow patterns that work for everyone. Patients and families must have easy access to the unit and should be able to easily navigate through the unit. Floor plans must be designed to ensure that all patients can be visibly monitored with ease, and each treatment area must be large enough to accommodate staff and equipment if emergencies should occur. Equipment and supplies must be stored in a fashion that facilitates easy access by the staff. The nursing station must be large enough to allow

for work space and use of computers so as not to violate privacy laws and confidentiality. A separate training room that is large enough to store equipment, supplies, and training aids is also essential. Special attention must be given to the design of isolation rooms. There are many stigmas associated with isolation rooms. Even the young patient understands that this area is different from the other treatment stations. Therefore, it is important that this room is as comfortable and pleasing as possible. If the patient can control any part of this environment, it is helpful. Installing lighting devices or interactive activities that can be changed and controlled by the patient is one way to make this accommodation. Providing a different décor in that room can also be helpful.

In pediatrics, there are additional environmental factors and considerations which must be incorporated into the physical design. Play therapy and music therapy have important roles. If these services are available, adequate space should be provided for these supplies and the activities. Bright colors, pictures, and other decorations are used to de-emphasize equipment and create a comfortable, relaxed setting. While the intent is to create a child-friendly environment, the atmosphere should not become visually overwhelming. It is also important to assure that the décor is age appropriate for all patients. This is challenging if the pediatric unit sees a wide age range of patients. In addition to televisions and computers, units might have exercise equipment, library carts, or other equipment and appropriate storage space, in an attempt to meet the needs of all the patients. Younger patients enjoy arts and crafts, and it is important that they be able to display their projects. Portable craft tables and rotating bulletin boards work well and can be adapted for different age groups.

While the specific treatment areas need to be esthetically pleasing, they must also be functional for the staff and meet the needs of the patients. Therefore, seating arrangements should be flexible enough to accommodate interactions, activities, and privacy as needed. Each treatment space ideally needs comfortable seating for family or visitors. Windows allow for diversion and help to foster a welcoming environment. Patient surveys have indicated that dialysis patients would like their treatment areas more "homey" and they want distractions or activities that help occupy their time. Simple things such as televisions, DVDs, music or computers can significantly decrease the boredom that arises during a treatment session, however these do require space. To promote a safe environment and reduce clutter, it is helpful for patients to have their own lockers or at least a space in which to keep their coats and personal belongings. To meet these needs in the best possible manner, it is helpful to have input from staff, patients, and family. Units that have gone through this process can also provide helpful suggestions and ideas to newly developed programs.

Materials Management

Materials management is a critical component of a dialysis unit and the responsibilities associated with it should not be taken lightly. At least one staff member should be trained in all concepts and procedures related to materials management. This includes receiving, storage, inventory control, replenishment of supplies [7], purchasing, and documentation requirements for each of these functions. Because of the variety of services provided and the wide range of patient age and sizes, the pediatric dialysis unit must maintain a large variety of equipment and supplies. Procuring these is often challenging since contracts with multiple suppliers may be needed and may prove costly. Delivery systems must be carefully selected to assure that they can accommodate small peritoneal exchange volumes or small extracorporeal circuits. And due to low demand, manufacturers frequently decrease production of pediatric-specific supplies.

All measures should be taken to minimize unit costs while maintaining treatment excellence. Unit managers must frequently reevaluate and analyze vendor contracts to maintain quality products and services in a cost-effective manner. Careful planning and tight control of inventory is important to maintain cost-efficient care. This is best accomplished with computerized inventory control systems.

Management of Facility Operations

The operations of a dialysis facility are complex and challenging. Status quo, if it ever existed, is now a thing of the past. It is of interest that while dialysis care and services have become more complex, resources and reimbursement have become more restricted. As mentioned earlier, innovative leadership which builds peer relationships and strengthens a caring culture is necessary to provide excellent services and optimum patient outcomes. While physicians direct and participate in these activities, it is the unit managers who are directly responsible for managing the day-to-day operations of the facility. The challenges facing them are often monumental and to be successful they must have the appropriate education and training for this position. Frequently, this role is filled by a nurse with excellent nursing skills but little management training, who has been promoted into the position. Assuming this expanded role and responsibilities without adequate education, resources, or support is a setup for failure. To be successful and to meet the goals of the facility, managers must have a good foundation in management practice and a supportive mentor so they can continuously develop leadership skills. A study given to 300 American Organization of Nurse Executives identified the skills necessary to accomplish the duties of a manager. The most important skills identified were effective communication and decision making. Additional skills that ranked high included: effective staffing strategies, performance evaluation, counseling, team-building, delegating, conflict resolutions, change process, and problem solving [7]. Results from a Gallup Organization report indicated that the single most important variable in employee productivity and loyalty is the quality of the relationship between employees and their direct manager [8]. This was more significant than pay, other perks, or the workplace environment.

The manager alone cannot meet the multifaceted goals of the unit. To maintain fiscal responsibility and yet provide high-quality patient care, it is necessary to have a multidisciplinary team that works together in a collaborative fashion. Maintaining a trained team is one of the biggest challenges today. Accordingly, recruitment and retention efforts are crucial.

Recruiting the appropriate staff is essential. Due to the diversity of technical, interpersonal, and critical thinking skills required in a pediatric dialysis program, a candidate with prior pediatric, critical care or dialysis experience is helpful. The necessary skills and behaviors required to perform the job should be defined prior to or during the interview process. Besides experience, it is important that the new hire demonstrate traits compatible with the facility culture. If not present, dissatisfaction quickly occurs resulting in a downward spiral and employee discord. Behavioral questions should be used to help define attributes of the candidate. Some facilities also incorporate personality testing to determine if the candidate's attributes are complimentary to the existing personnel. Advocating for your facility and describing why it is the best place to work is one of the most effective recruiting tools. Entice candidates with your performance records such as patient outcomes, research activities or other factors that favorably describe your workplace. Involving a variety of staff in the interviewing process fosters a team environment and will provide a variety of input. And although money is not the key factor, you must be at least competitive with salaries and benefits when offering a new position if recruiting efforts are to be successful.

Nursing shortages and staff turnover are major issues in health care today. To maintain high standards of patient care with increasing financial limitations, staff retention is a critical issue. Many studies have been conducted to identify key factors that influence retention. One important factor is orientation and career development. Staff members want to be successful in their jobs and want growth opportunities to be available. This begins with a detailed orientation program. Management must assure time and staffing is adequate for appropriate orientation and training of newly hired staff. A willing preceptor who is knowledgeable in established skill competencies should be assigned to each new employee. The goal of the orientation program is a gradual progression

of the new employee's independence with a designated preceptor guiding the progress toward acquisition of knowledge and mastery of skills. Orientation to the specialty can take from 6 weeks to 3 months depending on the new employee's prior experience and learning opportunities. In pediatrics, the occurrence of some clinical situations may be episodic and an employee may not complete the competency checklist by the end of orientation. Thus, simulated clinical experiences may be created to supplement learning. When the infrequently encountered clinical situation does occur, an experienced staff member should assist the novice to enhance skill development and confidence.

An ongoing staff development and education program must be developed based on the learning needs of the staff with a continual reassessment of high-risk procedures [2]. Quality improvement and quality assurance data can identify areas which warrant further review or education. Once a learning need is identified, educational material and periodic skill competencies can be developed to advance clinical knowledge and expertise.

Beyond clinical skills, nurses want customized professional development support. Managers can accommodate this by periodically reviewing educational opportunities and encouraging career advancement. Recognizing certifications, paying professional dues, and offering continuing education classes are additional ways to support career development.

Evidence supports that staff recognition is another key factor influencing staff retention. Employees want more than the established routine recognition programs that exist in hospitals today. They want a 360° recognition program with personalized acknowledgment of their contribution to the success of the facility [9]. It is important to remember that people work for people – not organizations. As human beings, we seek connection with others. People work hardest for bosses who consistently recognize and reward commitment [10–13].

The role between the nurse and physician is crucial. Nurses want collaborative working relationships with physicians. They want physician feedback on protocols, dedicated time to discuss issues, and mutual respect.

Finally, enhancing the quality of work life is the final important ingredient for staff retention. Employees today expect that the work climate will be attractive and accommodate both professional and personal needs [10–12, 14]. They want to be treated fairly and have input regarding job duties and work schedules. Surveys indicate that nursing turnover is twice as high in facilities where there are no scheduling options [15]. Staff wants to have pride in their job and organization. They want to deliver high-quality care and know that their provision of care results in optimal patient outcomes. It is therefore important that the manager procures appropriate resources and support to accomplish this goal.

Staffing the Dialysis Unit

In the United States, individual states have the authority to regulate dialysis clinics, which leads to significant variation in staffing regulations [16]. Some states regulate the ratio of licensed staff, such as nurses, to unlicensed staff, such as technicians. Other states have required patient-to-nurse ratios. Various states have nurse practice acts that limit the practice of patient care technicians in the dialysis clinic. Each nurse must determine what the regulations are in the state in which he or she practices.

As a result of the variation among states – not to mention the added variation in practices outside the United States – there is no recognized standard for how to staff a pediatric dialysis clinic. However, some of the considerations about how to staff a clinic have been studied recently.

Nurse-to-Patient Ratios: Do More Nurses Improve Patient Outcomes?

Although there is a clear association between higher numbers of registered nurses and decreased rates of adverse events and mortality in the hospital setting [17], that association has yet to be shown in the pediatric setting. Dialysis units with higher

numbers of registered nurses do experience decreased rates of skipped dialysis treatments [18], as well as lower rates of hepatitis C seroconversion rates [19]. A recent survey of chronic hemodialysis nurses [20] found that high patient-to-nurse ratios were associated with an increased likelihood of intradialytic hypotension, skipped dialysis treatments, and patient complaints. These studies provide the first empirical evidence that higher numbers of registered nurses can decrease adverse events in the adult dialysis program. It is unknown whether these effects also hold true in the pediatric dialysis program, where nurse-to-patient ratios are typically lower than in the adult program.

Another consideration in staffing is whether the length of the shift has an impact on safety. When determining how to staff the dialysis program, one must consider whether to staff 8-h, 10-h, or 12-h shifts. Many nurses, according to the literature, desire 12-h shifts and report increased job satisfaction, less emotional exhaustion, and more satisfaction with their work schedule. In addition, the units with nurses working 12-h shifts have lower vacancy rates. One of the hazards of working a 12-h shift that does need to be considered is that the shift often stretches longer than 12 h. A landmark study [21] of hospital nurses found that the risk of making an error increased significantly when the shift lasted longer than 12 h, when the nurse worked overtime, or when the nurse had worked more than 40 h in 1 week. However, a recent review [22] of studies examining the effect of shift length on the quality of patient care and on health care provider outcomes (such as job satisfaction and stress), found equivocal results and further research is needed. The implications for dialysis programs could be significant, particularly smaller programs that operate with fewer numbers of nurses.

Another consideration in staffing is managing on-call issues. Most pediatric dialysis programs must provide on-call coverage for home patients and acute treatments. Providing coverage can be challenging when the on-call nurse has already worked a full day in the dialysis unit or is scheduled to work the next day. The question arises: when does it become unsafe for the nurse to continue to provide patient care?

Physicians in residency training and nurses in the perioperative setting face the same issue, and research and guidelines from those disciplines provide dialysis nurses with some recommendations. Physicians in residency training, who work more than 24 h on-call, experience an increased risk of sticking themselves with a sharp object during a procedure, having a motor vehicle crash while driving home, and of making a serious or even fatal medical error [23]. Resident physicians in the United States are currently restricted to working no more than 30 consecutive hours in a shift and their work weeks must average 80–88 h per week [24]. Based on the safety data associated with shifts exceeding 24 h, the Institute of Medicine (IOM) is advocating for resident physician shifts to decrease to 16 h, which has been the practice in New Zealand since 1985. The European Union limits its physician-trainees to 13-h shifts [24].

The Association of Operating Room Nurses has developed guidelines for safe on-call practices [25]. They recommend implementing recuperation periods between regular shifts and call-back shifts, as well as developing a performance improvement system to track whether there is a relationship among errors, adverse events, and number of hours worked during call. They do not provide definitive recommendations about shift length or call length, but rather recommend that each unit should consider patient volume, acuity, and how often call-back occurs when determining on-call guidelines. Finally, they recommend that a sleep room be provided at the facility so that staff has the option to stay on site during call or when called back in order to alleviate sleep deprivation. This factor may be especially important if the staff member is scheduled to work the next day and only has a few hours left to sleep.

In summary, there are no published guidelines about how to most effectively staff a pediatric dialysis program. What little research we have to guide us in the dialysis population comes from the adult population, where the nurse-to-patient ratio is typically much higher. This factor makes it difficult to generalize those findings to the pediatric setting. However, concerns about safety

from shifts that last longer than 12 h and on-call shifts that last longer than 24 h may be valid in the pediatric setting as well, and deserve consideration as we determine how to most effectively staff our programs.

Patient Care Services

Patient care services focuses on meeting the physical and psychosocial needs of the patient. These services include modality selection, development and implementation of care plans, patient and family education, and delivery of patient care. To adequately accomplish these tasks, we must first take into account factors that impact the family when their child has a chronic illness.

Family Adjustment

When parents learn that their child has chronic kidney failure, the coping mechanisms of the family are tested. Some families have had years of interactions with the nephrology team and may have had time to prepare for dialysis. Other families may have received the diagnosis more suddenly and had little time to prepare. Either way, families must adjust to a change in routine and must learn how to care for their child's new medical needs.

As families adjust to having a child with kidney failure, parents experience increased levels of stress, anxiety, and depression [26–29]. Families with children receiving dialysis report an increased disruption in their family life and increased marital stress, but not increased marital breakup [30]. The overall burden of dialysis is stressful and is characterized by themes of uncertainty [31], social isolation [32], and increased vigilance, caretaking, and monitoring [32–34]. In one study [31], mothers of children on peritoneal dialysis described that they were often worried about the possibility of illness or death of their child, and they remained vigilant for complications by checking on their child at night. Fatigue, frustration, and loss of friends were common results that led to increased anxiety and depression among these mothers.

Many nephrologists and nephrology nurses might predict that dialysis modalities that are delivered in the home environment would play a role in how families adjust, since the burden of care giving is significantly higher for these families when compared with in-center modalities. However, studies examining this issue have yielded conflicting results. One study [26] found that parents of children receiving in-center hemodialysis had increased anxiety and depression when compared to parents of children receiving home hemodialysis or continuous ambulatory peritoneal dialysis. However, another study [34] found that home hemodialysis was more stressful for parents than in-center hemodialysis. The relationship between where children receive dialysis and how their families adjust is not fully understood due to the small number of studies in the literature and highlights the need for further investigation [35].

Children themselves also have difficulty adjusting to the burden of kidney disease and dialysis, and studies indicate that there may be both developmental and psychological consequences to the disease process. A study [36] of 16 children who received peritoneal dialysis during the first year of life found that although the children had normal IQ scores, half had behavioral and emotional difficulties. Similar psychological challenges have been identified in another study [37] of adolescent renal transplant recipients. In the long term, young adults who received dialysis as children have difficulty making the transition to adulthood. These dialysis survivors tend to live with their parents longer, have limited social networks, and have difficulty forming relationships with the opposite sex [38].

These studies confirm what we have always known: having a child on dialysis is stressful for both the child and the family. Perhaps the more important question is: does this affect outcomes? One study [27] found that poor adjustment to dialysis was associated with decreased adherence to therapy, which could affect the child's outcome. Another study [39] examined the likelihood of a

patient being referred for transplant by a nephrologist by creating scenarios of children and families with varying characteristics. In this study, the families who were less compliant with therapy were less likely to be referred for transplant. Therefore, there may be relationships among adjustment, adherence, and transplant referral. By paying attention to how families are adjusting to the burden of dialysis, we may in turn be able to ultimately improve the outcomes of these children.

Modality Selection

All dialysis modalities should be reviewed with the patient and family before the patient needs to start dialysis. If this is not possible, modality choices should be reviewed as soon as the patient is medically stable. Specific criteria are necessary if the patient/family is interested in a home modality. The home care provider must be physically able to perform dialysis-related tasks, possess cognitive and psychomotor skills to manage all aspects of the treatment, and be emotionally stable [40–44]. A partner for the home care provider is desirable but may not be necessary depending on the family situation. If a home partner is not available, an emergency backup plan needs to be established in the event of absence or illness of the primary caregiver.

An assessment of the home environment should be performed prior to the initiation of training. A home visit is utilized to assess the general cleanliness of the home, the availability of appropriate electrical access, the water source, telephone accessibility, and the presence of space for storage of supplies [45]. The dialysis team should problem solve with the family to make the necessary environmental changes as needed before home training begins. Burn-out has often been described as one of the biggest pitfalls in home therapy. Therefore, the patient and family must understand and feel assured that they can stop home treatments at any time and the medical team will support their decision. This can be for a short term if respite is needed, or on a continual long-term basis, understanding that a modality change may, in turn, be necessary.

Patient Care Plans

Care plans are developed to promote the maintenance of or improvement in the patient's physical condition, growth, developmentally appropriate activities, and appropriate coping skills for the psychosocial adjustment to chronic illness [5]. Services provided are a continuum of care that requires periodic review, evaluation, and adjustment to meet the needs of the patient.

Considerable improvement in patient outcomes, in both adult and pediatric chronic disease patients, occurs when patients are encouraged to participate in their own care [46]. This not only improves medical outcomes, but encourages independence and builds self-esteem. A care model or plan that will promote these goals should be utilized. Dorthea Orem introduced self-care as a model of nursing practice which is based on key success factors. Adaptations of this model are valid for ESRD programs and should be incorporated into the patient's care or transition plan. These self-care goals promote [46, 47]:

- Maintenance of the pre-ESRD level of involvement in daily activities
- Progression in developmentally appropriate activities
- Increasing involvement in self-care activities

While team input is necessary to develop multidisciplinary care plans, it is important to have someone responsible for the coordination of services. This task has been and continues to be the responsibility of the registered nurse. One nurse is usually assigned responsibility for a designated group of patients. While many facilities refer to the tasks associated with this as primary nursing, today the job description more closely aligns itself with a modified version of case management. This model maintains that one nurse is directly responsible for the ongoing coordination of care for a specific patient and family. Continuity of care and services is accomplished and maintained through this approach. Common duties of

Table 4.3 Responsibilities/duties of the primary nurse or care manager

Utilize the nursing process to assess, plan, implement, and evaluate the patient's care
Collaborate with team, patient, and family to develop care plans
Provide support, and follow-up care through phone contacts and clinic visits
Coordinate other health-related issues: i.e., dental visits, immunizations, etc.
Promote age-appropriate activities and other habilitation goals
Provide appropriate patient education
Promote school attendance and make school visits as necessary
Support home therapy and make home visits as necessary
Act as an advocate for patient and family
Promotes self-care

the primary nurse or case manager are included in Table 4.3.

Patient/Family Education

There are many considerations involved in establishing a pediatric dialysis training and education program. Teaching and educating families is a basic responsibility of pediatric health care providers [48]. When dealing with a chronic illness, education becomes an ongoing process of assessing, planning, teaching, and evaluation. The dialysis team is responsible for the initial and ongoing education and training needs of the patient and family. Establishing a thorough and consistent education/training program is critical [48–50]. Considering health literacy, developing the training materials, and creating a teaching plan are all necessary components for patient education.

Health Literacy and Patient Education Materials

When developing or evaluating the home training and patient education materials (PEMs), the clinic staff must consider the readability of those materials. Unfortunately, the average adult in the United States reads at the eighth-grade level [51], and most PEMs are written at the high school or even college reading level [52]. Since a significant number of people – perhaps up to 40% [51] – read below the fifth-grade level, PEMs should be written at the fifth- to sixth-grade level [52]. It is a waste of valuable nursing time to create materials that are, in essence, unreadable. Therefore, simple tools exist to help determine the grade level that the PEMs are written on. These tools are formulas that primarily take into account sentence length and word length, since longer words and sentences are more difficult for people with poor reading skills to read and understand. Ideally, this process should occur during the development of the education materials but it can be done retrospectively or during revisions. Table 4.4 explains the process for determining the readability of PEMs in electronic and non-electronic formats.

As much as possible, simplify the reading levels. Even adults who read well prefer materials that are easy to read and understand. When designing or rewriting PEMs, you must start by focusing on the actual words and sentence structure. Strive to make the words short (less than three syllables when possible) and easy to understand. Sometimes, a long, dialysis-specific word such as "effluent" may need two shorter words such as "drain fluid" to adequately explain its meaning [52]. Use a consistent word throughout the document, such as "pills," to mean medications or medicines. Define new words. Use the thesaurus feature in your word processor to suggest simpler words as well. Keep sentences less than 10–15 words long, as longer sentences are more difficult to read and understand. Commas and semicolons serve as natural places to divide up long sentences. Finally, write in the active voice rather than the passive voice. We tend to speak in the active voice but write in the passive voice; the active voice is easier to understand. An example of writing in the active voice is to say, "Take your binders with food each time you eat" rather than "your binders should be taken with food each time you eat."

Once the words and sentence structure are written at the fifth- to sixth-grade level, it is time to pay attention to the overall design of the PEMs. The goal is to create something that is visually appealing, uncluttered, and easy to follow.

Table 4.4 Determining readability of patient education materials

If patient education material is in electronic format	If patient education material is not in electronic format
Nearly all word processing programs will display readability statistics	Use the SMOG formula [53]
Readability statistics can often be found at the end of the spelling and grammar check	Pick ten sentences in a row at the beginning, middle, and end of the document (a total of 30 sentences)
Readability statistics change as you make changes in your document	Count every word in the sentences that has three or more syllables. Words that repeat count each time they appear. Proper nouns and hyphenated words of more than three syllables count also. Abbreviations are counted as the whole word they represent
Instructions can be found by searching for "readability" in the Help menu	Determine the square root of the total number of words with three or more syllables
	Add three to the square root. This is the grade level of the document. *Example*: Your 30 sentences have 44 words with three or more syllables. The square root of 44 is 6.6. Add 3 to 6.6 to get 9.6, which is the grade level of the document

A well-designed PEM will help the reader follow along and pick out the most important points. Highlight the most important things you want the reader to remember with bold face, underlining, or italics [52]. Set them off in boxes, or have the reader fill in the information with a "fill in the blank" style, since people tend to remember facts better when they write the information. It is best to use bulleted or numbered lists for procedures and a limited number of fonts, as too many font styles can be distracting or even difficult to read. Make sure that the font size is at least 14-point in order to ensure that it is large enough to be readable by those with poor vision. Be sure to repeat critical information more than once so it is clear that the information is important. Leave a lot of white space on the page and finally, use graphics and pictures to explain difficult concepts and to help illustrate procedures.

Health Literacy, which is defined as the ability to obtain, process, and understand health information, has become an area of significant interest since the IOM released their report on the health literacy status in the United States in 2004. This report noted that 90 million Americans have difficulty understanding and acting on health information, and a growing body of research has demonstrated that low levels of literacy are associated with worse outcomes in patients with chronic diseases. Unfortunately, there has been little research in the adult CKD population and no published research in the pediatric CKD population in this arena [54]. To date, a review of the research [54] of four published studies reveals a mix of literacy levels among the adult dialysis and transplant population. Once we fully understand the literacy levels of our population, both in the adult and pediatric world, the next step will be to determine whether there is a relationship between health literacy and short- or long-term outcomes.

Development of Training Materials

Patient and family training materials are an essential component of any dialysis program. These materials range from brief "hot topics" to detailed training manuals for home families. Care must be taken to assure that materials are developed for the in-center patients as well as the home patient. To help assure consistency of education, specific information related to key issues regarding the management of patient care must be addressed. Examples of topics commonly addressed include:

- Normal kidney function
- Complications of ESRD
- Treatment modalities
- Complications of treatment
- Diet and nutrition
- Fluid balance and control
- Medications
- Laboratory tests and values
- Infection control
- Dialysis catheter and exit-site care

A method of evaluating what the patient has learned is essential [55]. Quizzes can be developed to test the learner's knowledge. Competencies should be developed to evaluate the learner's ability to perform procedures. The quizzes and skill competencies not only give the teacher information about topics needing further emphasis, but also provide the family with immediate feedback and reinforcement of information.

Regardless of the therapy or population being taught, the development of educational materials requires the participation of all the members of the multidisciplinary team. The team should also be utilized to review and update education materials as needed.

Development of a Teaching Plan

Whether teaching a home dialysis family or a patient dialyzing in the facility, an individualized teaching plan should be developed by the nurse responsible for dialysis training. A teaching plan consists of an outline of the content to be taught, measurable behavioral objectives, learning activities, and teaching methods. The individual nurse chooses the specific learning activities and teaching methods to use. Learning activities include reading, hands-on use of equipment, demonstration and return demonstration of procedures, viewing different forms of media, listening to audio tapes, and role playing exercise. Teaching strategies may include lecture, discussion, demonstration, and learning labs [41].

Learning Needs Assessment

In order to develop a teaching plan, a careful assessment of the individuals who are training must first be performed. The family's readiness and ability to learn is examined. Language skills, previous experience and knowledge, coping mechanisms, religions, and cultural beliefs all impact each family member's ability to learn. Barriers to learning such as learning impairments (dyslexia, Attention Deficit Disorder), illiteracy, physical impairments (visual, auditory, speech), illness, and stressors must be considered when developing an individualized teaching plan [41, 48, 49, 55]. These barriers will influence the methods used to teach. It is desirable to provide some education to each member of the family. Even young siblings can benefit from brief education activities.

Although there are many theories, it is not known exactly how people learn. We do know, however, that people learn in various ways. Three basic styles of learning are visual, auditory, and kinesthetic. Once a learner's style is determined, appropriate teaching methods can be incorporated into an individualized teaching plan (Table 4.5) [48, 49].

When teaching a group of people, it is desirable to use a variety of teaching tools which cater to all three learning styles.

Table 4.5 Styles of learning

Learning style	Characteristics of the learner	Supportive learning methods used by the teacher or learner
Visual	Talks fast Talks in half sentences Talks with hands Needs descriptive words Looks at you with blank stare	Writes key words Underlines or highlights key points Draws pictures of words Draws diagrams Learner takes notes
Auditory	Speaks slower Has a full voice Wants all the facts	Speaks just loud enough to be heard Discusses with others Makes "sounds like" associations Makes rhymes
Kinesthetic	Cannot be rushed Touchers/feelers	Behavior modeling Hands on involvement

The Nurse as Teacher

Being able to teach others effectively is a skill, and many nurses lack formal training in how to teach [56]. Thus, it is critical for nurses who teach children and families about ESRD and dialysis modalities to have a basic knowledge of teaching methods in order to be able to teach effectively and to be able to evaluate whether the child and family understand the information that has been taught.

Nurses can be most successful as teachers when clear objectives are used as a guideline for the content being taught [56]. If not already present in the teaching materials, the nurse should ask what the patient should *know* or be able to *do* at the conclusion of the teaching. This information is then used to write specific objectives. For example, if a nurse was teaching a family about the signs of peritonitis, an objective for that content might be: "List three ways you would know if your child has peritonitis." Notice that objectives are limited to one concept and are written in a language that people without medical training can understand. The next objective might read: "Describe what you should do if you think your child has peritonitis." This approach accomplishes two things. First, it keeps the nurse who is doing the teaching on track and ensures that the critical content (the "need to know" rather than the "nice to know") is covered. Second, it allows the nurse to evaluate whether the family understands the information that is presented.

Many nurses approach teaching on an individual or small-group basis. In this venue, teaching by discussion rather than lecture is more effective. By asking questions of the family, the nurse has a good idea of their comprehension of the material presented. In addition, this approach makes the session active rather than passive, which allows for more effective learning.

There are several methods to ask questions in a way that meets the needs of the learner as well as the teacher [57]. Only ask one question at a time, and allow at least 10 s for the learner to respond to the question. Although 10 s seems like a long time, many learners need that much time to process the question and formulate an answer. Avoid saying, "Any questions?", as this approach usually does not prompt the learner to ask questions. Instead, tell the person or group that you expect them to have questions. And you can reinforce this message by making statements such as: "There were a lot of steps in that procedure. I'm sure you have some questions about what I demonstrated." Asking the learner to choose between a few possibilities can also help the nurse assess knowledge. For example, a question about one sign of peritonitis might be, "If your child has peritonitis, would the effluent be clear or cloudy?" Although this sort of question does not invite discussion, the family's answer quickly lets the nurse know if they understand the concept and whether additional teaching is needed. Questions can also be used to help families apply the information that has been presented. For example, after discussing how to assess their child for signs of proper fluid balance, the nurse could ask, "What would a weight gain of 2 lb and a blood pressure of 130/90 mmHg tell you about your child's fluid balance?" This question mimics the data that the parents would have at home and allows the nurse to see whether the family can determine that the child is hypertensive and fluid overloaded.

Additional methods have proven beneficial when teaching children and families. Trivia games have been used successfully when teaching peritoneal dialysis to adults [58]. Patients believed that the games were a fun, active way to learn and the educator found that the game reinforced content covered in the initial training sessions. Hands-on demonstration is an extremely important method for any skill-based content. The nurse should demonstrate the correct order of steps and avoid demonstrating incorrect techniques to the family. Many families also benefit from visual aids that show them the correct order of steps and a picture of someone performing that step of the procedure.

After teaching a concept, the nurse should evaluate whether the family understands the content and can apply the information. Some units prefer to have a written test to document a score. However, a high score on a test does not guarantee that a family can use and apply the information they were taught. It is also very difficult to

Table 4.6 Learning principles of children

Child learning principle	How to apply the principle
Need to know rules and limits	Children have to be told, sometimes shown how, and then told again, especially in new situations. The key is patience
Need for consistency	Staff members must work together to provide consistency in what is taught. Inconsistency can make the child feel confused and insecure or can encourage manipulative behaviors
Need for self-esteem	Belittling or shaming a child is a poor way to discourage a behavior and should be avoided. More effective is to show approval or encouragement of what the child is demonstrating or verbalizing *correctly*. Refrain from labeling a child as a slow learner
Need to have choices	The child needs to feel that he has some control over the learning situation. Give the child a choice when you can, such as when or where the teaching should occur
Need for play	Play is a child's work. By using medical play, the child will develop needed skills for his care

write valid test questions unless the nurse has had specific training in measurement and evaluation techniques. Thus, another evaluation method to use is a checklist that is derived from the teaching objectives. The evaluation of whether a family understands these objectives can either occur at the end of each training session or at the end of the entire training and involves the nurse talking with the family to ensure that they met the objectives. As objectives are met, they are documented and this checklist can then be placed in the patient's chart as evidence of successful training.

When teaching content that involves skills, it is important for the nurse to observe that the family can perform the skills correctly. These observations can also be documented on the evaluation checklist. Ideally, it is also helpful to try to simulate how the family will use the skill in the home environment. For example, after all the training objectives have been met by a family who is learning to perform peritoneal dialysis at home, the nurse could ask the family to set up the peritoneal dialysis machine and connect the child independently without the nurse in the room. Although the nurse is still available for questions, the family will perform the setup without assistance or observation, which simulates what will take place at home. If they are able to successfully complete this task at the end of training, the family feels confident that they can accomplish the same task at home without the nurse's presence. At the same time, the nurse feels confident that the family understands and can apply the information that has been taught during the training. This form of evaluation is very meaningful and provides more information than a score on a written exam.

Teaching Considerations in Children

When teaching children, the level of development must be evaluated. It is not uncommon for a chronically ill child to regress. This regression may be exacerbated by an acute illness or hospitalization. The teaching style and content should be based on the developmental level rather than the chronologic age of the child. In each developmental stage, there are conflicts which cause additional stress to the child. In order for optimal learning to take place, these stressors need to be minimized. Tables 4.6 and 4.7 provide methods to maximize the child's learning potential [12, 13, 48, 49, 59, 60].

Teaching Considerations in Adults

The adult learner may be under a significant amount of stress and feel overwhelmed with the amount of information he/she must learn in order to provide care for their child. All education and training sessions should be done in a relaxed and open setting where they can freely express their feelings. While it is necessary to convey information, it is also important to devote time to develop a positive relationship between the nurse and family. Table 4.8 outlines principles which enhance adult learning [48, 49, 61].

Ongoing Education

The education and training needs of the patient and family continue even after the initial training

Table 4.7 Developmental characteristics seen in dealing with children

Infancy/Toddler (0–30 months)
Stressors to child
Separation from parent
Fear of certain strangers (doctors, nurses, etc.), large objects or machines (scans, x-rays), and change of environment (hospital, clinic)
Loss of control of their environment
Fear of injury
Minimization of stressors
Minimize number of caregivers
Actively involve child in treatment, when possible
Minimize intrusive procedures; do not involve parents as participants in intrusive procedures; rather, enable their presence to comfort the child
Teaching tips
Involve parent in noninvasive cares
Provide choices in age-appropriate activities
Prepare child for procedures, through therapeutic plan and familiarity with medical equipment
Provide age-appropriate activities while waiting
Preschool (30 months–5 years)
Stressors to child
Separation from parents or caregivers
Fear of injury and death
Minimization of stressors
Enable parent to remain with child to provide emotional support
Ask questions of the preschooler and model honest communication
Teach planned coping strategies
Teaching tips
Encourage parental involvement in noninvasive care
Provide accurate preparatory information
Offer psychological preparation prior to and following procedures
Provide age-appropriate activities and play
School age (6–12 years)
Stressors to child
Separation from parent
Fear of staying alone, injury, or death
Forced in a dependent role in having their needs met and the anxiety of body control (i.e., catheter instead of voiding)
Minimization of stressors
Ensure preparation for and involvement in procedures
Involve patient in care
Help children recognize aspects of their effective coping
Teaching tips
Encourage choices among options if possible (i.e., IV in right or left hand)
Teach coping strategies
Provide age-appropriate activities
Adolescence
Stressors to child
Fear of being different from their peers and not fitting in
Fear of death
General lack of trust of anyone other than peer group
Minimization of stressors
Communicate honestly
Involve patient in care and decisions
Address long-term issues in follow-up
Teaching tips
Discuss potential psychological changes and physical responses
Provide opportunity for follow-up discussion and guidance as needed

Table 4.8 Learning principles of adults

Learning is a self-activity
Learning requires active participation by the learner. Learners will learn faster and retain more when they are actively involved in learning experiences
Learning is an interactive process
Hands-on learning experiences will maximize the amount of learning retained
Learning is unique to the learner
Learners are influenced by their past experiences, as well as by their physical environment. Provide for variable interests, opinions, learning styles, and pace of instruction
Learning is influenced by the motivation of learners
Learning is more readily acquired and retained when learners have a strong and sustained desire to learn. Motivation for learning is enhanced when learners can participate in identifying their own needs and planning to meet those needs
Learning is influenced by the readiness of the learner
Learners need to prepare for learning both physically and psychologically
Learning proceeds best when it is organized and clearly communicated
Select appropriate principles (easy to hard, known to unknown, first to last step). Have teaching aids ready when they are needed
Learning is social
Learning is a shared responsibility of teachers and learners. Enhance the social climate for learning by getting to know learners individually. This can be done by: engaging in informal discussions, communicating effectively, and being available as a guide and support
Learning is influenced by the learning environment
The learning environment is both psychological and physical. Provide a comfortable, relaxed, nonjudgmental atmosphere for learning
Learning is facilitated by immediate feedback
Timely rewarding of desired behavior tends to ensure that the behavior will recur. Be generous in dispensing positive feedback. Any negative feedback must be given in a timely, constructive, and sensitive manner
Learning is integrated with knowledge
Learners vary in the speed and effectiveness with which they integrate new learning with old learning. Explaining relationships between old and new concepts will assist learners in bridging these concepts

program has been successfully completed. Over time, breaks in technique or bad habits may develop. In addition, some skills not performed frequently may be forgotten. A clinic or home visit is a good opportunity to review or watch the home care provider demonstrate dialysis-related skills. Skills should be reviewed annually or more often if a problem exists. As the patient matures, they should take a more active role in their care. Special training sessions may be warranted to teach the patient a skill, or convey detailed information that they were not ready to receive during the initial training period. Education and training of the patient and family is a continual process of assessment, planning, teaching, and evaluation.

Care Implementation

Expectations regarding the roles of staff and patients, in relationship to care management, should be clearly outlined and discussed when the patient starts dialysis. Patients receiving treatments in the unit are seen frequently, and so it is easy for staff to assess their needs and provide care. This is more difficult in the home setting where we must rely on patient or family assessments and information. Phone contacts are commonly used to share information and problem-solve situations. However, other means of communicating, such as e-mailing or phone texting, are effective. Contact with the family should occur at least every 2 weeks, and more often if problems occur.

At routine intervals, the patient/family need to be seen in the clinic so the professional staff can assess their current medical status. During this visit, the patient and family meet individually with members of the multidisciplinary team. In this setting, the patient is assessed, medications, diet, laboratory tests and home records are reviewed, and any problems or concerns are addressed. This is also a time when reeducation can occur and transition goals can be updated.

It is important for the multidisciplinary team to meet routinely to review patient data and assure the delivery of consistent care [50, 62]. This care conference allows the team to candidly discuss the patient's health status and update the plan of care. In addition to this, the multidisciplinary team must meet and conduct an in-depth review with the patient and family at least annually. This family conference allows everyone to review the patient's status for the past year and involves the patient and family in establishing care goals. Additional family conferences may be scheduled anytime the family or medical team feels it is necessary.

Meeting with the patient and family outside of the hospital setting can be advantageous. A home visit provides an opportunity for the patient and family to speak in a more relaxed and familiar setting. Other activities such as camp, support groups, and holiday parties take place outside the clinic and provide a valuable opportunity for patients and families to socialize and share common experience and concerns. These also provide an opportunity for both the patients/families and staff to interact with each other in a venue outside of the medical setting.

Habilitation

Promoting normalcy and age-appropriate activities should be incorporated in all health care activities in pediatrics. School attendance and participation in activities is normal for children. In order to support the philosophy of habilitation, the multidisciplinary team must work with the school and family to assure that the patient can participate in as many school activities as possible. Teachers, teacher aides, or volunteers should be utilized to help hemodialysis patients with homework during their treatments. All hemodialysis schedules should be as flexible as possible to minimize time missed from school or school activities. The school teachers, principal, and school nurse need to be aware of any physical limitations and the need for excused absences for clinic visits. For some patients, it is beneficial for hospital staff to make a school visit to speak to the class about dialysis and kidney failure. Young school-aged children are especially receptive to this idea. Absences from school can become a problem. The child can quickly learn that if he voices a physical complaint, he may be allowed to stay home from school. If absences become a repeated problem, the medical team can help evaluate the validity of the situation and work with the family to develop a plan to increase school attendance.

Transition

Transition from adolescence to adulthood is a challenging yet important developmental progression for all children. Patients with CKD must deal with not only the challenges of this transition time, but are also forced to handle additional challenges as we prepare to move them from a health care setting that they are familiar with to a very different adult health care system. As mentioned earlier, chronic illness during childhood and adolescence can adversely affect normal maturation. Missed school and extracurricular activities, over-protection from parents, frequent visits to dialysis units or hospitals, and dependency on dialysis equipment and health professionals all compound to have a negative impact on our patients. Recent quality-of-life studies indicate that children on dialysis have lower self-esteem, and an increased incidence of depression, behavior disturbances, dependency on caregivers, poor school performance, lack of higher education or vocational training, cognitive delays, separation anxiety disorders, and poor social adjustments and peer relationships [63]. With this in mind, it is crucial that pediatric dialysis facilities have a detailed plan for transitioning their patients to an adult facility. A variety of issues should be addressed in such a plan (Table 4.9). An extensive discussion of transition is in Chap. 35.

Table 4.9 Transition topics for patient education

Patient-specific medical condition(s)
Medications including significance, doses
Laboratory tests – significance and interpretation
Dietary restrictions
Sexual health and high-risk behaviors
Educational/vocational plans
Medical complications – anemia, bone disease, hypertension, etc.
Maintaining appropriate health coverage – insurance
Ownership of health care – self-care

Quality Improvement

All facilities must develop, implement, and maintain a data-driven continuous quality improvement (CQI) program. The goal of a CQI program is to continually improve both patient outcomes and system efficiency. This is accomplished by reviewing certain aspects of the care we provide or evaluating the services that we provide. There are numerous things that can be monitored. Treatment adequacy, infections, access failures, and morbidity and mortality rates are just a few things that can be monitored in dialysis CQI programs. In the United States, there are also mandated regulatory requirements that must be monitored. Patient/family complaints and satisfaction should also be a part of your CQI plan. Characteristics or attributes of "good patient care" are viewed differently by professional staff and patients/families. Reviewing patient surveys can offer insight regarding the services you provide.

Benchmarking is another way to review the status of your program and can be a valuable tool for your CQI program. Benchmarking databases provide you with the ability to compare your outcomes to those in other centers while also providing consensus information which can help you establish appropriate target ranges for the outcomes you are monitoring. The International Pediatric Peritoneal Dialysis Network (IPPN) allows participants to view benchmark data for peritoneal dialysis care, and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) offers pediatric benchmarking of outcome data for all stages of CKD, transplant, and dialysis. These two databases house a wealth of information that can assist a program in the identification of areas in need of improvement or areas of high achievement.

References

1. Molzahn AE. Creating caring organization cultures in dialysis units. ANNA J. 1997;24:247–53.
2. Barnum BS, Kerfoot DM. The nurse as executive. Maryland: Aspen Publishers, Inc.; 1995.
3. Wellman J. Simple truths about staff retention. Provider. 2002;28:75–9.
4. Federal Register. Conditions for coverage of suppliers of end-stage renal disease (ESRD) services, subpart U. Health Care Financing Administration. HHS – Subchapter B – Medicare Program; 1996.
5. Burrows Hudson S, Prowant BF (Eds). Nephrology Nursing Standards of Practice and Guidelines for Care. Pitman, NJ: American Nephrology Nurses' Association; 2005.
6. Westlake Jr P. SAFE (strategy, assessment, flexibility, and efficiency) for future use? Stages in master planning, programming, and architectural design. J Ambul Care Manage. 1995;18:58–68.
7. Mathena KA. Nursing manager leadership skills. Int Nurs Rev. 2002;32:136–42.
8. Schwartz T. Life/Work. Fast Company, 2000. www.fastcompany.com/magazine/40/tschwartz.html
9. Meadows J. Destination nursing. Creating a destination hospital for nurses. Washington, DC: Nursing Executive Center; 2002.
10. Gelinas L, Bohler C. A prescription for staff retention. Clin Syst Manage. 2002;4:14–19.
11. High S. The ABC's of staff retention. J Med Pract Manage. 2001;17:93–6.
12. Neumann ME. Starting from scratch. What makes the ultimate dialysis facility? Nephrol News Issues. 1997; 11:31–2.
13. Riesz NJ. Keeping employees in place; your place. Clin Leadersh Manag Rev. 2002;16:109–12.
14. Anderson P, Pulich M. Retaining good employees in tough times. Part III: five more strategies for retention. Health Care Food Nutr Focus. 2001;17: 10–12.
15. Bame SI. Organizational characteristics and administrative strategies associated with staff turnover. Health Care Manage Rev. 1993;18:70–86.
16. Bednar B, Haight D, Street J. State-mandated staffing ratios within ESRD: benefits and costs. Nephrol News Issues. 2003;17(5):51–2.

17. Aiken LH, Clarke SP, Sloane DM, et al. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 2002;288:1987–93.
18. Saran R, Bragg-Gresham JL, Rayner HC, et al. Nonadherence in hemodialysis: associations with mortality, hospitalizations, and practice patterns in the DOPPS. Kidney Int. 2003;64:254–62.
19. Fissell RB, Bragg-Gresham JL, Woods JD, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int. 2004;65:2335–42.
20. Thomas-Hawkins C, Flynn L, Clarke SP. Relationships between registered nurse staffing, processes of nursing care, and nurse-reported patient outcomes in chronic hemodialysis units. Nephrol Nurs J. 2008; 35(2): 123–30. 145.
21. Rogers AE, Hwang W, Scott LDL, et al. The working hours of hospital staff nurses and patient safety. Health Aff. 2004;23:202–12.
22. Estabrooks CA, Cummings GG, Olivo SA, et al. Effects of shift length on quality of patient care and health provider outcomes: systematic review. Qual Saf Health Care. 2009;18:181–8.
23. Lockley SW, Barger LK, Ayas NT, et al. Effects of health care provider work hours and sleep deprivation on safety and performance. Joint Comm J Qual Patient Saf. 2007;33:7–18.
24. Czeisler C. It's time to reform work hours for resident physicians. Sci News. 2009;177:36.
25. Association of Operating Room Nurses. AORN guidance statement: safe on-call practices in perioperative practice settings. AORN J. 2005;81:1054–7.
26. Brownbridge G, Fielding DM. Psychosocial adjustment to end-stage renal failure: comparing haemodialysis, continuous ambulatory peritoneal dialysis, and transplantation. Pediatr Nephrol. 1991;5: 612–16.
27. Brownbridge G, Fielding DM. Psychosocial adjustment and adherence to dialysis treatment regimens. Pediatr Nephrol. 1994;8:744–9.
28. Tsai TC, Liu SI, Tsai JD, et al. Psychosocial effects on caregivers for children on chronic peritoneal dialysis. Kidney Int. 2006;70:1983–7.
29. Watson AR. Stress and burden of care in families with children commencing renal replacement therapy. Adv Perit Dial. 1997;13:300–4.
30. Reynolds JM, Garralda ME, Jameson RA, et al. How patients and families cope with chronic renal failure. Arch Dis Child. 1988;63:821–6.
31. MacDonald J. Chronic renal disease: the mother's experience. Pediatr Nurs. 1995;21(6):503–7.
32. Middleton D. A discursive analysis of psychosocial issues: talk in a "parent group" for families who have children with chronic renal failure. Psychol Health. 1996;11:243–60.
33. Nicholas DB. Meanings of maternal caregiving: children with end stage renal disease. Qual Health Res. 1999;9:468–78.
34. Reichwald-Klugger E, Tieben-Heibert A, Korn R, et al. Psychosocial adaptation of children and their parents to hospital and home hemodialysis. Int J Pediatr Nephrol. 1984;5:45–52.
35. Aldridge MD. How do families adjust to having a child with chronic kidney failure? A systematic review. Nephrol Nurs J. 2008;35:157–62.
36. Madden S, Ledgermann SE, Guerrero-Blanco M, et al. Cognitive and psychological outcome of infants dialyzed in infancy. Child Care Health Dev. 2003; 29:55–61.
37. Penkower L, Dew MA, Ellis D, et al. Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. Am J Transplant. 2003;3:1418–25.
38. Henning P, Tomlinson L, Ridgen S, et al. Long term outcome of treatment and end stage renal failure. Arch Dis Child. 1988;63:35–40.
39. Furth SL, Hwang W, Neu AN, et al. Effects of patient compliance, parental education and race on nephrologists' recommendations for kidney transplantation in children. Am J Transplant. 2003;3:34.
40. Grossman M. The role of the pediatric nephrology nurse in the dialysis unit. In: Fine R, Gruskin A, editors. End-stage renal disease in children. Philadelphia: WB Saunders Co.; 1984.
41. Counts CS. Core Curriculum for Nephrology Nursing. (5th ed). Pitman, NJ: American Nephrology Nurses' Association; 2008.
42. Nissenson AR, Fine RN. Dialysis therapy. Philadelphia: Hanley & Belfus, Inc.; 1993.
43. Nissenson AR, Gentile D. Clinical dialysis. Norwalk: Appleton & Lange; 1995.
44. Warady BA, Alexander SR, Balfe JW, et al. Peritoneal dialysis in children. In: Gokal R, Khanna R, Krediet RT, et al., editors. Textbook of peritoneal dialysis. Boston: Kluwer Academic Publishers; 1994.
45. Farina J. Peritoneal dialysis: a case for home visits. Nephrol Nurs J. 2001;28:423–8.
46. Zinn A. A self-care program for hemodialysis patients based on Dorothea Orem's concepts. J Nephrol Nurs. 1986;3:65–77.
47. Turner K. Orem's model and patient teaching. Nurs Pract. 1994;3(50):32–3.
48. Bartlett J, Jones L, O'Sullivan D. Teaching strategies for patients and staff. Kansas City: Children's Mercy Hospital, Education Department; 1997.
49. Laird D. Approach to training and development. Reading: Addison-Wesley; 1985.
50. Shurr M, Roy C. Components of a successful home dialysis program. Nephrol Nurse. 1980;2:51–60.
51. Doak CC, Doak LG, Root JH. Teaching patients with low literacy skills. Philadelphia: Lippincott; 1996.
52. Aldridge MD. Writing and designing readable patient education materials. Nephrol Nurs J. 2004;41: 373–7.

53. McLaughlin GH. SMOG grading-a new readability formula. J Reading. 1969;12:639–46.
54. Devraj R, Gordon EJ. Health literacy and kidney disease: toward a new line of research. Am J Kidney Dis. 2009;53:884–9.
55. Harrison CG. Developing an instructional program for ESRD patients. A team approach. J Nurs Staff Dev. 1986;2:144–9.
56. Burkart JA. Training nurses to be teachers. J Contin Educ Nurs. 2008;39:503–10.
57. Davis BG. Tools for teaching. San Francisco: Jossey-Bass; 2009.
58. Kennedy L. PD Trivia: making learning fun. CANNT J. 2006;16(3):46–8.
59. Parran L. The nursing shortage: part 2. Healthcare facilities take innovative approaches to recruitment and retention. ONS News. 2002;17:1–7.
60. Whaley WD. Whaley & Wong's: nursing care of infants and children. St. Louis: Mosby; 1995.
61. Betz CL. Teaching children through play therapy. AORN J. 1983;38:709–24.
62. Oberley ET, Leva R, Jorgensen LM. Ingredients of a successful home hemodialysis program. Part II. Nephrol News Issues. 1992;6:23–4. 26.
63. Goldstein SL, Gerson AC, Goldman CW, et al. Quality of life for children with chronic kidney disease. Semin Nephrol. 2006;26:114–17.

Dialysis in Developing Countries

5

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Keywords
Dialysis • Pediatric • Developing countries • Peritoneal dialysis

Introduction

It is difficult to estimate the number of children requiring dialysis in the developing world. In addition to the regional differences and the criteria for diagnosis, an important reason is the lack of adequate pediatric nephrology services across most developing counties. Furthermore, there are considerable differences in the number of patients with end-stage renal disease (ESRD) who receive any form of renal replacement therapy (RRT). For example, less than 5–10% of children diagnosed with ESRD in India receive dialysis and/or transplantation [1].

Kidney transplantation is considered the goal for children with ESRD. The need for donors and long-term treatment with immunosuppressive medications, and lack of state funding are major impediments toward an active transplant program. In contrast to developed countries where dialysis is a satisfactory long-term alternative form of therapy, most developing countries have had problems in organizing satisfactory dialysis services. Techniques of peritoneal dialysis (PD) and hemodialysis (HD) have been available in these regions for adult patients for more than four decades, but their application for children has lagged behind. The reduced accessibility to dialysis in children has been attributed to lack of expertise, experience and equipment, and relatively high costs. Nevertheless, over the last two decades, dedicated facilities for PD and more recently HD are becoming increasingly available for children.

Developing Countries

The World Bank [2] divides countries into three income groups on the basis of their gross national income (GNI) per capita: high (per capita GNI equivalent to US$ 11,906 or more), middle ($976–$11,905), and low ($975 or less). The latter two, comprising almost 100 countries, are collectively called "developing". Almost 80% of the world population of about 7 billion lives here. More than 1.4 billion people subsist on less than $1/day and almost half the population lives on less than $2.50 a day.

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The economic, human, and technical resources required for the treatment of ESRD make it a major health challenge. While indigenous healthcare delivery systems are popular in rural Africa and Asia, hospitals providing quality care are located in big cities. A major proportion of healthcare budgets for children are focused toward common causes of morbidity and mortality, including acute gastroenteritis, lower respiratory tract infections, and vaccine preventable diseases.

Patients attending government or public sector hospitals do not have to pay for consultation and basic management, but they need to bear the costs of sophisticated investigations (e.g., nuclear imaging, ultrasound, CT scan), medications, and disposables required for dialysis or surgery. These hospitals often lack infrastructure in terms of manpower and resources for taking care of the referred patients. The limited availability of high-quality advanced care in government centers results in patients seeking care through private and corporate hospitals where the patients pay for all services, either through "out of pocket" expenses or medical insurance.

Attempts have been made to recruit the community for supporting ESRD management in some geographic areas. For example, a major dialysis and transplant center in Pakistan [3], the Sindh Institute of Urology and Transplantation (http://www.siut.org), is funded by philanthropic individuals and corporate bodies, with the government providing limited funding. Similar sustainable models exist elsewhere.

Lack of Trained Manpower

The burden of acute and chronic kidney disease in children in the developing world is largely unrecognized. Where available, most programs focus on the problems of diabetes and hypertension in adults with chronic kidney disease. Children have limited access to all forms of renal replacement therapies. These limitations are further compounded by very few opportunities for advanced training of medical personnel in pediatric nephrology and dialysis. Over the past years, pediatric academic societies in a number of countries have assumed the responsibilities for education, training, and certification in Pediatric Nephrology. Recognizing the shortage of trained professionals in developing countries, the International Pediatric Nephrology Association has taken unique initiatives for developing and standardizing short-term training programs in these regions. International collaborations, through the IPNA, have resulted in specialty training for pediatricians, at specialized centers within their countries, in South and South East Asia, Africa, and South America.

This chapter focuses on specific issues encountered during development and operation of pediatric PD and HD services in developing countries.

Peritoneal Dialysis

The application and use of PD for children in developing countries began in 1970–1980. Because of its convenience, efficacy and safety, these facilities are now available in most countries, and play an important role in the treatment of childhood acute kidney injury (AKI). During the late 1980s, application of PD for ESRD in children in China was limited since a two-bag system was unavailable, resulting in high incidence of peritonitis and peritoneal membrane failure. With better technologies and techniques, and improved economic status, chronic ambulatory peritoneal dialysis (CAPD) is increasingly being implemented in major cities, including Shanghai, Guangzhou, and Beijing. The estimated number of children currently treated by chronic PD in China is 100. Similarly a database, maintained by a leading dialysate provider in India, shows 145 children on maintenance CAPD in India. These data are an underestimate, since there are more than one dialysis provider, and many older children and adolescents are cared for by "adult" nephrologists. Compared to the number of children in chronic PD, facilities for HD are even more limited. For example, the city of New Delhi has two dedicated pediatric HD units for a population of 8 million children.

Acute Kidney Injury

Systemic infections (complicated by multiple organ dysfunction), nephrotoxic medications, and primary renal disorders (hemolytic uremic syndrome, acute glomerulonephritis) are the leading causes of AKI in Chinese children. AKI is a common and serious complication following major surgeries, including those for complex congenital heart defects. Reports from other countries suggest that the causes of AKI in children are, except for some minor differences, similar across the world [4]. The application of adequate PD, which effectively corrects the fluid and electrolyte imbalance, is life saving for children [5].

Techniques

The indications for acute PD include hyperkalemia (K>6–6.5 mEq/L), azotemia, and fluid overload. For acute PD, stiff polyurethane catheters continue to be used in many centers. These are convenient to insert and inexpensive, but associated with risk of visceral trauma and infections. These catheters require removal after 48–72 h; prolonged stay is associated with a high risk of peritonitis. Currently, the soft Tenckhoff catheter with single cuff is most often used for acute PD. Several models of Tenckhoff catheter are available, with varying lengths of the intraperitoneal segment, which can be used even in neonates and young infants. Dialysates containing 1.5% glucose acetate or lactate are manufactured in many countries; production of solutions for CAPD is limited. Standard solutions (e.g., Baxter dialysis solutions) need to be imported and are more expensive.

The dialysate fill volume is 30–50 mL/kg, dwell time 45–60 min, and with 8–10 exchanges/day. Generally, 1.5% and 2.5% dextrose dialysate and, less commonly, 4.25% high-osmolarity peritoneal solution are used. The chief complications of acute PD include peritonitis in 20–30%, and dialysate leak or catheter blockage that requires reinsertion of catheter. The duration of dialysis depends on the severity of the illness, and generally lasts for 3–7 days, but might be longer in patients with severe acute tubular or cortical necrosis or crescentic glomerulonephritis.

In developing countries, PD is widely used for renal replacement in patients with AKI. However, it has been supplanted in recent years by HD and, recently, by hemofiltration. A randomized trial compared acute PD with hemofiltration in Vietnamese adult patients with acute renal failure, related to falciparum malaria or sepsis. The rate of resolution of acidosis and decline of creatinine was faster, and the mortality rates significantly lower in the group managed by hemofiltration [6]. While these results suggest that hemofiltration is superior to PD in adults with infection-associated acute renal failure, similar differences were not found in other studies.

Data on current practices, in developing countries, for renal replacement therapy in patients with AKI is unavailable. A survey in 2009, on 26 centers in India, on modes of renal replacement therapy for children with AKI found that a facility for acute intermittent PD was available at all centers. Facilities for intermittent HD and continuous renal replacement therapy were available in 86% and 17% centers, respectively. PD was the predominant modality (accounting for more than 80% of all dialysis) in 14 of the 22 centers, while four centers used HD more than PD. Dedicated facilities for pediatric HD were available in two centers. Factors considered important in choosing the mode of RRT were: patient size; presence or absence of hemodynamic instability; duration of AKI; severity of metabolic imbalance or fluid balance; and socioeconomic status of the care receiver (Vasudevan, unpublished).

The outcome of patients with AKI depends on its underlying etiology. Whereas the outcome of PD in neonates and patients with septicemia, multiple organ dysfunction and post-cardiac surgery patients is unsatisfactory, outcomes of AKI secondary to administration of nephrotoxic agents, acute glomerulonephritis, and intravascular hemolysis are better.

End-Stage Renal Disease

PD has been available since the 1980s, and is currently the therapy of choice for children with ESRD in the majority of developing countries [7, 8].

Etiology

Data from Children's Hospital of Fudan University shows that the chief causes of chronic renal failure include glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis (FSGS), renal dysplasia, reflux nephropathy, and polycystic kidney disease. A similar etiological profile, comprising obstructive uropathy, reflux nephropathy, glomerulonephritis, FSGS, and renal hypoplasia/dysplasia, is reported from other developing countries [1]. Prospective data from a National Registry on Chronic Kidney Diseases in India [http://www.ckdri.org] shows that the chief causes of CKD in children include obstructive uropathy (25%), reflux nephropathy (20%), and chronic glomerulonephritis (14%). The data from this Registry represents the tip of the iceberg, as most patients report to nephrologists beyond stage 4 CKD. More than 70% of patients with CKD stage 5 patients are not on any form of renal replacement therapy.

Initiating Dialysis

The indication for initiating renal replacement therapy is GFR ≤10–15 mL/min/1.73 m^2. In Children's Hospital of Fudan University, only 30% of dialysis patients had been followed up from the early stage of chronic kidney disease. Most patients presented for the first time with ESRD, often with marked oliguria and symptoms of uremia.

Procedure

Straight Tenckhoff catheters with a double cuff are commonly used. Although preferred, curled catheters are not easily available. In view of its simplicity and lower cost, CAPD is currently the preferred dialysis mode for children with ESRD in developing countries.

Training Professional Dialysis Nurses and Parents

Appropriate training of dialysis nurses and parents of patients is important to ensure quality of long-term PD. The centers should have the infrastructure to enable continued practical training for nursing staff and parents. Dialysis nurses should carry out regular home visits, and examine the environment and condition of dialysis at home.

Risk of Infections

Peritonitis is the most common complication of chronic PD. Infection rates in patients followed up at the Hospital of Fudan University are higher (annualized rate of 0.96) than reported elsewhere. Recurrent episodes of bacterial peritonitis often require catheter removal and replacement. A major challenge in developing countries is to provide adequate opportunities for education and training for nursing professionals and parents of young children, emphasizing the importance of sterile precautions and early recognition of peritonitis.

Nutrition, Growth, and Development

Nutrition has an important impact on promoting growth and development. In contrast to the industrialized world where malnutrition is rare and replaced by obesity as the primary nutritional problem in children on PD, the role of malnutrition in the developing world cannot be overemphasized. Chronic systemic illnesses and prolonged PD result in anorexia, loss of protein in the dialysate and hormonal imbalance, leading to malnutrition and delayed development. These biological mechanisms may combine with inadequate quantitative and qualitative food availability depending on economical constraints and cultural habits.

Children on PD require assessment of dietary intakes, and monitoring growth and development and nutritional counseling. The importance of ensuring adequate dialysis and improving intakes through nasogastric or gastrostomy feedings cannot be overemphasized. The use of amino acid–containing dialysis solutions and administration of recombinant human growth hormone is limited by their cost and availability.

Development of Peritoneal Dialysis Services

Constraints toward the development of an effective program for maintenance PD in developing countries include [9]:

1. *Delayed referral.* Most patients with CKD present late with oligoanuria and complications of renal failure, and require emergency HD. Only a fraction of patients are diagnosed early and provided with regular counseling and follow-up. The lack of prior communication results in an unpreparedness in parents, adversely affecting patients' outcomes. A regular follow-up that begins in early stages of CKD is likely to improve satisfaction, and reduce fear and anxiety concerning long-term dialysis, making families adhere to therapy.
2. *Lack of education.* Physicians, pediatricians, and parents need to be provided with appropriate knowledge regarding the benefits, limitations, and complications of maintenance ambulatory PD. There is clearly a need to enhance, among medical professions, the understanding regarding the role of CPD in patients with end-stage kidney disease.
3. *Limited adherence to therapy.* Adherence to therapy affects the quality of PD, including maintaining sterility during procedure, ensuring adequate numbers of cycles, and compliance with advice on medications and diet. While the lack of adherence is usually attributed to unsatisfactory living conditions and reduced exchanges to cut costs, dialysis units must provide opportunities for education and retraining, and follow-up care.
4. *Costs of dialysis.* Economic factors have an important impact on the development of childhood PD. Lack of state insurance limits the availability of CAPD for children in most developing countries. The cost of managing a patient on CAPD, in China and other developing countries, is far in excess of the family *per capita* income. Since dialysate bags of 1 L capacity are not available in many parts of the world, standard "adult" bags (2 L capacity) are used, resulting in wastage of dialysis fluid and increased cost.

The average cost of CAPD for children in China and India varies between 350 and 400 USD/month. Taking into consideration the cost of the cycler and other consumables, APD is likely to impose an additional cost of 300–550 USD/month in these countries, making this therapy unaffordable for most households. Initiatives by local governments and nongovernmental organizations aim to support the therapy of children with chronic kidney diseases. Whereas most dialysate fluid is imported, pharmaceutical companies in India, China, and other countries are increasingly involved in its indigenous manufacture. However, these manufacturers need to invest for stringent quality control of dialysate solutions, manufacture compatible cyclers, and develop a network of distribution centers with trained technical and nursing staff.

Hemodialysis

Provision of pediatric HD requires a specialized and integrated health-care team to manage the medical, nursing, nutrition, development, and psychosocial aspects of care for children with ESRD. It is recommended that children be hemodialyzed in dedicated pediatric dialysis units, with a multidisciplinary support team, which supports individualized and integrated therapy. Since the expense and commitment in terms of manpower and equipment required for such units is considerable, with few exceptions, children in most developing countries, especially in Asia, are dialyzed in adult units. Most centers are located in cities, are in the private sector, and have limited accessibility to all sections of the society. Children bear the brunt of lack of dedicated HD services.

Vascular Access

An effective vascular access is necessary for chronic HD, through internal arteriovenous fistulae (AVF), shunt (AVS), graft (AVG), or

central venous catheter [10]. While creation of a functional AVF, either at the wrist or elbow, is the optimal vascular access for chronic HD, few surgeons have expertise for vascular microsurgery in small children. The benefits of AVF include lower rates of infection, thrombosis and stenosis, and greater freedom with regards to activity. Permanent vascular access of an AVF or AVG can function for many years and is preferred over indwelling catheters in children and adults. The central venous catheter is a suboptimal choice for vascular access and should be considered as a bridge to a more permanent vascular access.

The type of access used often depends on local expertise and experience, patient age and size, the time available before dialysis is planned to begin, and the presumed waiting time before transplantation [11]. In most centers, a central venous, double lumen catheter is the initial choice, particularly in AKI or chronic renal failure with acute presentation, in small children, and in the cases where an early transplantation or transition to CAPD is planned. Although access through internal jugular vein is preferred, the femoral route is used in subjects requiring urgent dialysis. Increasing experience, adherence to standard protocols, and the use of antibiotic lock therapy have resulted in considerable decline in the risk of infections, thrombosis, and other complications.

HD Machines and Dialyzers

While most centers in large cities use up-to-date models of HD machines, economic constraints force units to use outdated equipment, or have refurbished machines received as donations. Erratic power supply, insufficient funds for preventive maintenance, and lack of trained service engineers result in repeated breakdowns. There is limited availability of newer-generation dialyzers made of biocompatible membranes such as polysulfone and polymethylmethacrylate. The incidence of anaphylactoid, complement-mediated immediate membrane reactions is far lower with the latter. Dialyzer reuse is routine, although reprocessing is done manually. These practices result in inadequate dialysis, pyrogen reactions, and repeated episodes of sepsis.

Dialysis Prescription

In view of delayed diagnosis and limited availability, the initiation of dialysis is usually delayed until patients are in a state of advanced uremia and have developed complications [12]. A majority receive fewer than 12 h/week of dialysis [13]. While the prevalent practice in most adult HD units is to give two 3–4-h sessions of dialysis every week, children managed in pediatric units usually receive three sessions a week. However, the duration of dialysis is often cut short to accommodate more patients.

Dialysis Cost

Compared to the developed world, maintenance HD is less expensive in developing countries. The annual costs for maintenance HD in the latter are less than US$8,000–12,000, chiefly due to lower staff salaries and cheaper consumables [14]. Private hospitals charge a fixed amount from the patient for each dialysis session, varying between US$15 and $50. The cost of HD in public-funded hospitals is a fraction of the above. For patients with ESRD on maintenance HD, approximately 30–50% of the total cost of treatment is spent on medications and 40–60% on the dialysis procedures. In many public-funded hospitals in India, HD is offered only to those planned for renal transplantation. Except in a few countries, government- or insurance-funded HD facilities for children continue to be limited.

Comorbidities on Dialysis

There is limited data on the morbidity and outcomes of maintenance dialysis in children. Most data in this regard is therefore based on information from adults.

Infections

Infections are an important cause of morbidity and mortality in patients on maintenance dialysis. A combination of unsatisfactory living conditions, inadequate dialysis, malnutrition, and frequent blood transfusions is responsible for the high frequency of infections. Based on data in adults, infections and cardiac diseases were the chief causes of death in dialyzed patients [12, 15]. Infection rates are higher in government-funded hospitals that cater to patients from the lower socioeconomic groups. *Staphylococcus aureus* and gram-negative bacilli are the commonest organisms. The incidence of catheter-related *S. aureus* infection has risen in recent years. Respiratory and urinary tracts are the other common sites of infection. Patients often present late with septicemia and/or multiple organ failure.

Tuberculosis

Tuberculosis is endemic in several developing countries. Impaired cell-mediated immunity further increases the susceptibility to tuberculosis among the dialysis population. The incidence of tuberculosis in adult dialysis patients varies from 4% to 9% in developing countries in Asia [12, 16]. The usual sites of disease are pleuropulmonary and lymph node. Demonstration of acid-fast bacilli is difficult and the tuberculin test is not helpful in making the diagnosis, because of its high positivity in the general population and cutaneous anergy in patients with azotemia. Therapy of patients with tuberculosis consists of a combination of isoniazid (INH), rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by INH and rifampicin for next 7–10 months. INH and ethambutol are excreted by the kidneys and require dose modifications in dialyzed patients. The role of INH prophylaxis in prevention of tuberculosis in patients on dialysis is controversial. Children detected to be tuberculin positive or with recent history of exposure to a patient with sputum-positive tuberculosis should receive prophylaxis with INH for 6 months.

Hepatitis

Viral hepatitis is among the commonest viral infections encountered in adult dialysis patients. Lack of effective screening of patients and blood products, unsatisfactory isolation practices, frequent transfusions, and failure to vaccinate patients against hepatitis B virus (HBV) are responsible for the high incidence of hepatitis. Because of their limited number, many units do not have dedicated machines for HBV positive individuals and even where machines are so designated, cross-contamination occurs through inadequately trained staff and sharing of disposables. Widespread HBV vaccination as part of their immunization schedules has resulted in a marked decline of the risk of infection with this agent.

Currently, hepatitis C virus (HCV) is the most common cause of viral hepatitis among dialyzed patients. Cross-contamination in the dialysis units, rather than transfusion of infected blood products, is the most important source of infection. HCV infection has greater significance than HBV because of the nonavailability of a vaccine for the former. The prevalence of anti-HCV positivity in adult dialyzed patients ranges from 10% to 80% [17, 18]. The genotypes reported include 1a, 1b, 2a, 3a, and 4 [19, 20]. While the Centers for Disease Control (US) does not recommend isolation of anti-HCV positive patients in dialysis units, many "adult" units in developing countries with high rates of HCV positivity have dedicated machines for exclusive use by HCV-positive patients. This strategy has significantly reduced seroconversion rates in adult dialysis units in India from 36.2% to 2.8% [21].

Human Immunodeficiency Virus (HIV)

HIV infection is not a major problem in dialyzed children in developing countries. There is also limited data on the proportion of dialyzed patients who are infected with HIV, in African countries with high positivity rates. The reported prevalence of this infection in dialysis units varies from 0.5% to 2% [22]. HIV-positive patients

either discontinue dialysis on their own or are refused further care by the dialysis units. Given the threat of an exponential increase in the numbers of HIV-positive patients, including children, it is anticipated that many such patients would develop ESRD and require dialysis.

Nutrition

Malnutrition is an important cause for morbidity and mortality in patients on maintenance dialysis. Almost 75% of children with ESRD in India show features of moderate-to-severe malnutrition at presentation [1]. In a study in adult patients from New Delhi, 77% of patients were hypoalbuminemic [23] with the average serum albumin 2.4 g/dL at initiation of dialysis program. Delay in initiation and delivery of inadequate dialysis play important roles, and patients often continue on a low-protein diet for want of proper dietary advice. Protein energy malnutrition leads to decrease in cell-mediated immunity, increases the incidence of infections, worsens metabolic bone disease, and prevents development of adequate antibody response to vaccines.

Conclusions

The choice of renal replacement therapy is chiefly determined by its availability, local expertise, and affordability. CPD provides an opportunity to extend effective dialysis therapy to infants and young children with ESRD. It also provides a growth and nutrition advantage over HD, and preserves residual renal function. The availability of HD is often limited to urban tertiary care centers. On the other hand, CPD being a simpler technique has the potential to cater to a much larger population including those staying far from the urban health-care centers. The last few years have witnessed significant technical advances in CPD such as improved connecting systems and provision of PD cyclers. For these reasons, chronic PD is being increasingly utilized as a safe and effective mode of renal replacement in children. The major concerns limiting the widespread application of CPD for children in developing countries include limited local production of dialysate fluid, nonavailability of smaller dialysate bags, and thus the high cost of therapy. CPD also requires substantial commitment on the part of the family and caretakers, compared to a rather passive role of bringing the child to a HD center.

Automated PD and HD machines with precise control of ultrafiltration and continuous volume monitoring, physiologically compatible dialysate, and biocompatible dialyzers have ushered in a technological revolution in management of children with ESRD. Integrated care with emphasis on nutrition, growth and development, and mineral bone disease, and the optimized use of erythropoietin and growth hormone have led to improved somatic growth, better cardiac function and quality of life for children. However, the practice of these therapies for children in developing countries is determined by expertise and experience of the physicians and prevailing socioeconomic conditions. It is necessary that pediatricians in developing countries acquire the requisite knowledge and skills to meet the specific needs of children on renal replacement therapy.

References

1. Hari P, Singla IK, Mantan M, Kanitkar M, Batra B, Bagga A. Chronic renal failure in children. Indian Pediatr. 2003;40:1035–1042.
2. http://web.worldbank.org/
3. Rizvi A, Aziz R, Ahmed E, Naqvi R, Akhtar F, Naqvi A. Recruiting the community for supporting the end-stage renal disease management in the developing world. Artif Organs. 2002;26:782–784.
4. Cerdá J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. Nat Clin Pract Nephrol. 2008;4:138–153.
5. Tu X, Chen WX, Jiang N, Liu XL. Nursing care for infants with acute renal failure after cardiac surgery treated by peritoneal dialysis. J Nursing Sci. 2009; 124:35–36.
6. Phu NH, Hien TT, Mai NTH, Chau TTH, Chuong LV, Loc PP, Winearls C, Farrar J, White N, Day N. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med. 2002;347:895–902.

7. Cao Q, Xu H, Zhou LJ, Huang WY, Shen Q, Wang QL. Effect of adequacy of peritoneal dialysis on nutritional status in children with peritoneal dialysis. J Appl Clin Pediatr. 2007;22:1323–1324.
8. Cao Q, Xu H, Zhou LJ, Sun L, Rao J, Wang QL. Application of automated peritoneal dialysis in 7 children with chronic renal failure. J Nephrol Dial Trans. 2005;14:536–539.
9. Wang T, Wang HY. The problem and prospect in the development of Chinese peritoneal dialysis. Chin J Intern Med. 2003;42:757–759.
10. Chand DH, Valentini RP, Kamil ES. Hemodialysis vascular access options in pediatrics: considerations for patients and practitioners. Pediatr Nephrol. 2009;24:1121–1128.
11. Hari P, Kanitkar M, Mantan M, Bagga A. Hemodialysis in children. Indian Pediatr. 2002;39:375–380.
12. Jha V, Chugh KS. The practice of dialysis in the developing countries. Hemodial Int. 2003;7:239–249.
13. Barsoum R. Overview: end-stage renal disease in the developing world. Artif Organs. 2002;26:737–746.
14. Jha V, Chugh KS. Management of end stage renal failure around the world: impact of economic development. In: Rashid HU, editor. South Asian renal disease. New York: Marcel Dekker Inc.; 1997. p. 317–325.
15. Mazzuchi N, Schwedt E, Fernandez JM, Cusumano AM, Ancao MS, Poblete H, Saldana-Arevalo M, Espinosa NR, Centurion C, Castillo H, Gonzalez F, Milanes CL, Infante M, Ariza M. Latin American registry of dialysis and renal transplantation: 1993 annual dialysis data report. Nephrol Dial Transplant. 1997;12:2521–2527.
16. Zhang X, Hou F, Wei D. Tuberculosis in chronic renal failure patients with or without renal replacement therapy. Chung Hua Nei Ko Tsa Chih. 1995;34:666–669.
17. Johnson DW, Dent H, Yao Q, Tranaeus A, Huang CC, Han DS, Jha V, Wang T, Kawaguchi Y, Qian J. Frequencies of hepatitis B and C infections among hemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. Nephrol Dial Transplant. 2009;24:1598–1603.
18. Huang CC. Hepatitis in patients with end-stage renal disease. J Gastroenterol Hepatol. 1997;12:S236–S241.
19. Noronha IL, Schor N, Coelho SN, Jorgetti V, Romao Junior JE, Zatz R, Burdmann EA. Nephrology, dialysis and transplantation in Brazil. Nephrol Dial Transplant. 1997;12:2234–2243.
20. Bosmans JL, Nouwen EJ, Behets G, Gorteman K, Huraib SO, Shaheen FA, Maertens G, Verpooten GA, Elseviers MM, de Broe ME. Prevalence and clinical expression of HCV-genotypes in hemodialysis-patients of two geographically remote countries. Belgium Saudi-Arabia Clin Nephrol. 1997;47:256–262.
21. Agarwal SK, Dash SC, Gupta S, Pandey RM. Hepatitis C virus infection in hemodialysis: the 'no-isolation' policy should not be generalized. Nephron Clin Pract. 2009;111:c133–140.
22. Sakhuja V, Sud K, Maitra S, Jha V, Sehgal S, Chugh KS. Prevalence of HIV infection in a dialysis unit. Indian J Nephrol. 1994;4:42–44.
23. Saxena S, Jayraj PM, Mittal R, Shukla P, Agarwal SK, Tiwari SC, Dash SC. Clinical and laboratory features of patients with chronic renal failure at the start of dialysis in North India. Indian J Nephrol. 1995;5:4–8.

Part II

Considerations Around the Initiation of Dialysis

The Decision to Initiate Dialysis in a Pediatric Patient

6

Larry A. Greenbaum and Franz Schaefer

Keywords
Hemodiaylsis • Children • Pediatric • Renal Function • Hyperkalemia • Hyperphosphatemia

Overview

The initiation of chronic dialysis in a child is a dramatic event for the patient and family. Dialysis begins a new and often frightening stage of the child's medical care. The urgent need to begin dialysis is obvious in some instances, such as after bilateral nephrectomy or in the child with uremic pericarditis. These are absolute indications for initiating dialysis. In other patients the timing of dialysis initiation is 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 renal function is usually a critical part of this process. In addition, a variety of clinical and laboratory findings are relative indications for commencing chronic dialysis. Some of these relative indications can be managed with medications and dietary counseling, but this approach is not always successful, necessitating the initiation of dialysis.

In the absence of absolute indications, there is no consensus on the appropriate timing of dialysis initiation. There is considerable debate regarding the merits of "early" initiation of dialysis in adults. The data needed to address this issue in children is nonexistent 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.

Children need a systematic plan of monitoring prior to dialysis initiation. Along with optimizing medical care, this allows the early identification of indications for dialysis. Some relative indications for dialysis may be amenable to medical management. For the child who will soon need dialysis, access and training needs can be anticipated, potentially avoiding unnecessary morbidity and expense from emergency initiation of dialysis.

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Methodology for Measuring Renal Function

Assessment of a patient's renal function is useful for determining when to initiate dialysis. In this context, renal function is usually defined as the patient's glomerular filtration rate (GFR). This purposely ignores other aspects of kidney function, such as erythropoietin production and synthesis of calcitriol, because dialysis does not replace these functions. GFR provides an estimate of functioning nephrons, but there are inherent limitations. First, there is an increase in single nephron GFR in chronic renal failure; this allows GFR to be maintained at a higher level than the reduction in functioning nephrons would dictate [1]. GFR may therefore overestimate the functional renal mass. However, for decisions about dialysis initiation this is of limited importance since it is GFR that dictates the need for dialysis. The second issue is that GFR may be transiently affected by a variety of factors other than the intrinsic renal disease. For example, intravascular volume depletion, nonsteroidal anti-inflammatory drugs, and antihypertensive therapy, especially with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin 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 the elimination of the 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 and is impractical clinically. Inulin is ideal for measuring GFR because it is freely filtered at the glomerulus and there is no tubular reabsorption or secretion.

Alternatives to inulin for measuring GFR include radioisotope markers, such as chromium 51-EDTA, iothalamate sodium I^{125} and technetium 99-DTPA [2], and the contrast agent iohexol [3]. These techniques are expensive and require multiple blood draws over 3–4 h, making them less than ideal for frequent monitoring. There is usually a good correlation between inulin clearance and the GFR estimated by radioisotopes, although some studies indicate that the accuracy decreases at low GFR [4]. Single-sample methods, while more convenient, are especially problematic at low GFR [5].

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 CrCl to overestimate GFR. The effect of creatinine secretion is fairly 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 [6]. 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 [7]. 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:

$$\mathrm{CrCl} = \frac{U_{vol} \cdot U_{Cr} \cdot 1.73}{\mathrm{Min} \cdot S_{Cr} \cdot \mathrm{BSA}} \qquad (6.1)$$

where CrCl = 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 (1,440 for 24 h), S_{Cr} = serum creatinine (mg/dL), BSA = body surface area in m^2.

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

An alternative to a standard CrCl is to administer cimetidine to the patient prior to the study.

Cimetidine, by decreasing tubular secretion of creatinine, improves the accuracy of the CrCl in predicting GFR. One study of 53 children showed that a 2 h cimetidine protocol resulted in a CrCl that closely approximated a simultaneous inulin clearance [8].

Urea clearance underestimates GFR because of tubular reabsorption of urea. The calculation of urea clearance requires a timed urine collection and a serum urea concentration:

$$C_{Urea} = \frac{U_{vol} \cdot U_{urea} \cdot 1.73}{Min \cdot S_{urea} \cdot BSA} \quad (6.2)$$

where C_{urea} = Urea clearance (mL/min/1.73 m^2), U_{vol} = Urine volume (mL), U_{urea} = urine urea concentration (mg/dL), Min = collection period in minutes (1,440 for 24 h), S_{urea} = serum urea concentration (mg/dL), BSA = body surface area in m^2.

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 and in adults is quite accurate at low levels of GFR [9, 10].

In children, an estimate of GFR may be calculated from the serum creatinine using an equation [11]. This equation uses patient height and a constant, which may vary based on age and gender to attempt to correct for differences in muscle mass:

$$GFR = \frac{Height\ (cm) \cdot k}{S_{Cr}} \quad (6.3)$$

where GFR = glomerular filtration rate (mL/min/1.73 m^2) and S_{Cr} = serum creatinine concentration (mg/dL). The traditional Schwartz equation uses the following constants: k = 0.55 for boys 2–12 and girls 2–18 years; k = 0.70 for boys 13–18 years; k = 0.45 for children <2 years; k = 0.33 for infants <2.5 kg.

More recently, a study of children with CKD recommends a constant of 0.413 irrespective of age and gender [12]. The decrease in the constant is predominantly secondary to changes in the methodology for measuring creatinine, with the most recent constant based on the enzymatic method for measuring creatinine. The older constant was derived using the Jaffe method. 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 [13–16]. The formulas appear especially problematic in malnourished children and at the low levels of renal function where decisions regarding dialysis initiation need to be made. There are a variety of factors that decrease the accuracy of using 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 and thus creatinine generation is proportional to muscle mass, which varies greatly in children, mostly related to size, but also due to gender, age, and individual differences. In adults there are racial differences in creatinine generation [17].

Children with uremia may lose muscle mass due to malnutrition, possibly reducing the rise in serum creatinine concentration. Spinal cord injury or 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 renal insufficiency due to phosphorus restriction and anorexia. Extrarenal creatinine excretion increases in patients with chronic renal failure [18]. Moreover, tubular creatinine secretion increases as the GFR decreases [6]. 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 chronic renal failure can affect creatinine secretion [7].

The serum protein cystatin C, an endogenous protein, is an alternative to creatinine for estimating GFR [19]. It is unclear whether cystatin C is superior to creatinine for estimating GFR in children, although the combination of cystatin C and creatinine may be used to create more accurate, albeit more complex equations for estimating GFR [12, 19, 20]. However, there is not a general

agreement on the correct constants to utilize for cystatin C estimates of GFR [12, 20, 21], perhaps partially due to differences in methodologies for measuring cystatin C. Additionally, cystatin C is not readily available and is more expensive than serum creatinine.

For adult patients, the Cockcroft–Gault formula is widely used to estimate GFR [22]. An alternative formula, based on data from the Modification of Diet in Renal Disease (MDRD) study, provides a more accurate method for estimating GFR in adults, although it requires fairly complex calculations [23]. These equations are of limited utility in children [24].

Dialysis adequacy is conventionally measured by calculating Kt/V for urea (Kt/V_{urea}) [25, 26]. Calculation of Kt/V_{urea} from residual kidney function is an alternative to estimates of GFR as a way of determining the need for dialysis. Calculation of Kt/V_{urea} requires a 24-h urine collection and serum urea concentration:

$$\text{Weekly } Kt/V_{urea} = \frac{U_{vol} \cdot U_{urea}}{V_{TBW} \cdot S_{urea}} \cdot 7 \qquad (6.4)$$

where U_{vol} = urine volume (liters/day), U_{urea} = urine urea concentration (mg/dL), S_{urea} = serum urea concentration (mg/dL), V_{TBW} is total body water (liters). Multiplication of the daily urea clearance by 7 calculates the weekly urea clearance. The KDOQI guidelines recommend estimating TBW using tables derived from a study of children receiving peritoneal dialysis [26, 27].

Kt/V_{urea} may be misleading in patients with malnutrition. Poor nutrition reduces patient weight and hence V_{TBW}, leading to an increase in Kt/V_{urea} and the impression that urea removal is better than it appears. For patients on peritoneal dialysis, the KDOQI guidelines recommend calculation of V_{TBW} using ideal weight as opposed to actual weight [26]. This may be especially important in using Kt/V_{urea} as a guide to the decision to initiate dialysis since it is the patient with malnutrition who is postulated to receive the most benefit from dialysis initiation.

In predialysis patients the relationship between Kt/V_{urea} and CrCl is different than in patients receiving dialysis. This is because of tubular reabsorption of urea and the lower clearance of creatinine than urea by dialysis. Therefore, for the same CrCl, Kt/V_{urea} in predialysis patients is lower than in patients on dialysis [28]. In one study of adult predialysis patients, Kt/V_{urea} correlated better than CrCl with protein intake, a surrogate marker of nutritional status [28]. Yet, in another study in adults there was a good correlation between CrCl and dietary protein intake [29].

All of the different methodologies have drawbacks. There is no consensus on the method that best identifies the patient who needs to initiate dialysis. Different decisions occur depending on the method [30].

Predialysis Patient Monitoring

Systematic patient monitoring is necessary in children with chronic renal failure 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 or creation of a vascular access for hemodialysis or performance of a preemptive kidney transplant. Table 6.1 outlines

Table 6.1 Evaluation schedule for children with chronic renal failure

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, hand X-ray, neurodevelopmental assessment in infants

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

the necessary components for monitoring children with a GFR < 30 mL/min/1.73 m^2.

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 renal failure that cause significant morbidity and mortality. There is usually a dramatic or marked improvement with 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 produce 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.

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 the precise level of renal function, along with the methodology for measuring renal function, that is, an absolute indication for dialysis. In addition, there are recommendations that the presence of malnutrition lowers the threshold for dialysis initiation based on the level of renal function. 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. We summarize in Sects. "Relative Indications for Initiating Dialysis" and "Timing of Elective Dialysis Initiation" the data and opinions regarding the level of renal function and the role of malnutrition as relative or absolute indications for dialysis initiation.

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 chronic renal failure [31]. 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 [32–36]. Hyperkalemia usually does not become problematic until the GFR is less than 10–20 mL/min, unless potassium intake is excessive or excretion is reduced [33, 37]. Hyperkalemia develops at a higher GFR in adults and children with hyporeninemic hypoaldosteronism, which may also cause a type IV renal tubular acidosis [35, 38, 39]. Similarly, other patients have a decreased tubular responsiveness to aldosterone and this pseudohypoaldosteronism may cause hyperkalemia at higher levels of GFR [40–43]. 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 chronic renal failure 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 standard infant formula does not vary greatly, limiting the effectiveness of formula selection. Low-potassium formulas adapted to the needs of children with advanced CKD are available in individual countries (e.g., Nefea, MetaX in Germany). It should be noted, that soy-based and elemental formulas are especially high in potassium. Human milk has 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, preparing formula with deionized water decreases the potassium content [44].

Increasing potassium excretion can help ameliorate the hyperkalemia of chronic renal failure. Loop diuretics increase urinary potassium excretion; adequate sodium intake is necessary for maximum effectiveness. Discontinuation of medications that decrease urinary potassium excretion, such as ACE inhibitors, angiotensin II blockers, nonsteroidal anti-inflammatory drugs, or potassium sparing diuretics, can have a significant effect on the serum potassium level [45, 46]. Although not usually a significant mechanism of potassium excretion, stool potassium losses become more important as renal function declines [47]. Constipation should be treated since it may decrease stool potassium losses. Sodium polystyrene sulfonate (Kayexalate®), an exchange resin, binds potassium in the gastrointestinal tract, significantly increasing stool potassium losses [48]. Typically given orally or via a G-tube, sodium polystyrene sulfonate is very effective in treating hyperkalemia in children with chronic renal failure. Pretreatment of formula with sodium polystyrene sulfonate is effective, but may cause constipation and problems with other electrolytes, especially increased formula sodium content [44, 49, 50].

Because of the effectiveness of dietary and medical intervention, 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 medication usually contributes to refractory hyperkalemia. Hemodialysis and peritoneal dialysis are quite effective at removing body potassium, although dietary restriction, and occasionally medical management, is usually still necessary.

Hyperphosphatemia

A decrease in filtered phosphate parallels the decrease in GFR in chronic renal failure. With mild to moderate renal insufficiency, an increase in the fractional excretion of phosphate by the remaining nephrons initially compensates, permitting the serum phosphorus to remain normal [51]. As the GFR falls, compensation is inadequate and hyperphosphatemia ensues, typically at CKD stages 2 or 3 [52–54]. Hyperphosphatemia causes secondary hyperparathyroidism by suppressing 1,25-dihydroxyvitamin D production and calcium levels and through direct stimulation of PTH secretion [55–57]. Correction of hyperphosphatemia is essential for controlling secondary hyperparathyroidism. In addition, hyperphosphatemia may elevate the serum calcium-phosphorus product and contribute to vascular calcifications [57–59]. In adult patients with CKD, serum phosphate levels predict mortality and progression of CKD [58–60].

The management of hyperphosphatemia in chronic renal failure depends on a reduction in phosphate intake by a combination of dietary phosphate restriction and the use of phosphate binders [61]. Early in renal failure, before hyperphosphatemia develops, reduction in phosphate intake helps to control secondary hyperparathyroidism

[51, 54, 62–64]. For infants, dietary phosphate restriction is facilitated by the availability of formula with a low phosphate concentration (e.g., Similac PM 60/40). Liquid nutritional supplements with a low phosphate content are also available for older children. As renal function declines, dietary restriction, because of nutritional constraints and limitations of food palatability, is often inadequate to control hyperphosphatemia, necessitating the use of phosphate binders. Calcium carbonate is an effective phosphate binder in children with chronic renal failure, although excessive use may cause hypercalcemia and contribute to systemic calcifications [65]. Sevelamer, a calcium-free phosphate-binding agent, has been effectively utilized to control hyperphosphatemia in children [66], and has been shown to slow the rate of vascular calcifications in adult patients [67]. However, all available phosphate binders must be administered in large doses (several grams per day) to be effective; 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 control 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, nonadherence 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 the 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 [29, 68–71]. In children, this may adversely affect growth [43]. Further, studies in adult patients show an association between malnutrition when starting dialysis and decreased patient survival [29, 72–81]. Nutritional parameters improve in adult patients after initiation of dialysis [69, 71, 82–87]. 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 [84]. 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 [83, 87].

The improved survival with increased dialysis dose, the mortality risk associated with malnutrition, and the improvement in nutritional status with dialysis are the basis for recommendations to initiate dialysis therapy when a patient has advanced chronic renal failure and malnutrition [26, 88, 89]. Yet, there are no prospective studies demonstrating that the early initiation of dialysis improves outcome. An alternative solution to the combination of malnutrition and advanced renal failure is the initiation of aggressive dietary intervention, which has proven successful in some adult patients [90, 91]. This approach, using severe restriction of dietary protein, is not utilized in children due to concerns about the effects of protein restriction on growth and development. Alternatively, aggressive nutritional supplementation, possibly using a gastrostomy tube, may reverse malnutrition in some children without the need for dialysis [92, 93].

There is no one ideal marker of malnutrition. Signs of poor nutrition in children with chronic renal failure may include inadequate weight gain, poor linear growth, and a low serum albumin. A low serum albumin is misleading in the child with nephrotic syndrome and significant urinary protein losses. Other indications of malnutrition include a low serum prealbumin, transferrin or cholesterol, inadequate dietary protein, decreased creatinine excretion, and a loss of muscle mass. If indices of malnutrition cannot be improved by conservative interventions, then the child with advanced chronic renal failure should begin dialysis.

Growth Failure

Growth retardation is a common complication of chronic renal failure in children [94]. The causes of "uremic" growth failure include malnutrition (most markedly in infants), electrolyte losses and fluid losses (in children with hypo/dysplastic kidney disorders), metabolic acidosis, osteodystrophy, anemia, 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 [95]. In children with stable predialytic chronic renal failure, recombinant growth hormone therapy is indicated. The efficacy of this therapy strongly depends on residual renal function, mandating a timely start of treatment [96,97]. Unresponsiveness to growth hormone may be considered as an argument to start dialysis, although improved growth rates are not consistently observed after initiation of standard peritoneal or hemodialysis [98]. Recently, short daily hemodiafiltration was demonstrated to improve responsiveness to growth hormone leading to remarkable, complete catch-up growth [99]. 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 renal function that is an absolute indication for initiating dialysis in children is uncertain. There is a paucity of pediatric data and the adult literature is fraught with conflicting conclusions and opinions [100–108]. The debate is complicated by uncertainty regarding the best methodology for evaluating residual renal function (see Sect. "Methodology for Measuring Renal Function"). The IDEAL study directly addressed this question in adults [109]. Patients were randomized to dialysis initiation at an estimated GFR of 10–15 mL/min/1.73 m^2 or at an estimated GFR of 5–7 mL/min. 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 [109].

A European multicenter study reported the estimated GFR at initiation of renal replacement therapy (RRT) in a large cohort of pediatric patients [110]. The median estimated GFR was10.4 mL/min/1.73 m^2, with the small percentage of the patients who received a preemptive transplant having a significantly higher estimated GFR at the time of transplant (13.5 mL/min/1.73 m^2). Variables associated with a lower estimated GFR 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.

Consensus Statements Regarding Dialysis Initiation

The National Kidney Foundation's KDOQI guidelines recommend considering the risks and benefits of dialysis when a patient reaches stage 5 CKD (estimated GFR <15 mL/min/1.73 m^2), although dialysis at a higher GFR is an option if a specific indication is present (e.g., malnutrition or growth failure refractory to medical management) [25, 26]. Caring for Australasians with Renal Impairment (CARI) recommends starting dialysis when the GFR is below 6 mL/min/1.73 m^2, although earlier initiation should be considered if there is evidence of uremia or malnutrition when the GFR is below 10 mL/min/1.73 m^2 or even at higher GFRs if a specific indication is present [89].

The European guidelines recommend a threshold level of 6 mL/min/1.73 m^2, but that dialysis should be considered if the GFR is 8–10 mL/min/1.73 m^2 to avoid starting at a level less than 6 mL/min/1.73 m^2 [111]. The Canadian Society of Nephrology clinical practice guidelines recommend the initiation of dialysis when the GFR is less than 12 mL/min/1.73 m^2 and there is evidence of uremic symptoms or malnutrition [88]. A GFR less than 6 mL/min/1.73 m^2 is an absolute

indication for dialysis. The principal rationale for 6 mL/min/1.73 m^2 is the high likelihood, given the normal rate of loss of GFR in chronic renal failure, that an unacceptably low GFR will be present within 6 months [88].

Arguments for Early ("Timely") Initiation

This is based on the observation that adults who start dialysis with a lower GFR have increased morbidity and mortality [101, 112, 113]. This may be secondary to the effects of malnutrition since decreased residual renal function is associated with poor nutrition and poor nutrition when starting dialysis is associated with increased morbidity and mortality (see Sect. "Malnutrition"). Moreover, in the 1990s many adult patients initiated dialysis at a lower GFR than was recommended [28, 114, 115]. 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 [106, 116]. In the United States, the percentage of patients starting dialysis with a GFR > 10 mL/min/1.73 m^2 increased from 25% to 54% between 1996 and 2005 [106]. This has been associated with observations suggesting that early initiation of dialysis may be harmful, with increasing mortality in patients who start early [103, 117]. However, this detrimental effect of early dialysis may be secondary to increased age and comorbidity in the patients who start early [104]. Older patients have had the most dramatic increase in early initiation of dialysis over the last decade [106]. Additionally, 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 estimated GFR due to poor nutritional status, a well-defined risk factor for morbidity and mortality (see Sect. "Malnutrition"). This would create additional bias suggesting that early initiation of dialysis is harmful.

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 [101]. These include lead-time bias, referral time bias, and patient selection [88]. 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 [107, 118]. Moreover, early initiation of dialysis may be associated with increased mortality [100, 105]. In adult patients, late referral to a nephrologist is a predictor of poor outcomes [119–124]. Such patients are more likely to have a lower GFR at dialysis initiation, again tending to bias the outcome against late initiation of dialysis. In addition, late referral patients are more likely to have a history of noncompliance with follow-up and more significant comorbid conditions [101].

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]. In one study of early initiation of peritoneal dialysis in adult patients, there were a significant number of complications [126]. These issues are especially important in children given the need for a lifetime of end-stage renal disease 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 renal function is associated with better outcomes in adults receiving dialysis [127, 128], and dialysis accelerates the loss of residual renal function [129]. This is more significant with

hemodialysis than continuous ambulatory peritoneal dialysis, both in adults and children [130–133]. The use of automated PD may [134, 135] or may not provoke a more rapid decline than classical CAPD [131, 136]. Of particular relevance to children, it appears that short, high-turnover NIPD may exert similarly detrimental effects on residual renal 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 other factors.

Choice of Mode of Dialysis

Kidney transplantation is the optimal therapy for most adults and children with end-stage renal disease [137]. In many instances transplantation is not an immediate option because of the lack of a suitable donor. For some patients, psychosocial issues may 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. There is debate in the adult literature regarding the optimal form of therapy. There are no randomized studies that properly address this issue. A number of nonrandomized studies show no difference in outcome, although other studies suggest an advantage for either hemodialysis or peritoneal dialysis [139–143]. Among adult patients, technique failure is more common with peritoneal dialysis [144, 145]. Selection bias has made it difficult to perform comparative studies of morbidity and mortality between peritoneal dialysis and hemodialysis in pediatric patients [146].

Peritoneal dialysis may be especially advantageous during the first 2 years of therapy [141, 147]. This may be related to the improved preservation of residual renal function with peritoneal dialysis [132, 133, 144]. 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 renal 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 [148, 149]. Moreover, a high transporter state in children on peritoneal dialysis is associated with poor growth [150]. 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 of living-related donors and 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 [142, 151, 152]. 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 [153]. Problems include difficulties with vascular access, refractory anemia, inadequate urea removal, and the risk of hemodynamic instability [153]. 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.

The choice of dialysis modality is based on a number of considerations. There are relative and absolute contraindications for both modalities (see Tables 6.2 and 6.3). Psychosocial considerations are quite important given the family commitment needed to make peritoneal dialysis

Table 6.2 Contraindications to hemodialysis in children

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

Table 6.3 Contraindications to peritoneal dialysis in children

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

successful. Unless there are contraindications, peritoneal dialysis is the preferred modality for the majority of children, although both the family and the patient must be comfortable with the decision.

References

1. Mackenzie HS, Taal MW, Luyckx VA, Brenner BM. Adaptation to nephron loss. In: Brenner BM, editor. Brenner and rector's the kidney. 6th ed. Philadelphia: W. B. Saunders; 2000. p. 1901–42.
2. Adefuin PY, Gur A, Siegel NJ, Spencer RP, Hayslett JP. Single subcutaneous injection of iothalamate sodium I 125 to measure glomerular filtration rate. JAMA. 1976;235(14):1467–9.
3. 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.
4. Morton KA, Pisani DE, Whiting Jr JH, Cheung AK, Arias JM, Valdivia S. Determination of glomerular filtration rate using technetium-99 m-DTPA with differing degrees of renal function. J Nucl Med Technol. 1997;25(2):110–4.
5. Li Y, Lee HB, Blaufox MD. Single-sample methods to measure GFR with technetium-99 m-DTPA. J Nucl Med. 1997;38(8):1290–5.
6. 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.
7. 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.
8. Hellerstein S, Erwin P, Warady BA. The cimetidine protocol: a convenient, accurate, and inexpensive way to measure glomerular filtration rate. Pediatr Nephrol. 2003;18(1):71–2.
9. 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.
10. 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.
11. Schwartz GJ, Haycock GB, Edelmann Jr CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259–63.
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. Davies JG, Taylor CM, White RH, Marshall T. Clinical limitations of the estimation of glomerular filtration rate from height/plasma creatinine ratio: a comparison with simultaneous 51Cr edetic acid slope clearance. Arch Dis Child. 1982;57(8):607–10.
14. Hjorth L, Wiebe T, Karpman D. Correct evaluation of renal glomerular filtration rate requires clearance assays. Pediatr Nephrol. 2002;17(10):847–51.
15. Seikaly MG, Browne R, Bajaj G, Arant Jr BS. Limitations to body length/serum creatinine ratio as an estimate of glomerular filtration in children. Pediatr Nephrol. 1996;10(6):709–11.
16. Skinner R, Cole M, Pearson AD, Keir MJ, Price L, Wyllie RA, et al. Inaccuracy of glomerular filtration rate estimation from height/plasma creatinine ratio. Arch Dis Child. 1994;70(5):387–90.
17. 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.
18. Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. Clin Sci. 1980;58(4):327–35.
19. 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.
20. 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.
21. Bouvet Y, Bouissou F, Coulais Y, Seronie-Vivien S, Tafani M, Decramer S, et al. GFR is better estimated

by considering both serum cystatin C and creatinine levels. Pediatr Nephrol. 2006;21(9):1299–306.
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31–41.
23. 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.
24. Pierrat A, Gravier E, Saunders C, Caira MV, Ait-Djafer Z, Legras B, et al. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. Kidney Int. 2003;64(4):1425–36.
25. National Kidney Foundation. KDOQI clinical practice guidelines for hemodialysis adequacy: 2006 update. Am J Kidney Dis. 2006;48(suppl 2):S2–90.
26. National Kidney Foundation. KDOQI clinical practice guidelines for peritoneal dialysis adequacy: 2006 update. Am J Kidney Dis. 2006;48(suppl 2):S91–175.
27. Morgenstern BZ, Wuhl E, Nair KS, Warady BA, Schaefer F. Anthropometric prediction of total body water in children who are on pediatric peritoneal dialysis. J Am Soc Nephrol. 2006;17(1):285–93.
28. Mehrotra R, Saran R, Moore HL, Prowant BF, Khanna R, Twardowski ZJ, et al. Toward targets for initiation of chronic dialysis. Perit Dial Int. 1997; 17(5):497–508.
29. 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.
30. Kuhlmann MK, Heckmann M, Riegel W, Kohler H. Evaluation of renal Kt/V as a marker of renal function in predialysis patients. Kidney Int. 2001;60(4): 1540–6.
31. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch Intern Med. 2009;169(12):1156–62.
32. Bourgoignie JJ, Kaplan M, Pincus J, Gavellas G, Rabinovitch A. Renal handling of potassium in dogs with chronic renal insufficiency. Kidney Int. 1981; 20(4):482–90.
33. Gonick HC, Kleeman CR, Rubini ME, Maxwell MH. Functional impairment in chronic renal disease. 3. Studies of potassium excretion. Am J Med Sci. 1971;261(5):281–90.
34. Perez GO, Pelleya R, Oster JR, Kem DC, Vaamonde CA. Blunted kaliuresis after an acute potassium load in patients with chronic renal failure. Kidney Int. 1983;24(5):656–62.
35. Rodriguez-Soriano J, Vallo A, Sanjurjo P, Castillo G, Oliveros R. Hyporeninemic hypoaldosteronism in children with chronic renal failure. J Pediatr. 1986;109(3):476–82.
36. van Ypersele de Strihou C. Potassium homeostasis in renal failure. Kidney Int. 1977;11(6):491–504.
37. Kahn T, Kaji DM, Nicolis G, Krakoff LR, Stein RM. Factors related to potassium transport in chronic stable renal disease in man. Clin Sci Mol Med. 1978;54(6):661–6.
38. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int. 1980;17(1):118–34.
39. Schambelan M, Sebastian A, Biglieri EG. Prevalence, pathogenesis, and functional significance of aldosterone deficiency in hyperkalemic patients with chronic renal insufficiency. Kidney Int. 1980;17(1): 89–101.
40. Hene RJ, Koomans HA, Boer P, Roos JC, Dorhout Mees EJ. Relation between plasma aldosterone concentration and renal handling of sodium and potassium, in particular in patients with chronic renal failure. Nephron. 1984;37(2):94–9.
41. Perez GO, Pelleya R, Oster JR. Renal tubular hyperkalemia. Am J Nephrol. 1982;2(2):109–14.
42. Sebastian A, Hulter HN, Kurtz I, Maher T, Schambelan M. Disorders of distal nephron function. Am J Med. 1982;72(2):289–307.
43. 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.
44. Fassinger N, Dabbagh S, Mukhopadhyay S, Lee DY. Mineral content of infant formula after treatment with sodium polystyrene sulfonate or calcium polystyrene sulfonate. Adv Perit Dial. 1998;14:274–7.
45. 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.
46. Palmer BF. Renal complications associated with use of nonsteroidal anti-inflammatory agents. J Investig Med. 1995;43(6):516–33.
47. Hayes Jr CP, McLeod ME, Robinson RR. An extravenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Am Physicians. 1967;80:207–16.
48. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. N Engl J Med. 1961;264:115–9.
49. Bunchman TE, Wood EG, Schenck MH, Weaver KA, Klein BL, Lynch RE. Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. Pediatr Nephrol. 1991;5(1):29–32.
50. Rivard AL, Raup SM, Beilman GJ. Sodium polystyrene sulfonate used to reduce the potassium content of a high-protein enteral formula: a quantitative analysis. J Parenter Enteral Nutr. 2004;28(2):76–8.
51. Portale AA, Booth BE, Halloran BP, Morris Jr RC. 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.
52. Better OS, Kleeman CR, Gonick HC, Varrady PD, Maxwell MH. Renal handling of calcium, magnesium

and inorganic phosphate in chronic renal failure. Isr J Med Sci. 1967;3(1):60–79.
53. Hosking DJ, Chamberlain MJ. Calcium balance in chronic renal failure. A study using in vivo neutron activation analysis. Q J Med. 1973;42(167):467–79.
54. Slatopolsky E, Caglar S, Gradowska L, Canterbury J, Reiss E, Bricker NS. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake. Kidney Int. 1972;2(3): 147–51.
55. Chan JC, Kodroff MB, Landwehr DM. Effects of 1,25-dihydroxyvitamin-D3 on renal function, mineral balance, and growth in children with severe chronic renal failure. Pediatrics. 1981;68(4):559–71.
56. Kilav R, Silver J, Naveh-Many T. Parathyroid hormone gene expression in hypophosphatemic rats. J Clin Invest. 1995;96(1):327–33.
57. 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.
58. 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.
59. 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.
60. 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.
61. Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2010;25(3):385–94.
62. Aparicio M, Combe C, Lafage MH, de Precigout V, Potaux L, Bouchet JL. In advanced renal failure, dietary phosphorus restriction reverses hyperparathyroidism independent of changes in the levels of calcitriol. Nephron. 1993;63(1):122–3.
63. Combe C, Aparicio M. Phosphorus and protein restriction and parathyroid function in chronic renal failure. Kidney Int. 1994;46(5):1381–6.
64. Llach F, Massry SG. On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. J Clin Endocrinol Metab. 1985;61(4):601–6.
65. 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.
66. Pieper A-K, Haffner D, Hoppe B, Dittrich K, Offner G, Bonzel K-E, et al. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. Am J Kidney Dis. 2006;47(4): 625–35.
67. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005;68(4):1815–24.
68. 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.
69. 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.
70. 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.
71. 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.
72. 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.
73. 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.
74. Bergstrom J. Nutrition and mortality in hemodialysis. J Am Soc Nephrol. 1995;6(5):1329–41.
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. 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.
77. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, et al. Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. Am J Kidney Dis. 1996;28(4): 541–8.
78. 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.
79. 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.
80. 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.

81. 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.
82. 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.
83. 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.
84. 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.
85. 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.
86. Parker 3rd TF, 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.
87. 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.
88. 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.
89. Kelly J, Stanley M, Harris D. The CARI guidelines. Acceptance into dialysis guidelines. Nephrol. 2005;10(Suppl 4):S46–60.
90. Coresh J, Walser M, Hill S. Survival on dialysis among chronic renal failure patients treated with a supplemented low-protein diet before dialysis. J Am Soc Nephrol. 1995;6(5):1379–85.
91. Walser M, Hill S. Can renal replacement be deferred by a supplemented very low protein diet? J Am Soc Nephrol. 1999;10(1):110–6.
92. 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.
93. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25(4):699–704.
94. 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.
95. 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.
96. 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.
97. 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.
98. 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.
99. 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.
100. 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.
101. Churchill DN. An evidence-based approach to earlier initiation of dialysis. Am J Kidney Dis. 1997;30(6):899–906.
102. Golper TA. The rationale for healthy start dialysis. Blood Purif. 1999;17(1):1–9.
103. 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.
104. 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.
105. Mehrotra R, Nolph KD. Treatment of advanced renal failure: low-protein diets or timely initiation of dialysis? Kidney Int. 2000;58(4):1381–8.
106. Rosansky SJ, Clark WF, Eggers P, Glassock RJ. Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? Kidney Int. 2009;76(3):257–61.
107. 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(8):2125–32.
108. Walser M, Mitch WE, Maroni BJ, Kopple JD. Should protein intake be restricted in predialysis patients? Kidney Int. 1999;55(3):771–7.
109. 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.
110. 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: 3325–32.
111. Dombros N, Dratwa M, Feriani M, Gokal R, Heimburger O, Krediet R, et al. European best

practice guidelines for peritoneal dialysis. 2. The initiation of dialysis. Nephrol Dial Transplant. 2005; 20(Suppl 9):ix3–7.
112. Bonomini V, Feletti C, Scolari MP, Stefoni S. Benefits of early initiation of dialysis. Kidney Int. 1985;17(9):S57–9.
113. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. Am J Nephrol. 1995;15(4):283–9.
114. 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.
115. 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.
116. 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.
117. 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.
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. Arora P, Obrador GT, Ruthazer R, Kausz AT, Meyer KB, Jenuleson CS, et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. J Am Soc Nephrol. 1999;10(6):1281–6.
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. Holland DC, Lam M. Suboptimal dialysis initiation in a retrospective cohort of predialysis patients–predictors of in-hospital dialysis initiation, catheter insertion and one-year mortality. Scand J Urol Nephrol. 2000;34(6):341–7.
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. 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.
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. Burkart JM. Clinical experience: how much earlier should patients really start renal replacement therapy? J Am Soc Nephrol. 1998;9(12 Suppl): S118–23.
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. Termorshuizen F, Korevaar JC, Dekker FW, Jager KJ, van Manen JG, Boeschoten EW, et al. Time trends in initiation and dose of dialysis in end-stage renal disease patients in The Netherlands. Nephrol Dial Transplant. 2003;18(3):552–8.
129. Rottembourg J. Residual renal function and recovery of renal function in patients treated by CAPD. Kidney Int. 1993;40:S106–10.
130. 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.
131. 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.
132. 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.
133. Schulman G. The role of hemodialysis and peritoneal dialysis for the early initiation of dialysis. Blood Purif. 2001;19(2):175–8.
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. 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.
136. 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.
137. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA. 1993;270(11):1339–43.
138. McDonald SP, Marshall MR, Johnson DW, Polkinghorne KR. Relationship between dialysis modality and mortality. J Am Soc Nephrol. 2009; 20(1):155–63.
139. Vonesh EF, Snyder JJ, Foley RN, Collins AJ. Mortality studies comparing peritoneal dialysis and

hemodialysis: what do they tell us?. Kidney Int, 2006 (Nov); Suppl (103):S3–11.
140. Weinhandl ED, Foley RN, Gilbertson DT, Arneson TJ, Snyder JJ, Collins AJ. Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. J Am Soc Nephrol. 2010;21(3):499–506.
141. 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.
142. 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.
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. 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.
145. 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.
146. 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.
147. 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.
148. 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.
149. 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.
150. 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.
151. Maiorca R, Vonesh EF, Cavalli P, De'Vecchi A, Giangrande A, La'Greca G, et al. A multicenter, selection-adjusted comparison of patient and technique survivals on CAPD and hemodialysis. Perit Dial Int. 1991;11(2):118–27.
152. 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.
153. 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.

Additional References

Allon M. Treatment and prevention of hyperkalemia in end-stage renal disease. Kidney Int. 1993;43(6):1197–209.

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. Am J Kidney Dis. 1990;16(3):224.

The modification of diet in renal disease study. Am J Kidney Dis. 16(3): 224–235.

Slatopolsky E, Robson AM, Elkan I, Bricker NS. Control of phosphate excretion in uremic man. J Clin Invest. 1968;47(8):1865–74.

Initiation of Maintenance Renal Replacement Therapy in Infants

7

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Keywords
Renal replacement • Infants • Hemodialysis • Peritoneal dialysis • Dialysis initiation

Introduction

Decisions concerning the initiation of dialysis during infancy are complex and serve as a prime example of why a pediatric dialysis healthcare team must be comprised of a multidisciplinary group of experts. Team members should include a social worker, nutritionist/dietician, nurses with experience in management of end-stage renal disease (ESRD) in infants, as well as the medical staff. In addition, the views of the parents must be seriously considered in the decision process. The complexity of the medical and psychosocial issues mitigates against care being provided by a single individual, if results are to be optimized. Additional input may be required from the dialysis technologist or from home or community providers. Finally, although dialysis in infants often poses significant clinical and technical challenges, it is frequently psychosocial and economic issues that dominate the patient management decisions.

The use of maintenance hemodialysis (HD) for children was first described by Fine and colleagues in 1968 [1] and was limited to a small group of adolescents. More than a decade later, the use of continuous ambulatory peritoneal dialysis (CAPD) was reported [2], and seemed to provide an opportunity to extend dialysis to younger children. Subsequent reports confirmed that long-term peritoneal dialysis (PD) was possible for infants [3, 4], although concerns about growth and development in this age group were emphasized. Whereas improvements in technology have permitted the successful use of HD for infants with acute renal failure [5], the use of this renal replacement modality for long-term care of this population may be problematic. Nonetheless, maintenance treatment of infants with both peritoneal and hemodialysis is possible, although before starting, parents should be cautioned about the demands of therapy, that desired outcomes may not be achieved, and that the emotional cost of treatment is considerable.

The ensuing discussion will review the options that exist with respect to the provision of

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maintenance renal replacement therapy (RRT) for infants, focusing on those factors unique to this population. This chapter addresses issues related to the initiation of dialysis, potential complications, and ethical considerations with this population. Lastly, the outcomes of infant dialysis, as reported in the literature, will be summarized.

Dialysis Options

Hemodialysis

HD is rarely the modality of choice for the initiation of maintenance dialysis in infants [6]. Estimates of its use in infants have ranged from 3% to 14% [7–9]; however, in most observational studies, HD was utilized only after PD failed [10, 11]. Mortality rates notwithstanding, the drawbacks of infant HD include its special equipment needs and the labor intensity. For successful HD, each component of the equipment (machine, filters, bloodlines, and vascular access) must be specifically adapted for infants. More frequent dialysis (> thrice weekly) is also often required in younger patients because of the difficulty that can occur achieving consistent blood flow rates with this equipment [12]. In addition, because the infant diet is predominantly liquid-based, more frequent treatments are often required to achieve appropriate ultrafiltration and to allow for optimal nutrition, especially in the oliguric infant. This increase in dialysis frequency places great demands both on the family and the dialysis staff.

Another potential drawback to infant HD has been the need for blood priming for treatments and the associated risk for increased antigen exposure, all of which can have a negative impact on subsequent transplant availability. However, larger infants (>5 kg) have been treated chronically using albumin or saline priming with success [11], potentially diminishing this drawback. On a positive note, published experience does provide evidence that it is possible to maintain infants on chronic HD and achieve adequate growth and development [10, 11].

Peritoneal Dialysis

PD has long been the dialysis modality of choice for infants, since the introduction of CAPD in the late 1970s, in large part due to the lack of need for vascular access and the excellent patient tolerance of the procedure. Its technical requirements include a flexible catheter small enough for insertion into an infant and a supply of dialysate in small bags to allow for the infusion of appropriately smaller volumes, compared to older children and adults. The introduction of cycling machines allowed for frequent, small volume exchanges and overnight dialysis with less caregiver burnout. Salusky et al. reported their successful clinical experience with cycling PD in eight infants (aged 2.5–8.5 months) in the mid-1980s [13]. However, these initial cycling machines had excessive dead space in the tubing, such that the recirculated volume of dialysate in infants could be nearly 40% of the exchange volume. The development of machines with smaller tubing dead space and less dialysate recirculation has further facilitated and improved this dialysis modality in infants.

PD is, however, fairly rigorous for parents, as it is most often performed nightly in infants. Some have speculated that on occasion, the sudden death that may occur in an infant on PD may actually be secondary to hyperkalemia from dialysis not being performed in the prescribed manner. However, the rigors on the family may be less overall than with HD, which often requires a constant parental presence during treatments, in addition to regular travel to and from the dialysis center, allowing less time to be spent at home. For those situations in which care provision or home scenarios are not acceptable for home dialysis, PD may be provided in the hospital setting.

Timing of Dialysis Initiation

There are no scientific data stating exactly when dialysis should be initiated during infancy, especially if all infants with impaired kidney function are considered. For those who are oligo-anuric or with life-threatening metabolic disturbances, the

decision is straightforward as death will occur, often within a few days, if dialysis is withheld. However, for infants who are capable of maintaining neutral fluid and metabolic balance, the optimal time to start dialysis is much less clear. There is frequent reticence on the part of parents and staff to institute therapy, even in the absence of potential ethical dilemmas, which may lead to delays in dialysis initiation.

Renal Function Considerations

The guidelines presented by both the Kidney Disease Outcomes Quality Initiative (KDOQI) [14] and the European ad hoc committee for elective PD in pediatric patients [15], which recommend the level of renal dysfunction at which dialysis should be initiated, have no proven validity in infants in whom the glomerular filtration rate (GFR) in the normal state is quite low. An analysis of data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) derived from 300 infants who initiated dialysis revealed that those less than 12 months of age at dialysis initiation had a median GFR of 6 mL/min/1.73 m^2, compared to 8–11 mL/min/1.73 m^2 for those 12–24 months old [12]. These data, in turn, show that the estimated GFR is not used as an absolute threshold for dialysis initiation in this population.

Delays in the initiation of dialysis may be warranted by the need for urologic surgical procedures, for long-term preparation of the genitourinary system and reduction of infection risk, and possibly by preservation of renal function following surgical correction of severe, persistent upper tract obstruction with severe hydronephrosis [16, 17]. Criteria for surgical intervention in pediatric patients with upper tract obstruction have been published and include renal failure and worsening hydronephrosis; however, these indications are also not absolute and will vary by surgeon [18].

Some reticence about early dialysis initiation during infancy may also be secondary to the hopes, of both staff and parents, that renal function will improve as a result of postnatal maturation. Whereas the GFR of a normal term newborn is less than 10% of that in adults, it increases rapidly, doubling within the first 2 weeks of life and continuing to increase up to 2 years of age [19]. This rise in total GFR is secondary to increases in single nephron GFR, paralleled by an increase in renal plasma flow and individual glomerular hypertrophy (increases in size, surface area, and capillary permeability). Similarly, these changes may also occur, although less pronounced, in infants with renal dysplasia or acquired postnatal hypoxic insults to the kidney. Studies looking at the progression of renal dysplasia in children not requiring RRT have shown that GFR may improve in this population at an early age, but significant improvement is less likely in those with a lower initial GFR [20, 21]. Nevertheless, single-center reports of infant dialysis populations have cited their reason for terminating dialysis as recovery of renal function in 10–15% of their subjects [10, 22] and a NAPRTCS review by Carey et al. reported that up to one-eighth of all neonates on dialysis were able to discontinue dialysis because of recovered renal function [23]. In contrast, Coulthard et al. reported a much lower percentage (4.6%) of patients experiencing recovery of function when all infants with ESRD, including those not treated, were considered [24]. Therefore, the prospect of dialysis being only a temporary measure in infants with severely impaired kidney function is not great and likely should not be overemphasized in discussions with most families about the prospect of initiating long-term RRT.

Nutritional Considerations

Nutrition is a primary concern in all children with chronic kidney disease (CKD), but its importance is greatest during infancy. At this stage, statural growth and increase in brain growth and head circumference is primarily driven by nutrition and early deficits may be difficult to overcome later. The recently published KDOQI guidelines for nutrition in children with CKD recommend evaluation of nutritional parameters in infants, as frequently as every 2 weeks [25], as shown in Table 7.1 [25]. Additionally, most of the primary indications for dialysis initiation, as cited by the KDOQI guidelines, are conditions (acidosis, hyperkalemia, hyperphosphatemia, growth failure, fluid overload, and neurologic sequelae of uremia) which may be amenable to intense dietary

Table 7.1 Recommended parameters and frequency of nutritional assessment for children with CKD Stages 2 to 5 and 5D

	Minimum interval (mo)									
	Age 0 to <1 year			Age 1–3 years			Age >3 years			
Measure	CKD 2–3	CKD 4–5	CKD 5D	CKD 2–3	CKD 4–5	CKD 5D	CKD 2	CKD 3	CKD 4–5	CKD 5D
Dietary intake	0.5–3	0.5–3	0.5–2	1–3	1–3	1–3	6–12	6	3–4	3–4
Height or length-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Height or length velocity-for-age percentile or SDS	0.5–2	0.5–2	0.5–1	1–6	1–3	1–2	6	6	6	6
Estimated dry weight and weight-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.25–1	1–3	1–2	0.5–1	3–6	3–6	1–3	1–3
BMI-for-height-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Head circumference-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1–2	N/A	N/A	N/A	N/A
nPCR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1[a]

Abbreviation: N/A, not applicable

[a]Only applies to adolescents receiving HD

and medication management [14]. Therefore, early and frequent evaluation of both biochemical and growth parameters are necessary to minimize sequelae of malnutrition, but also to anticipate potential nutritional needs once starting dialysis.

Precise documentation of dietary intake in infants should be recorded, although this is somewhat more complex in breastfed infants. It is mandatory to document intake accurately in uremic infants so that any reduction below recommended calorie and protein intakes for age can be identified and corrected quickly. Similarly, meticulous care is also required to ensure that calcium and age specific phosphate values are maintained in the normal range, the latter goal often requiring the initiation of dialysis. Lastly, though difficult to confirm, renal salt wasting may occur in infants and a therapeutic trial of sodium chloride supplementation in the infant with advanced CKD may be advised to determine any possible contribution to growth, especially given that additional sodium loss will typically occur with the initiation of PD [25].

Whereas the amelioration of uremia by dialysis may improve appetite and reduce vomiting, this does not frequently occur. In fact, the installation of large dialysate volumes into the peritoneal cavity may aggravate these symptoms. Therefore, the introduction of enteral tube feeding, if possible, prior to the initiation of dialysis is recommended [26] and decisions to start dialysis should include discussions about a long-term tube feeding strategy. Adequate nutritional outcomes may be achieved by either a nasogastric or gastrostomy tube; however, the timing of their introduction is often closely tied to the plan for dialysis initiation. PD catheters and gastrostomy tubes may be inserted as part of the same surgical procedure [15]. When performed in this manner, dialysis should be withheld for the first 48 h to ensure there is no leakage from the gastrostomy tube site. A gastrostomy tube may be added after PD catheter insertion, but with increased risk of infection, particularly if inserted percutaneously [27]. Prophylactic antibiotics and antifungals have been shown to reduce this risk [28]. Some would also suggest the initial use of a nasogastric tube when the patient is significantly malnourished to enhance nutrition prior to surgery for gastrostomy placement as a means of decreasing the risk for postoperative complications (e.g., infection, poor wound healing).

Growth and Development Considerations

Although the precise cause of developmental and growth delay in uremic infants has not been clarified, one must consider the uremic milieu as potentially harmful and as an important clinical indicator for dialysis initiation. Improved developmental outcomes in uremic infants have been noted over the past few decades, coinciding with the elimination of aluminum containing phosphate binders, optimization of nutrition, use of erythropoiesis-stimulating agents, and increasing awareness of the potential benefits of earlier and "adequate" dialysis. However, it is impossible to separate the individual contributions of each of these factors on the observed improvement in development; therefore, each (including earlier dialysis) should be factored into the decision to initiate dialysis.

The most objective measure of the need to start dialysis in infants may be growth impairment. Growth delay, like developmental delay, is most often multi-factorial and may require a period of months rather than weeks to manifest and, therefore, should not be the sole criterion upon which the decision to initiate dialysis is based. However, an inability to correct several of the factors that contribute to growth delay (inadequate nutrition, persistent acidosis, and renal osteodystrophy) through dietary and pharmacologic measures alone should have a strong influence on the decision to initiate dialysis.

Ethical Considerations

The ethical and legal issues that need to be considered when deciding whether or not to proceed with dialysis during infancy, have been debated for many years. In 1987, Cohen reviewed these issues and suggested that dialysis for infants could be considered more of an experimental or innovative intervention than an accepted therapy. She concluded that "when parents elect conservative treatment for their very young infants who are born with End-Stage Renal disease (ESRD), rather than dialysis or transplantation, this is a choice that is medically, ethically, and legally

Table 7.2 Ethical decisions: Guidelines for practice

1.	Always act in the child's best interests
2.	Never rush the decision; continue treatment until it can be properly made
3.	Assemble all the available evidence
4.	Respect the opinions of everyone in the team
5.	Discuss the issues with the whole family
6.	Attempt a consensus whenever possible
7.	Make sure everyone appreciates the burden of care
8.	Try to avoid adding to the guilt of anyone involved
9.	Consider the child's palliative and terminal care
10.	Offer support for all those affected, parents and staff alike
11.	Remember, we can only do the best we can and sometimes there is no ideal solution

acceptable [29]." Nine years later, when considering the same issue, despite substantial improvements in technology that had been achieved in the interim, Bunchman concluded that "the decision by the family or the medical team not to institute dialytic therapy must be honored and offered as a reasonable option [30]." Bunchman added that "early intervention with aggressive management of infants would be optimal, with the understanding that discontinuation or withdrawal of care in the future is an option." He also drew attention to the need for the healthcare team to objectively outline the long-term care burden and outcomes associated with dialysis to the patients' families and emphasized the difficulty of truly obtaining "informed consent" at such a stressful time. These issues were again discussed in 2000 by Shooter and Watson [31] who stated that decision-making for pediatric patients should be in the hands of the patient, the hospital team, and the parents; since infants cannot speak for themselves, decisions must be made by proxy. They pointed out that when there is disagreement between family members about the course of action to take, as well as potential conflicts between hospital staff members, these very difficult decisions become even more complex. They provided some guidelines, as outlined in Table 7.2 [31], on actions to consider when confronted with such complex patient issues.

In an attempt to clarify the ethical dilemmas that doctors face when deciding whether or not to treat patients with ESRD, the Spanish Pediatric Nephrology Association also produced guidelines on this issue [32]. These authors also mentioned how difficult, but important it is to try to obtain informed consent for procedures in young children. They stated that information should be provided to families that includes a discussion of quality of life as a major consideration. Parents should be counseled, advised, and supported before, during, and after decision-making. Withholding or withdrawing dialysis was considered a reasonable option in these guidelines if the net benefit to the child would not justify the risks and burdens of the treatment. These guidelines are outlined in Table 7.3 [32].

It is of interest that the first guideline listed in Table 7.3 states that "a patient must have real possibilities for kidney transplantation." Whereas this has also historically been a consideration for patients starting dialysis at The Hospital for Sick Children in Toronto, it is no longer so. Provided the expected quality of life for the child is considered satisfactory and members of the healthcare team in conjunction with the family elect dialysis, then it is considered reasonable to initiate this treatment even for those in whom the likelihood of transplantation is considered small.

The second guideline in this table suggests that "patients with irreversible disease that makes survival extremely unlikely will not be considered as candidates for dialysis." Whereas we are in general agreement with this philosophy for children, dialysis may be offered to some children with a terminal illness if the child's quality of life is satisfactory and the patient or the family do not want to terminate life early because of a complication resulting from non-treatment of renal failure. However, given the intensity of care necessary and the frequent medical interventions required of infants on dialysis, it is difficult to envisage a situation in which an infant should be dialyzed when the likelihood of survival is extremely poor.

The ethical and legal issues outlined above are extremely useful to help guide decision-making about initiating or withholding dialysis treatment for infants with ESRD. However, it is also of great value to understand what the attitudes are of medical professionals with respect to this decision-making process. In a survey published in 1998, 93% of an international group of pediatric

Table 7.3 Guidelines for treatment of ESRD in children

1.	All pediatric patients receiving dialysis must meet the following criteria
	(a) The patient must be diagnosed with ESRD
	(b) Signed informed consent must be given by the parents/legal guardian
	(c) The patient must have real possibilities for kidney transplantation
	(d) There must be reasonable expectation that the patient will have an acceptable quality of life during dialysis therapy and after kidney transplantation
	(e) The patient and parent/guardian must demonstrate a willingness to participate in and cooperate with the dialysis procedures and medical advice
2.	Patients with irreversible diseases that make survival extremely unlikely will not be considered as candidates for dialysis
3.	Those patients meeting the criteria stated in guideline 1 will not be refused treatment for economic, social, or psychological factors, nor in relation to age, sex, race, or a physical handicap
4.	Dialysis treatment will not be withdrawn against the wishes of the patient and parents/guardian
5.	The cessation of dialysis will be considered if therapeutic results are not satisfactory or will not be reasonably achieved. A decision to stop treatment must always be made with the agreement of the responsible physician, the patient, and the parents/guardian

nephrologists responded that they offered dialysis treatment for ESRD to *some* infants aged <1 month and 41% reported that they offered RRT to *all* infants in this age group; 53% offered RRT to *all* such infants aged 1–12 months [33]. The presence of coexisting serious medical abnormalities or anticipated morbidity for the child ranked as the most important factors influencing their decision to withhold such treatment. The least influential factor concerning the decision to initiate or withhold such treatment was consideration of hospital or governmental budgetary issues. Most importantly, more than 80% of pediatric nephrologists believed that it was sometimes ethically acceptable for parents to refuse RRT for their children <1 month of age, and 61% held this belief concerning older (1–12 months) children.

Additional information about how nephrologists make decisions about life sustaining treatment in children was obtained from interviews with 46 French speaking pediatric nephrologists [34]. This study was not restricted to infants in early life, but nonetheless 97.8% answered that in their opinion it is sometimes necessary to withdraw or to withhold life sustaining treatment in children and the quoted reasons for this were "to avoid poor quality of life or to avoid artificial prolongation of life by medical means and to limit suffering for children when there's no hope for improvement." Interestingly, when asked if there was a difference between withdrawal of treatment or withholding of the same treatment, it was felt by the great majority that withdrawal of life-sustaining treatment is more difficult because this act may provoke or accelerate death. It was also interesting that in contrast to the survey by Geary, most doctors in this French survey (85%) did not wish to involve parents in the decision-making process.

Coulthard and Crosier reviewed the treatment of infants aged less than 2 years with ESRD in the UK and Ireland [24]. Of 192 such children, 177 (92%) were treated with dialysis or transplantation. Decisions not to treat were typically made by mutual agreement between clinicians and families. Although a relatively large number of children aged <1 month (n = 31) were treated, 45% of these patients died. In addition to physician advice, other influences on parental decision-making may include religious authorities [11], depending on the importance families place in their faith.

To determine if attitudes toward withholding care from infants with ESRD had changed over a 10 year period, the survey published by Geary in 1998 was repeated in 2008. In recognition of the fact that many of these decisions now often involve interdisciplinary members of the pediatric nephrology team, nurses and social workers were also surveyed. Ninety-eight percent (98%) of respondents stated that they offer RRT to some infants less than 1 month of age, compared with only 93% in 1998 ($p < 0.05$). In contrast, only 30% of nephrologists surveyed in 2008 offered RRT to all children <1 month of age compared to the figure of 41% in the earlier study. This

suggests that technology and patient outcomes have not advanced sufficiently to make the provision of RRT mandatory or the expectation for all young infants. As in 1998, 50% of nephrologists recommended treatment for all children aged 1–12 months. It is noteworthy that nurses rated the presence of oligo-anuria as an important factor influencing the decision to withhold RRT more so than nephrologists. Also, nurses rated the families' right to decide about the initiation of life sustaining therapy more highly than did respondent nephrologists. These disagreements of opinion between different members of the health care team emphasize the need for open discussion among team members when confronted with an infant with ESRD to aim for a consistent approach to treatment prior to speaking to the family so that the parents are not further confused during this stressful period of time.

Economic Considerations

The survey of Spanish pediatric nephrologists suggested that the economic cost of dialysis is the least important criterion in a long list of potential factors determining the advisability of starting dialysis in infants [35]. Similarly, in the previously mentioned international survey of pediatric nephrologists, hospital and governmental budget constraints ranked very low as considerations whether or not to initiate RRT for ESRD in infants [33]. Nonetheless, it is appropriate to consider the costs to the healthcare system of dialysis in infants.

In 1982, Baum at al. estimated the overall annual costs of dialysis as US $19,600 and $54,300 for pediatric CAPD and HD, respectively [36]. This study was based on a review of Medicare costs throughout the United States, provided no information about laboratory or medication costs, and was restricted to children between the ages of 3 and 20 years. A more detailed study by Coyte et al. found that the cost of pediatric CAPD was US $36,000, continuous cycling PD $37,000, and HD $57,000 annually [37]. This study was based on the detailed analysis of only a small number of patients older than age 2 and greater than 20 kg of body weight. Neither study addressed the added costs that characteristically occur in infants due to the greater number of average hospital days per annum [38] and the common need for more frequent dialysis sessions per week when compared to older children [12]. The common need for supplemental enteral feeding inherently increases direct costs in this population as well.

Both studies reflected only a healthcare system perspective rather than a total societal perspective of costs. It is likely that the cost of dialysis for infants, from both a societal and family perspective, is much greater than the sample values outlined above. The rigorous nature of dialysis in infants may preclude a family member from working full-time, unless other care arrangements can be made. The family's socioeconomic status, although not ranked as a highly influential factor by healthcare providers, must be considered. This is not to suggest that economically disadvantaged people should have less opportunities for dialysis than others, but rather that the financial burden to be carried by the families should be detailed in advance and discussed because of the influence it may have on this decision. The importance of the contribution from the social service team members on this issue cannot be overemphasized.

Unique Features of Infant Dialysis

As the infant with ESRD prepares to initiate dialysis, a number of issues should be considered to enhance the efficacy of the procedure and minimize treatment related complications.

Infant Hemodialysis

More infant-specific HD equipment has become available over the past two decades which has facilitated the use of this modality. Smaller dialysis circuits and tubing are available which may avoid the need for blood priming of lines and which requires less than 10% of the infant's intravascular blood volume to be in an extracorporeal location. If blood priming is needed, diluting the blood to a hematocrit of 30–40% may decrease

its viscosity and the associated increased resistance, while the use of leukopore blood may decrease the white blood cell load and potential antigen exposure. The infant's vascular access should also be characterized by low resistance to help avoid thrombosis. Therefore, the access should have a wide diameter and the shortest length possible, while still permitting appropriate surgical placement of the access tip in the atrial-vena caval junction. The standard blood flow rate for an infant's HD treatments is [39]:

$$(\text{body weight}[\text{kg}]+10)\cdot 2.5 = \text{blood flow rate}(\text{mL/min})$$

which translates to a rate of ≤50 mL/min in infants under 10 kg. Adequate anticoagulation is especially important in the setting of these low blood flow rates to decrease the risk of thrombosis. Heparinization is best accomplished with a heparin load of 10–20 units/kg and a maintenance rate of 10–20 units/kg/h to achieve standard activated clotting times of 150–200 s [40].

The infant HD treatment requires great circumspection by the dialysis staff, as the infant is at risk for complications throughout the session. In the hypervolemic infant, there may be an increased susceptibility to pulmonary edema and the need for supplemental oxygen. At the same time, ultrafiltration rates may be limited to 0.2 mL/kg/min as higher rates may cause hemodynamic instability. Additionally, the ultrafiltration monitors on HD machines have an error rate of ±50 mL/h, so infants could theoretically have an inadvertent excessive or reduced ultrafiltrate of as much as 150–200 mL during a 3–4 h treatment. This error rate may be minimized for a particular dialysis machine, once the variation rate is known and its range can be tightened by the biomedical support team [40]. Strict attention to maintaining accurate infant scales are also needed to minimize the risk for volume related complications. Maintenance of the infant's body temperature may be challenging with such large blood volumes in an extracorporeal location. As such, increased dialysate temperatures may be needed to maintain normothermia. Lastly, the return of blood to the infant must be performed slowly if it represents more than 10% of the patient's blood volume, as it may in essence represent a transfusion to the patient with a risk of hemodynamic compromise if performed rapidly.

Infant Peritoneal Dialysis

Specific technical details about performing PD in infants are covered elsewhere in this book. However, there are several issues which should be considered at therapy initiation.

The frequency of peritonitis is higher in infants under 1 year of age (once every 14.2 months) than in all children (once every 18 months) [7] and is a major cause of patient morbidity. One related issue that is especially pertinent to the infant initiating dialysis, but about which there is conflicting evidence, is the impact of a gastrostomy tube/button on the peritonitis rate. Ledermann et al. reported that the incidence of peritonitis in their gastrostomy fed infants was comparable to that reported for all children on PD by the NAPRTCS registry [27]. However, the peritonitis incidence in this study was twice as great when gastrostomy tube insertion was conducted after, compared to prior to dialysis initiation. Ramage et al. similarly noted a markedly increased incidence of peritonitis in children with gastrostomy tubes, and that the organisms causing peritonitis were similar to those infecting gastrostomy tube exit-sites [26]. Therefore, the PD catheter exit site should, if possible, be placed contralateral to the stomach and any current/potential gastrostomy site, as well as away from any other ostomy openings, as shown in Fig. 7.1. Additional recommendations regarding the gastrostomy placement strategy as it relates to peritonitis risk, with particular reference to the timing of placement, are noted above refer to the Nutrition chapter. Downward pointing dialysis catheter exit-sites have been associated with lower peritonitis rates in older children, but this has not been confirmed in infants. Concerns also exist that a downward pointing site may be a risk factor for infection in children with frequently soiled diapers; therefore, the location of the exit-site should be outside of the diaper region, and occasionally on the chest wall.

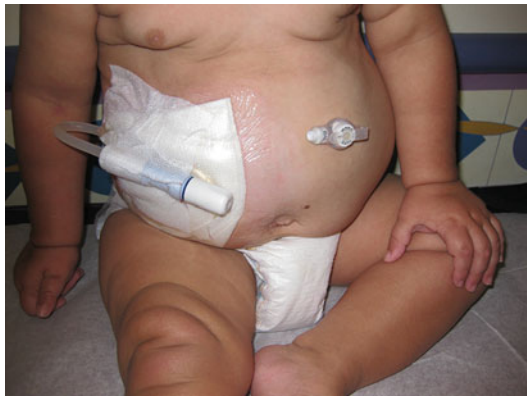

Fig. 7.1 Infant with PD catheter

Another potential factor that may contribute to an increased frequency of peritonitis during infancy may be a selective IgG deficiency associated with this therapy [41, 42]. While regular infusions of intravenous immunoglobulin have not yet been shown to decrease the risk of peritonitis in children, the subject has not been well studied [43]. Relative immaturity of other parts of the infant's immune system may also contribute to this risk [44]. Since membrane failure is associated with the number and severity of peritonitis episodes in children, all possible steps to minimize infections and, hence, preserve the peritoneum should be undertaken [45].

Whereas the use of double-cuffed catheters is recommended for pediatric PD [15], the possibility of erosion of the proximal cuff through the skin is probably greater in infants than in older children, particularly if the infant is malnourished. No specific recommendation is therefore possible regarding the number of cuffs that an infant PD catheter should have. Although the institution of dialysis in older children is often delayed for several weeks to allow healing of the exit-site, this may lead to more catheter occlusion in infants and may not be desired or even possible, based on the urgency of the clinical situation. If dialysis is started soon after catheter placement, the frequency of dialysate leakage may be increased, especially in the youngest infants [8], which may require a reduction in fill volumes, use of fibrin glue [46], or even temporary conversion to HD to allow for healing. Occlusion of the catheter by omentum may occur more frequently in infants as well and partial omentectomy should be considered at the time of catheter placement. Lastly, the development of hernias in young infants on PD is much more common than in older children [8, 13]. Prophylactic surgery to prevent hernia development is not mandated, but identification and correction of hernias at the time of catheter placement is recommended [38].

When PD is prescribed for infants, the exchange volume should be scaled to body surface area (BSA) and not weight, as a result of the age independent relationship between peritoneal surface area and BSA. In addition, the exchange volume at dialysis initiation should be only 600–800 mL/m^2 to optimize patient tolerance and minimize intraperitoneal pressure (IPP). It has been suggested that PD may also be particularly suitable for infants because of the potentially better preservation of residual renal function, or at least urine volumes [47]. Whereas, this has been documented in children on PD, in contrast to those on HD [48, 49], it has not been documented specifically in infants. Noteworthy is the fact that the presence of preserved renal function has been associated with improved growth in children on PD [50].

Outcomes of Infant Dialysis

The pediatric nephrology team should be well versed on the outcome of infants receiving dialysis so that they can provide this important data to families who are being asked to help make decisions regarding the long-term care of their infant with ESRD.

Growth and Development

Historically, growth and development have been significantly impaired in most infants requiring dialysis, but advances in treating the sequelae of ESRD have permitted normal or near normal development and reasonable growth. Nearly a decade ago, Warady et al. showed improved developmental outcomes in patients who initiated dialysis during infancy (<3 months old) with the

avoidance of aluminum binders and the regular use of supplemental feedings [51]. Of 28 surviving infants followed long-term, nearly 80% had normal developmental scores and only 4% had significant developmental delay. Coulthard et al. reported that 87% of their cohort was able to attend school and be placed in regular classrooms [24] while Shroff et al. reported that none of her 68 subjects without significant comorbidities were found to have learning difficulties [9]. Growth tends to be most severely impaired with an earlier age of ESRD onset and with the coexistence of comorbid conditions [52]. However, catch-up growth may occur in patients once on dialysis, especially in the case of infants [9]. As an example, Laakkonen et al. reported catch-up growth in 64% of their infants on PD with early dialysis initiation and aggressive nasogastric tube feeding [38]. Much the same has been demonstrated by the NAPRTCS. Most of the studies that have addressed growth were conducted without the use of recombinant growth hormone, which has now been shown to produce catch-up growth in treated infants (<1 year old) with CKD [53], increasing the likelihood of achieving near normal growth on dialysis.

Mortality

There is limited data available reporting long-term (>5 years) outcomes of patients who initiated maintenance RRT during infancy. However, there is a growing body of evidence from single-center observational experience and registry data that does provide short-term outcomes and may prove helpful when advising families. Early reports on young children receiving dialysis gave mortality rates of nearly 16% per year [40] and infant PD mortality rates >40% [54]. However, national registry data give a much less bleak picture. Children less than 1 year of age when initiating dialysis have had 5-year survival rates reported as high as 73% in Australia and New Zealand [55] and 66% in the United Kingdom [56]. Laakkonen et al. reported a mortality rate of only 9% in children <2 years old at the time of PD initiation [38]; however, these subjects were followed only during their time on dialysis (14 months), limiting the availability of outcome data. Similarly, the NAPRTCS found the 1-year survival of infants <2 years of age at dialysis initiation in 2001–2006 to be 86.1%. A more recent retrospective study by Wedekin et al. reported a 5-year survival of 82% for infants who received PD [57]. Mortality rates of patients receiving HD have seemingly been higher, with retrospective single-center studies giving overall rates of 30–40% [10, 11] but data has been limited to a very small numbers of patients.

Many feel that these studies and registry data underestimate the improvement in the survival rates of most infants who receive dialysis, as younger infants and those with substantial comorbidities are currently being treated [45]. While likely true, it should also be recognized that nearly all of these studies and registries analyze a selected population, those infants already deemed worthy candidates for dialysis, and do not include those to whom dialysis was not offered.

There are several risk factors associated with mortality in infants on dialysis that must be considered as part of the decision process regarding dialysis initiation. Oligo-anuria has been associated with the worst outcomes [10, 54] in several case series. Recently, Hijazi et al. found oligo-anuria to be the greatest risk factor for mortality in their analysis of 52 infants, with an odds ratio of 41 [8]. Interestingly, the international survey of pediatric nephrologists noted that the presence of oligo-anuria was only a minor influence on their decision-making regarding offering infant dialysis [33], highlighting a potentially concerning discrepancy between the clinical data that exists and practice recommendations.

Additional risk factors for infant mortality consist of a number of comorbidities, [54] namely, neurodevelopmental delay, congenital heart disease, malignancy, heritable metabolic disorders, and syndromes with multisystem involvement. Shroff et al. found the presence of other comorbidities to be associated with a relative mortality risk of 7.5 [9] while Hijazi et al. calculated an associated odds ratio of nearly 4.5 [8]. Unfortunately, the presence of other comorbidities is not always known at the time decisions are

being made about dialysis initiation and their presence has been cited as the leading reason for treatment withdrawal in infants [24].

Finally, younger age at the time of dialysis initiation has been associated with higher mortality, with neonates noted to have poor outcomes associated with the provision of both HD and PD [11, 24]. Rheault et al. specifically analyzed this population and noted a 3-year survival rate of only 48% [22]. However, mortality was highest during the initial hospitalization as 70% of those surviving to discharge went on to renal transplant. A specific analysis of NAPRTCS data on neonatal dialysis revealed an overall mortality of 24%, comparable to that of young infants [23]. In this analysis, however, a significantly better outcome was found in the neonatal cohort dialyzing since 1999 when compared to those who received dialysis prior to that time, suggesting that overall outcomes in neonates seem to be improving with advances in knowledge and technology.

Summary

The increasing number of reports of successful dialysis during infancy have been encouraging, such that no longer can RRT in infants be considered experimental [58]. However, this therapy remains demanding for the healthcare team and most importantly, for the family. Therefore, decision-making regarding the initiation of therapy in infants can by complex and should involve the multi-disciplinary team to address anticipated problems with care and to give realistic expectations of outcome. Lastly, the socioeconomic and ethical issues surrounding each individual case, which have also evolved with advances in technology and will likely continue to do so, should always be considered.

References

1. Fine RN, De Palma JR, Lieberman E, Donnell GN, Gordon A, Maxwell MH. Extended hemodialysis in children with chronic renal failure. J Pediatr. 1968; 73(5):706–13.
2. Akman S, Guven AG, Ince S, Yegin O. IgG and IgG subclasses deficiency in children undergoing continuous ambulatory peritoneal dialysis and its provocative factors. Pediatr Int. 2002;44(3):273–6.
3. Fine RN. Peritoneal dialysis update. J Pediatr. 1982; 100(1):1–7.
4. Moncrief JW, Popovich RP. CAPD update: continuous ambulatory peritoneal dialysis. New York: Masson Pub.; 1981.
5. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int. 1994;45(3):903–6.
6. Donckerwolcke RA, Bunchman TE. Hemodialysis in infants and small children. Pediatr Nephrol. 1994;8(1): 103–6.
7. Cameron JS. Host defences in continuous ambulatory peritoneal dialysis and the genesis of peritonitis. Pediatr Nephrol. 1995;9(5):647–62.
8. 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.
9. 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.
10. 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.
11. 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(4):1336–45.
12. Leonard MB, Donaldson LA, Ho M, Geary DF. A prospective cohort study of incident maintenance dialysis in children: an NAPRTCS study. Kidney Int. 2003; 63(2):744–55.
13. Salusky IB, von Lilien T, Anchondo M, Nelson PA, Fine RN. Experience with continuous cycling peritoneal dialysis during the first year of life. Pediatr Nephrol. 1987;1(2):172–5.
14. II. NKF-K/DOQI. Clinical practice guidelines for peritoneal dialysis adequacy: update 2000. Am J Kidney Dis. 2001;37(1):S65–136.
15. Watson AR, Gartland C. Guidelines by an ad hoc European committee for elective chronic peritoneal dialysis in pediatric patients. Perit Dial Int. 2001; 21(3):240–4.
16. Karnak I, Woo LL, Shah SN, Sirajuddin A, Ross JH. Results of a practical protocol for management of prenatally detected hydronephrosis due to ureteropelvic junction obstruction. Pediatr Surg Int. 2009;25(1): 61–7.
17. Wagner M, Mayr J, Hacker FM. Improvement of renal split function in hydronephrosis with less than 10 % function. Eur J Pediatr Surg. 2008;18(3):156–9.
18. Yiee J, Wilcox D. Management of fetal hydronephrosis. Pediatr Nephrol. 2008;23(3):347–53.

19. Guignard JP, Torrado A, Da Cunha O, Gautier E. Glomerular filtration rate in the first three weeks of life. J Pediatr. 1975;87(2):268–72.
20. Gonzalez Celedon C, Bitsori M, Tullus K. Progression of chronic renal failure in children with dysplastic kidneys. Pediatr Nephrol. 2007;22(7):1014–20.
21. Ismaili K, Schurmans T, Wissing KM, Hall M, Van Aelst C, Janssen F. Early prognostic factors of infants with chronic renal failure caused by renal dysplasia. Pediatr Nephrol. 2001;16(3):260–4.
22. Rheault MN, Rajpal J, Chavers B, Nevins TE. Outcomes of infants <28 days old treated with peritoneal dialysis for end-stage renal disease. Pediatr Nephrol. 2009;24(10):2035–9.
23. 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.
24. Coulthard MG, Crosier J. Outcome of reaching end stage renal failure in children under 2 years of age. Arch Dis Child. 2002;87(6):511–7.
25. 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.
26. 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.
27. 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.
28. von Schnakenburg C, Feneberg R, Plank C, et al. Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int. 2006;26(1):69–77.
29. Cohen C. Ethical and legal considerations in the care of the infant with end-stage renal disease whose parents elect conservative therapy. An American perspective. Pediatr Nephrol. 1987;1(2):166–71.
30. Bunchman TE. The ethics of infant dialysis. Perit Dial Int. 1996;16(Suppl 1):S505–8.
31. Shooter M, Watson A. The ethics of withholding and withdrawing dialysis therapy in infants. Pediatr Nephrol. 2000;14(4):347–51.
32. Riano I, Malaga S, Callis L, et al. Towards guidelines for dialysis in children with end-stage renal disease. Pediatr Nephrol. 2000;15(1–2):157–62.
33. Geary DF. Attitudes of pediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133(1):154–6.
34. Fauriel I, Moutel G, Duchange N, et al. Decision making concerning life-sustaining treatment in paediatric nephrology: professionals' experiences and values. Nephrol Dial Transplant. 2005;20(12):2746–50.
35. Riano Galan I, Malaga Guerrero S. A survey on the inclusion criteria in pediatric dialysis and transplantation programs in terminal renal failure. An Esp Pediatr. 1998;48(1):33–8.
36. Baum M, Powell D, Calvin S, et al. Continuous ambulatory peritoneal dialysis in children: comparison with hemodialysis. N Engl J Med. 1982; 307(25):1537–42.
37. Coyte PC, Young LG, Tipper BL, 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.
38. Laakkonen H, Holtta T, Lonnqvist T, Holmberg C, Ronnholm K. Peritoneal dialysis in children under two years of age. Nephrol Dial Transplant. 2008;23(5): 1747–53.
39. Fischbach M, Edefonti A, Schroder C, Watson A. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.
40. Bunchman TE. Chronic dialysis in the infant less than 1 year of age. Pediatr Nephrol. 1995;9(Suppl): S18–22.
41. Bouts AH, Davin JC, Krediet RT, et al. Immunoglobulins in chronic renal failure of childhood: effects of dialysis modalities. Kidney Int. 2000; 58(2):629–37.
42. 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.
43. Verrina E, Honda M, Warady BA, Piraino B. Prevention of peritonitis in children on peritoneal dialysis. Perit Dial Int. 2000;20(6):625–30.
44. Schaefer F. Management of peritonitis in children receiving chronic peritoneal dialysis. Paediatr Drugs. 2003;5(5):315–25.
45. Shroff R, Ledermann S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2009;24(3):463–74.
46. 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.
47. Fischbach M. Ask the expert is peritoneal dialysis (CAPD or APD) appropriate for small children with prune belly syndrome and terminal renal failure? Pediatr Nephrol. 2001;16(11):936–7.
48. 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.
49. 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.

50. 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.
51. Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol. 1999;13(9):759–65.
52. 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.
53. 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.
54. Ellis EN, Pearson D, Champion B, Wood EG. Outcome of infants on chronic peritoneal dialysis. Adv Perit Dial. 1995;11:266–9.
55. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
56. Tomson C, Ford D, Ansell D. The UK renal registry: an overview. Br J Hosp Med (Lond). 2008;69(10):548–9.
57. Wedekin M, Ehrich JH, Offner G, Pape L. Renal replacement therapy in infants with chronic renal failure in the first year of life. Clin J Am Soc Nephrol. 2010;5(1):18–23.
58. Bunchman TE. Infant dialysis: the future is now. J Pediatr. 2000;136(1):1–2.

Urological Issues in Pediatric Dialysis

8

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Keywords
Pediatric dialysis • Urological issues • Chronic kidney disease • Posterior urethral Valves • Vesicoureteric reflux

Abbreviations

CIC	Clean intermittent catheterization
CKD	Chronic kidney disease
CRF	Chronic renal failure
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
LUT	Lower urinary tract
PBS	Prune belly syndrome
PD	Peritoneal dialysis
PUV	Posterior urethral valves
PVRV	Post void residual volumes
UVJ	Ureterovesical junction obstruction
VCUG	Voiding cysto-urethrogram
VUR	Vesicoureteric reflux

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Introduction

The prevalence of stage 5 chronic kidney disease (CKD) in the pediatric population is approximately 50 cases per million. It has been noted to be increasing in all age groups, but especially among older children [1]. In contrast to adults where glomerulopathy and vasculopathy are the major causes of disease, at least 40% of the CKD in children is due to congenital urological abnormalities [2–6]. As a result of this predominance of urological issues in the pediatric population, the urologist is an essential member of any team tasked with the management of pediatric CKD. Similarly, health care providers dealing with these patients benefit from understanding the urological management principles for this patient population.

In this chapter, we outline the common urological conditions that cause renal failure; we discuss their diagnosis, pathophysiology, and provide an overview of management from a urological perspective. Where relevant, we have highlighted any unique implications for the dialysis patient and/or the transplant recipient. Understanding that dialysis represents a treatment phase between the development of stage 5 CKD and renal transplantation, it is important to

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discuss issues present prior to the initiation of dialysis and following renal transplantation. In addition to this, we will look at the indications for nephrectomy in the CKD patient and the urology specific pre-transplant workup.

Urological Causes of Chronic Kidney Disease

As with most pediatric pathology, the causes of CKD can be divided into congenital and acquired conditions [4, 7–16]. The causes have been listed by anatomical location in Table 8.1. The most important of these are highlighted and are the conditions that we have chosen to focus on in the chapter (Table 8.1).

Posterior Urethral Valves

Posterior urethral valves (PUVs) are abnormal membranous folds unique to the male prostatic urethra. While one must be aware of other causes of congenital lower urinary tract (LUT) obstruction, such as urethral atresia and obstructive ureteroceles, PUVs are undoubtedly the most common. They are encountered in 1 of 10,000–25,000 births [17–19].

Advances in antenatal diagnosis, better perinatal medicine and early PUV management have led to a decrease in the neonatal mortality rate associated with PUVs. In spite of these advances and the introduction of antenatal interventions, there has been little improvement in the proportion of these patients ultimately developing CKD [20]. Twenty to sixty percent of these boys will manifest with evidence of CKD in childhood and 11–51% will eventually progress to stage 5 disease during long-term follow-up [21–24].

Table 8.1 Urological causes of chronic kidney disease in children

	Causes
Congenital	*Renal dysplasia*
	Ureteropelvic junction obstruction
	Ureterovesical junction obstruction
	Ureteroceles
	Vesicoureteric reflux
	Neuropathic bladder
	Posterior urethral valves
	Prune belly syndrome
Acquired	Obstructing renal tract calculi
	Obstructing neoplasms
	Neuropathic bladder
	Urethral strictures

Increasingly, the diagnosis is being suspected in the antenatal period with typical ultrasound features that include oligohydramnios, bilateral hydroureteronephrosis, a thick-walled bladder, and a dilated posterior urethra (Fig. 8.1). Children who escape prenatal diagnosis present at different ages in the postnatal period with a variety of features that include respiratory insufficiency, renal insufficiency, urosepsis, failure to thrive, poor urinary stream, and urinary incontinence. This variety of presentations represents a spectrum of disease, where lesser forms of obstruction are often detected later in life and may be associated with less impact on overall renal function.

In an attempt to prevent or attenuate renal damage that occurs in utero, prenatal interventions have sought to bypass the urethral obstruction with open or percutaneous diversion of the fetal urinary system. The decision to attempt antenatal intervention is aided by the analysis of fetal urinary markers (sodium, chloride, osmolality, and B_2-microglobulin). Currently the favored and most common approach to the fetal lower tract obstruction is percutaneous placement of a vesicoamniotic shunt. This achieves the required supra-urethral diversion while being minimally invasive, obviating the need for a maternal hysterotomy and fetal vesicostomy. Although technically feasible, antenatal interventions have failed to reliably prevent renal insufficiency and are associated with a fetal mortality rate that ranges from 33% to 43%. Not all the reported deaths are directly related to the intervention, however, as many of the series include deaths that the intervention failed to prevent (pulmonary hypoplasia). These procedures are also associated with significant morbidity in the form of urinary ascites, visceral herniation, shunt malfunction, and migration [25–28].

Regardless of the timing of the postnatal presentation, an ultrasound of the kidneys, ureter,

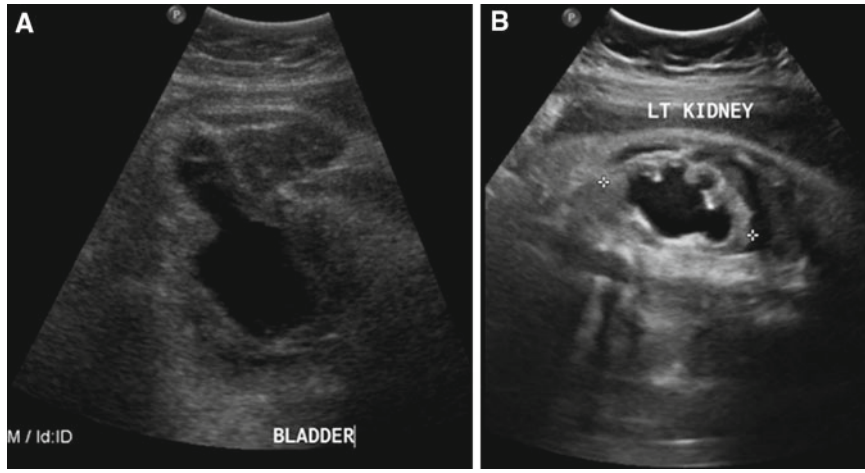

Fig. 8.1 Sonographic features suggestive of PUVs detected during antenatal evaluation: (**a**) thick-walled bladder with prominent posterior urethra, the "key-hole" sign; (**b**) high-grade hydronephrosis

and bladder is often the first imaging study requested, and will often demonstrate many of the above-mentioned ultrasonographic features. Following this, a voiding cysto-urethrogram (VCUG) is indicated to confirm the diagnosis. Typical features on VCUG include a dilated posterior urethra with a clear sharp transition to a normal distal channel, an associated valve cusp, thickened open bladder neck, and a trabeculated bladder. Vesicoureteric reflux (VUR) is also often present (Fig. 8.2). During the workup it is important to look for features that may be associated with a more favorable prognosis. Although not always predictive of a good outcome, the presence of a "pop-off" has been reported to be protective in some children. These include unilateral VUR into an ipsilateral dysplastic/nonfunctioning kidney, a perinephric urinoma, urinary ascites, and a patent urachus [29–34].

Accepting that we cannot alter preexisting renal dysplasia and understanding that many of these children will eventually develop CKD, our role in their management is to delay the onset of renal failure by optimizing the function of the ureters, bladder, and urethra. Management is initially directed at systemic stabilization and decompression of the urinary tract. Initial urological instrumentation usually involves urethral

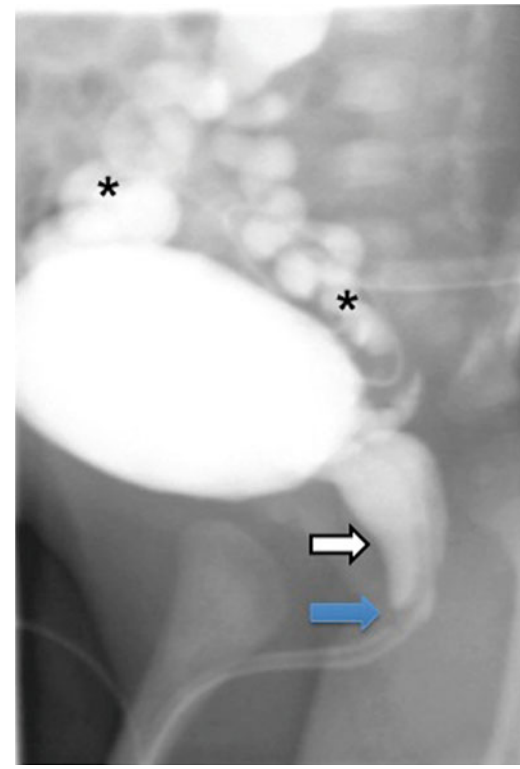

Fig. 8.2 Features of PUV on VCUG: prominent posterior urethra (*white arrow*) with a change in caliber compared with the anterior urethra at the site of the valves (*blue arrow*). Associated bilateral vesicoureteral reflux (*asterisk*)

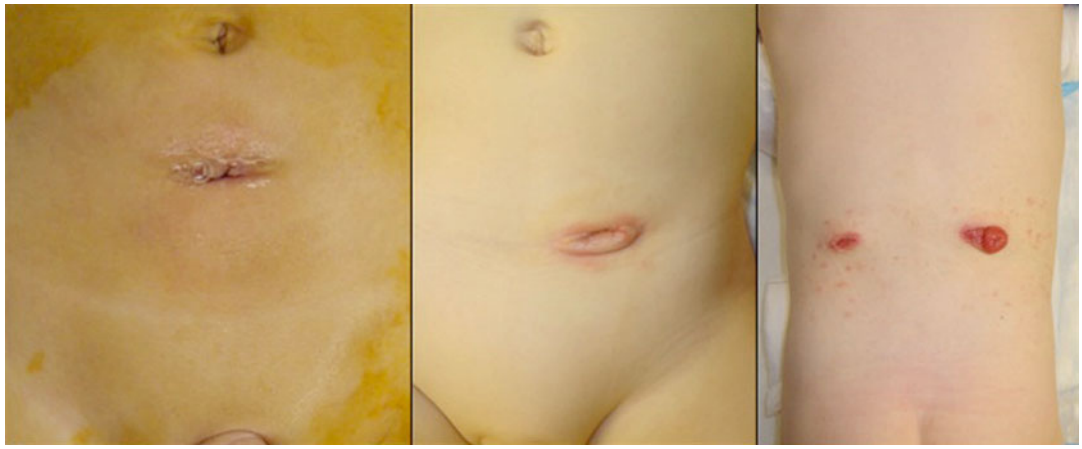

Fig. 8.3 Appearance on physical examination of different forms of cutaneous urinary diversion: (**a**) vesicostomy, (**b**) distal ureterostomy, and (**c**) bilateral pyelostomies (patient prone)

catheterization in the early neonatal period, even before the diagnosis has been confirmed. This simple intervention temporarily bypasses the obstruction, allows accurate monitoring of urine output, and helps avoid emergent surgical intervention while associated abnormalities are identified and their management optimized. Following this, a VCUG can be obtained by instilling contrast through the catheter. Subsequent definitive urethroscopic valve ablation can be attempted in all but the smallest infants. Premature or small infants whose urethras will not accommodate a scope 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 (UVJ) 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. 8.3).

Many institutions will perform a circumcision at the time of the valve ablation or vesicostomy in order to decrease the risk of urinary tract infections (UTIs). A recent study by Mukherjee showed that there was an 83% reduction in the incidence of UTI in those children with valves who had been circumcised [35]. A more conservative approach would be to perform a circumcision only in the event of demonstrated predisposition to recurrent UTIs. This intervention is often heavily influenced by cultural and religious expectations.

Following valve ablation the obstructive process is usually relieved, yet the functional consequences are less predictably improved. Urodynamic findings in these boys remain highly variable and prone to change over time as renal function, growth, and the acquisition of continence further challenge the stability of the bladder [36, 37]. The primary goal of the urological management in PUVs is preservation of upper tract function. This is achieved by ensuring an infection-free urinary tract with a bladder that stores urine at low pressure and empties efficiently. The secondary goals would include continence and attaining an adequate lower tract for the effective drainage of a renal allograft in those that require it.

Lower tract dysfunction that is poorly controlled can adversely affect existing renal function. DeFoor and Ansari have demonstrated that residual bladder dysfunction is an independent risk factor for CKD [10, 22]. In 1980, Mitchell coined the term "valve bladder syndrome" identifying deleterious features of lower tract dysfunction that could reliably predict renal deterioration. The phrase describes the development or persistence of

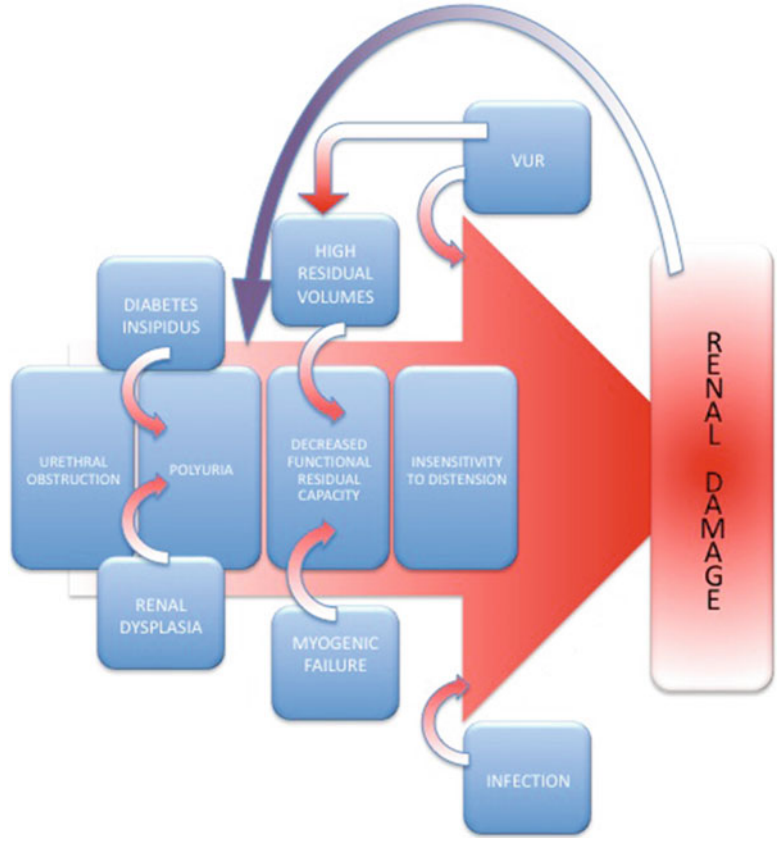

Fig. 8.4 Issues to consider in the monitoring of patients with PUV. Adequately addressing these problems helps prevent or slow renal deterioration, and provides a conceptual framework upon which to consider interventions and tailor treatment

hydroureteronephrosis in the presence of a poorly compliant, thick-walled bladder, incontinence, and polyuria [38]. 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 renal deterioration in valve patients [39]. Looking at these three factors in more detail gives us a very plausible explanation for how an overwhelmed bladder, with borderline function, can facilitate rather than cause, upper tract damage: *Polyuria*, caused by nephrogenic diabetes insipidis, has the potential to overload the bladder of the most diligent voider. *Insensitivity to overdistension* 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 [40]. Pseudoresidual volumes can be generated by VUR when urine is refluxed into dilated ureters during filling and voiding, only to be dumped back into the bladder immediately post void. An additional source of pseudoresidual volume is found in the patients with a hypertrophied detrusor muscle. This hypertrophy creates a functional UVJ obstruction during bladder filling, an obstruction that is relieved in the post void period allowing for the retained urine to drain from the dilated ureters (Fig. 8.4) [41].

As a result of a better understanding of the condition, clinicians no longer accept hydroureteronephrosis as unavoidable in the upper tracts of valve patients. Management has become proactive and more aggressive, 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. Where polyuria and decreased functional capacity are an issue, routine daytime interventions may be unable to prevent hydronephrosis. Nocturnal CIC or overnight indwelling catheterization have been

shown to reduce diuresis, decrease the incidence of UTIs, improve continence, and decrease upper tract dilation [39, 42, 43].

VUR in PUV children is found in 50–70% of patients and is usually secondary to the obstructed bladder outlet [44, 45]. Because of its association with worse renal dysplasia, high-grade reflux can predict higher morbidity and mortality [46, 47]. Adequate treatment of the valvular obstruction will lead to spontaneous resolution of VUR in most cases (62%), and, therefore, VUR should be treated as conservatively as possible [45, 48]. 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 PUVs has been associated with a better renal functional prognosis than standard valve patients [46, 49]. The reason for this is thought to be due to the dysplastic kidney's protective effect as the renal pelvis and ureter absorb most of the abnormal pressures generated by the bladder during voiding. However, Narasimhan and colleagues showed that while the syndrome did seem to favor a better outcome, half of their patients had some form of renal scarring, voiding dysfunction, UTIs, diurnal incontinence, and hydroureteronephrosis [49]. This data would support the contention that every boy with PUV, regardless of the presence of "favorable prognostic features," should have close multidisciplinary team follow-up in order to identify and appropriately treat potential threats to the remaining renal function.

Vesicoureteric Reflux in the Pediatric Dialysis Patient

Renal damage or abnormal development related to VUR (reflux nephropathy) is often congenital, representing renal dysplasia that is likely to coexist with reflux rather than be directly caused by it (Fig. 8.5). Subsequently, postnatal renal function may be further threatened by pyelonephritis, which is facilitated by reflux of infected urine into the abnormal renal unit [50–53]. As discussed in the previous section, secondary reflux can be associated with transmission of high bladder pressures to the upper tracts, which can further compromise the renal parenchyma. Differentiation between primary and secondary reflux has important therapeutic implications. In this section, we concentrate on primary VUR, while secondary reflux is discussed under the specific primary conditions.

Primary VUR accounts for 7–25% of pediatric CKD cases [4, 54, 55]. Ardissino looked at 343 patients who had VUR and CKD and found that almost 60% of his series required renal replacement therapy prior to the age of 20. Given this high incidence of end-stage renal disease, he suggests that children with reflux-associated CKD have a relatively poor renal prognosis and deserve particular attention [56]. Neither medical

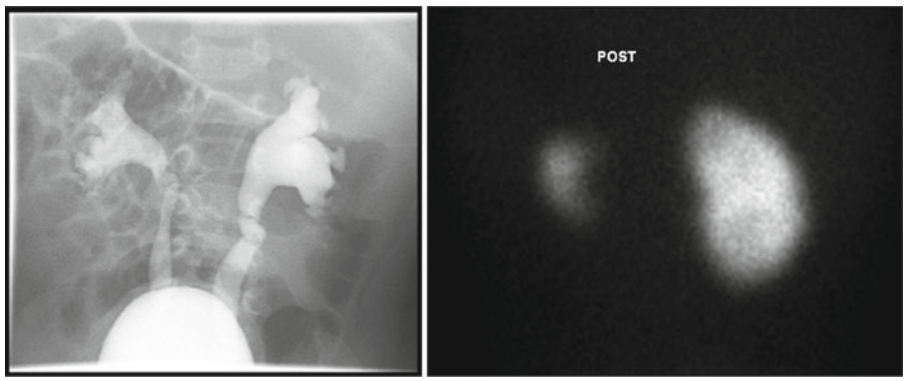

Fig. 8.5 Findings suggestive of renal dysplasia: (**a**) bilateral high-grade reflux detected in infant without a history of urinary tract infections; (**b**) DMSA scan demonstrates poor function of the left renal moiety and photopenic defects

nor surgical management can alter the function of a dysplastic kidney and should therefore concentrate on preventing further damage by early diagnosis and treatment of febrile UTIs (pyelonephritis) and the correction of bladder and bowel dysfunction (increased fluid intake, prophylactic antibiotics, treatment of constipation, biofeedback, and bladder training). By increasing fluid intake, more urine is produced. This in turn increases the volume and frequency of voiding, effectively flushing the LUT and mechanically clearing it of bacteria. Prophylactic antibiotics have long been held as the cornerstone of conservative management of VUR [57]. Recent large series have begun to question this conventional wisdom [58–60]. In the absence of more definitive data on the topic it would seem prudent to continue with the selective use of antibiotics based on a holistic assessment of individual patients and their parents.

Bladder training is aimed at those children with an element of dysfunctional voiding. The process involves the education and retraining of the voiding process to achieve a volitional, regular, and complete void. Emphasis is placed on 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 (bladder and bowel dysfunction). Active management of constipation has been shown to improve voiding dysfunction, incontinence, enuresis, urgency, and UTIs [61–63].

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 that includes circumcision in males, endoscopic sub-ureteric injection of a bulking agent (such as dextronomer/hyaluronic acid), and ureteric reimplantation. Although surgical reimplantation is more invasive than endoscopic therapy, it carries a higher overall success rate in terms of reflux correction. This is an important distinction when considering the child with borderline renal function and a predisposition to recurrent scarring UTIs. An argument can be made for a more aggressive approach in these patients, consisting of early prophylactic circumcision and surgical reimplantation of the ureter.

In regard to the reflux patient with CKD who requires dialysis, the indications for medical management or surgical intervention are usually no different from those patients with normal renal function. One must be aware that once transplanted these children will be immunosuppressed and have an additional renal unit. Following renal transplantation, UTIs occur commonly in children with VUR; approximately 60% of these patients experience at least one episode [64, 65]. The risk is highest in the first year posttransplantation and then decreases over time [66]. Although VUR has not been documented as an independent risk factor for UTI in this population [67, 68], it has been associated with acute pyelonephritis in two pediatric studies [66, 68] and yet, has not been convincingly linked to graft loss [66, 68–70]. Thus, considering the potential for increased morbidity in the setting of immunosuppression, due consideration should be giving to addressing pre-transplant vesicoureteral reflux, particularly 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 renal transplantation, VUR into the allograft is common and varies according to the ureteral implantation procedure used [66, 67, 71, 72]. As a result, it is not common practice to routinely "screen" for reflux posttransplant. Nevertheless, in the setting of recurrent UTIs posttransplant, a VCUG is warranted to exclude reflux into the native or transplanted kidneys. Treatment for posttransplant reflux–associated UTIs 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 renal unit. Recently, the sub-ureteric injection of dextronomer/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 and there is a lack of long-term follow-up. Cloix and Williams reported reflux resolution following ureteric injection in only 29% and 44% of their patients, respectively [73, 74]. Similarly, surgical reimplantation is not without problems in transplanted patients. Neuhaus reported transient obstruction and a persistent increase in serum creatinine in 60% of his reimplanted children [72]. 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, we believe surgical intervention is rarely indicated in this patient population.

Neurogenic Voiding Dysfunction

Under normal circumstances the detrusor muscle and the sphincter complex function in a coordinated fashion that optimizes both storage and emptying. During the filling phase, the detrusor muscle is relaxed and said to be compliant as it fills without an increase in pressure. As capacity is reached, the compliance decreases. A full bladder is detected by stretch receptors and perceived centrally. If voiding is appropriate, 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 [75]. Disrupted innervation can lead to an alteration of this normal, coordinated interaction.

Neurogenic voiding dysfunction is an all-inclusive term that describes those 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 hyperreflexic bladders with sphincter dyssynergia. Lower motor neuron lesions tend to produce an areflexic bladder with variable sphincter function. Unfortunately, there is a huge range of neurological lesions that variably affect the detrusor muscle, striated urethral sphincter, and the smooth muscle of the bladder neck. This highly variable situation makes classification difficult; as a result, popular classifications tend to focus on the dysfunction rather than on the underlying cause [76]. Wein simplified the problem by describing the voiding dysfunction in two broad categories: a failure of storage and a failure of emptying [77]. Adequate storage requires bladder compliance, capacity, and an outlet resistance at the bladder neck. 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. 8.6). Based on this understanding one can see how the neurogenic bladder may be incontinent, continent, or hypercontinent.

Regardless of the detrusor compliance, poor tone in the sphincter mechanism usually leads to incontinence. Provided it is associated with low leak point pressures, there should be no threat to the functioning of the upper tracts. The "hostile bladder" is found in situations where hyperreflexic, poorly compliant, small capacity bladders are combined with high outlet resistance. This resistance is caused by sphincter hypertonia and detrusor-sphincter dyssynergia (DSD). In these situations, high filling and voiding pressures are transmitted to the kidney, leading to dysfunction and, if not corrected, permanent damage [78].

Following the diagnosis of neurogenic voiding dysfunction, initial management is directed at maintaining acceptable bladder storage pressures, ensuring efficient emptying and preventing UTIs [79]. Early medical management and close monitoring are the cornerstones of a successful 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 8.2. The majority of children with "hostile bladders" are managed

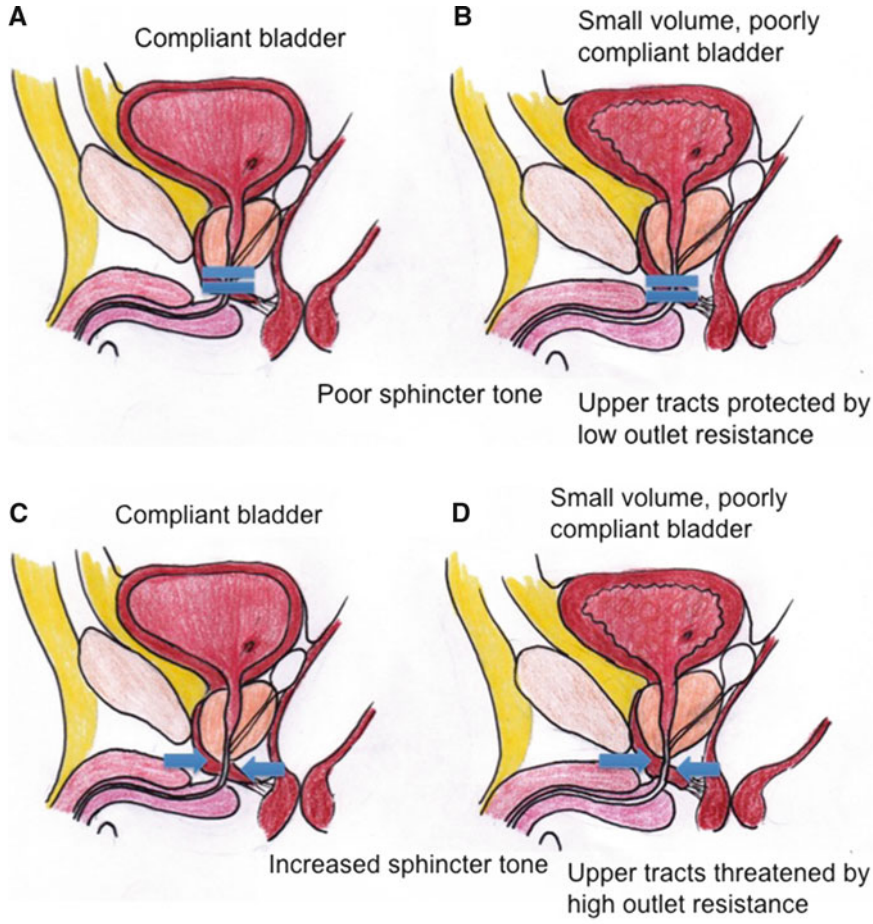

Fig. 8.6 The four broad scenarios created by bladder and sphincter neurology: (**a**) good bladder compliance with poor sphincter tone, (**b**) poor bladder compliance with poor sphincter tone, (**c**) good bladder compliance with increased sphincter tone, (**d**) poor bladder compliance with increased sphincter tone

Table 8.2 Basic concepts of management for neurogenic voiding dysfunction based on Wein classification

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

with a combination of CIC (to ensure regular and complete emptying) [80–82], anticholinergics (to attenuate uninhibited detrusor contractions, increase capacity and decrease tone) [83, 84], α-Blockers (introduced to decrease the sphincter muscle tone) [85, 86], and prophylactic antibiotics (to prevent recurrent UTI).

Surveillance is a crucial component of the management of the neurologically impaired child. In myelodysplasia in particular, 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 renal growth failure, scarring, loss of corticomedullary differentiation, hydronephrosis, bladder wall thickening, and significant residual volumes. In the patients who are able to void, urinary flow rates demonstrate abnormal flow curves and combined with electromyography may demonstrate DSD. Urodynamic studies are useful in monitoring bladder dynamics during the filling and emptying phases. 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, as would be the case in a patient with a tethered cord.

In the event that the above 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 [87, 88] and sphincterotomy (in older male patients) [89]. Vesicostomy produces an incontinent diversion, a safe and reliable method of decompressing the upper tracts in young children with neurogenic bladders [90].

When continence is a 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) [7]. These patients may benefit from a surgically constructed continent catheterizable channel, usually fashioned with the appendix (Mitrofanoff channel) or reconfigured small bowel (Monti channel) [91]. These conduits should be as short and straight as possible to avoid intubation issues, and run into the bladder from an easily accessible, cosmetically sensitive 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. 8.7).

Fig. 8.7 Patient with an appendico-vesicostomy (Mitrofanoff channel), performing self-catheterization through stoma located at the umbilicus

When it comes to specific surgical interventions for improving compliance, increasing capacity and decreasing uninhibited detrusor contractions there are a number of surgical options that disrupt the detrusor muscle and augment the bladder. Enterocystoplasty is the most commonly used technique 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 intestinal

patch can be ileum, colon, or stomach but the most commonly used segment appears to be the ileum [92, 93]. Because of the absorptive and secretory functions of the gastrointestinal epithelium, metabolic abnormalities may develop over time and become clinically relevant in children with marginal renal function. In order to offset the metabolic impact of the intestinal segments the bladder can also be augmented using tissue naturally lined by urothelium. With the exception of ureterocystoplasty, the urodynamic results of these procedures are less reliable and associated with only a modest improvement in many cases. Ureterocystoplasty is, on the other hand, very effective and describes the use of the dilated tortuous ureter of a poorly functioning renal unit to augment the bladder [94, 95]. Auto-augmentation effectively creates a diverticulum of bladder mucosa that is allowed to protrude from a wide surgical incision in the detrusor muscle, thereby increasing compliance capacity.

A summary of the advantages and disadvantages of common bladder augmentation procedures is provided in Table 8.3

Table 8.3 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 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/ileo-colic
Large diameter
Reliable blood supply
Mobile segments
Ileocaecal 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 alkanization required if renal function impaired
Mucus production +++
Bladder stone and UTI risks +++
? Higher perforation rate
? Tumor formation
Gastrocystoplasty
• Greater curvature of stomach
No absorption of urinary waste
Secretes acid ameliorating metabolic acidosis
Less mucus, stones, and infections
May facilitate emptying
Hematuria dysuria syndrome notable in sensate, incontinent patients
Caution in defunctioned bladders: bleeding, ulcers, and perforation
Less compliant
? turno formatio Less capacious
Ileocystoplasty
• Preterminal ileum
Reliable blood supply and length
Most compliant bowel segment
Hyperchloremic metabolic acidosis
Mucus production ++
Stones and infection
Vitamin B_{12} deficiency
? Tumor formation

Bladder Augmentation and End-Stage Renal Disease

It is reasonable to expect that if a severely dysfunctional bladder has caused or facilitated the failure of the native kidneys then a kidney transplanted into the same environment will be exposed to the same hostile forces and is therefore at risk. Initially severe bladder dysfunction was a contraindication to transplantation, but over time, effective reconstruction of the lower tract allowed for the creation of a safe reservoir for urine storage. This has allowed for successful renal transplantation in children with stage 5 CKD and severe LUT dysfunction.

The safety and timing of bladder augmentation in the child with stage 5 CKD (ESRD) has been the subject of a number of studies [96–103]. The cumulative graft survival rates for the children who underwent major LUT reconstruction seem favorable but are difficult to accurately

compare for a lack of standardized follow-up period [98, 100, 101, 104]. Having established the safety of transplantation in these patients, timing of the reconstruction in relation to the transplantation became the next important question. Basiri conducted a retrospective study looking at three groups of 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. Graft survival and incidence of symptomatic UTI were no different in the two augmented groups but the group that did not require augment did significantly better in both outcomes. Basiri suggested that the increased incidence of UTI could be the cause of lower graft survival rates in the augmented groups [99]. In additional studies, DeFoor acknowledged the high rate of posttransplant sepsis in the series by Koo [104] and Hatch [101] and contrasted this to his own report on a series of 20 patients who underwent enterocystoplasty pre-transplant. DeFoor suggested that prophylactic antibiotics and the predominance of gastrocystoplasty (85%) were likely contributors to the unusually low rate of UTI seen in his patients [98].

In summary major LUT reconstruction appears safe prior to renal transplantation. It should be remembered that these bladders are inherently dysfunctional and the augmentation cannot be expected to completely negate the consequences of that dysfunction. In conjunction with this, the reconstructive procedures carry with them inherent metabolic, functional, and surgical risks that often persist throughout life. It is unlikely, therefore, that graft survival can be expected to be as good or better than it is in children with normal bladders, but it is encouraging that results are seldom shown to be significantly worse.

Prune Belly Syndrome

Three abnormalities define prune belly syndrome (PBS): an absence or deficiency of abdominal wall musculature, bilateral cryptorchidism, and dilated uropathy involving the urethra, bladder, and ureters (Fig. 8.8). PBS has an incidence of 1 in 29,000 to 1 in 40,000 live births. The precise cause of PBS remains unknown [105, 106]. The full-blown syndrome is unique to the male patient; a "pseudoprune" disorder can occur in both males and females and describes the identical pathology to the PBS but lacking the complete triad of features [107–109]. Associated pulmonary, cardiac, orthopedic, and gastrointestinal abnormalities are relatively common and contribute to overall morbidity and mortality [110]. The underlying pathology and possible clinical presentation is summarized in detail in Table 8.4 [111, 112].

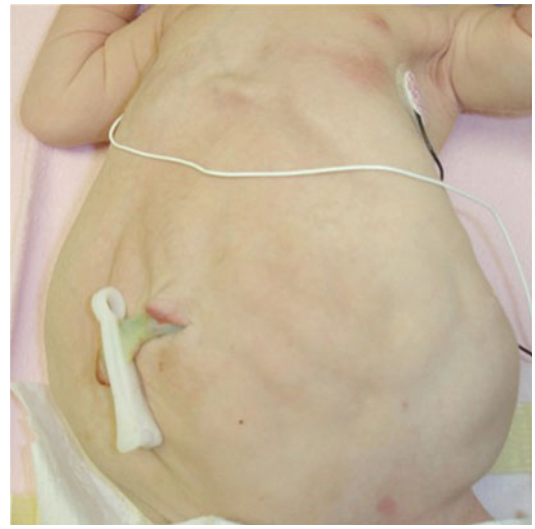

Fig. 8.8 Characteristic abdominal wall appearance in a newborn boy with prune belly syndrome

From a urological perspective, 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, a consequence of gross dilation. If obstruction is present, 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

Table 8.4 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 spermatagonia or azoospermia • Paternity may be possible with assisted reproductive techniques
Genital conduits	• Epididymal-testicular dissociation • Ectopic, thickened vas • 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 diverticulae common • Hypoplastic or absent verumontanum • Reflux into the vas can be seen • Obstructive 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 • Uretero pelvic 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

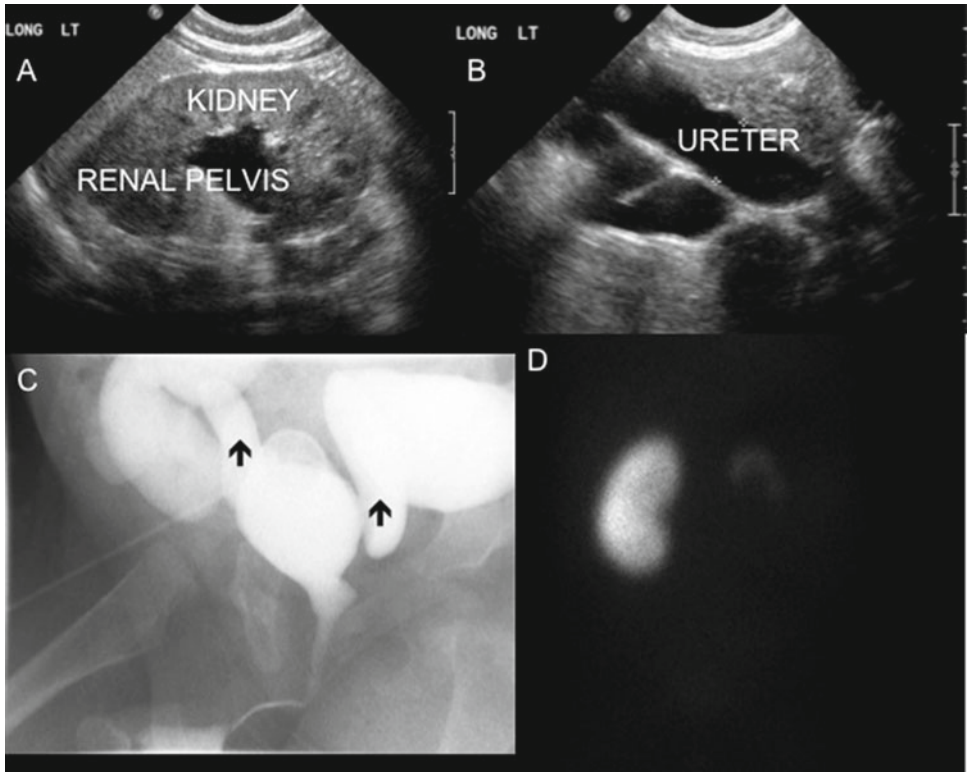

Fig. 8.9 Imaging studies in a patient with prune belly syndrome: (**a** and **b**) hydroureteronephrosis with dilated and tortuous ureter; (**c**) VCUG after vesicostomy creation demonstrating bilateral high-grade reflux into dilated distal ureters (*arrows*); (**d**) posterior view of a DMSA scan demonstrating poor right renal differential function

Table 8.5 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 renal function
3	No renal dysplasia No pulmonary hypoplasia	Excellent prognosis provided upper tracts are protected

there have been recurrent febrile UTIs, a nuclear medicine scan is indicated (Fig. 8.9).

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 has to be individualized. It is useful to consider the child with PBS as fitting into three broad categories as outlined by Woodard [113] (Table 8.5). Category 1 children have severe pulmonary and renal dysplasia and have a very poor prognosis. Outcome is largely determined by pulmonary function and possible associated cardiac defects. Urological management should aim to identify obstructing uropathy and, if present, may involve diverting the upper tracts if appropriate for the individual patient. Category 2 patients tend to have no immediate threat to life but renal dysfunction is significant. Baseline renal function has to be monitored and optimized. Management should involve a multidisciplinary team with active participation of pediatric nephrologists and urologists. The structural integrity of the renal tracts has to be regularly assessed and conditions that

threaten the kidneys need to be identified and treated early. Category 3 patients demonstrate good renal function despite their grossly dilated urinary tracts. They have a good prognosis, because they lack renal dysplasia, but they still require close monitoring for signs of deteriorating renal or urinary tract function.

Management of these complex patients is aimed at delaying the onset of renal failure. It should include prophylactic antibiotics because of the potential for VUR and urinary stasis. Timed voiding, double voiding, and CIC, when necessary, are recomended to facilitate complete bladder emptying. Pyleostomies, ureterostomies, or vesicostomies are unusual interventions that may be required to divert the urinary stream above 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 [114, 115]. The timing of and indication for the above interventions vary with each patient and institutional protocols.

There is debate on the best management of children with PBS. Where the debate lingers is the question of how aggressive to be when considering surgery. Aggressive reconstruction involves simultaneous and early (3 months to 1 year of age) resection, tapering and reimplantation of the ureters, bilateral transabdominal orchidopexy, abdominoplasty, and may include reduction cystoplasty or resection of the urachal diverticulum [116]. With the lack of a clear benefit in bladder capacity or voiding efficiency[117], reduction cystoplasty is not recommended by all proponents of the more aggressive approach [118]. Conversely, the conservative approach argues that surgery cannot improve baseline renal function and should not be prophylactic but rather reserved for those patients in whom obstruction, stasis, or reflux is causing a problem [115, 119].

Regardless of how well we manage these children, some will progress to stage 5 CKD. In this event, PBS is not a contraindication to either peritoneal dialysis (PD) or renal transplantation. While PD does pose some unique challenges with respect to anchoring the PD catheter to the attenuated abdominal wall [120], it is successful at temporarily replacing renal function. Renal transplantation in children with PBS has not shown a statistically significant difference in graft or patient survival [121, 122].

Urological Issues in the Pre-transplant Workup

Unlike adult patients, pediatric transplant recipients often have urological issues that have caused or contributed to their renal failure. It is therefore imperative that the pediatric urologist is integrally involved in the pre-transplant workup and optimization of these patients. The pre-transplant 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. 8.10) and, in the case of a living donor, the renal 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 pre-transplant 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 is in contrast to the dysfunctional bladder that could threaten the survival of the allograft if not addressed prior to surgery. In this regard, pre-transplant undiversion or sham bladder cycling via urethral or suprapubic catheter has been suggested as an important diagnostic step in the workup of these patients.

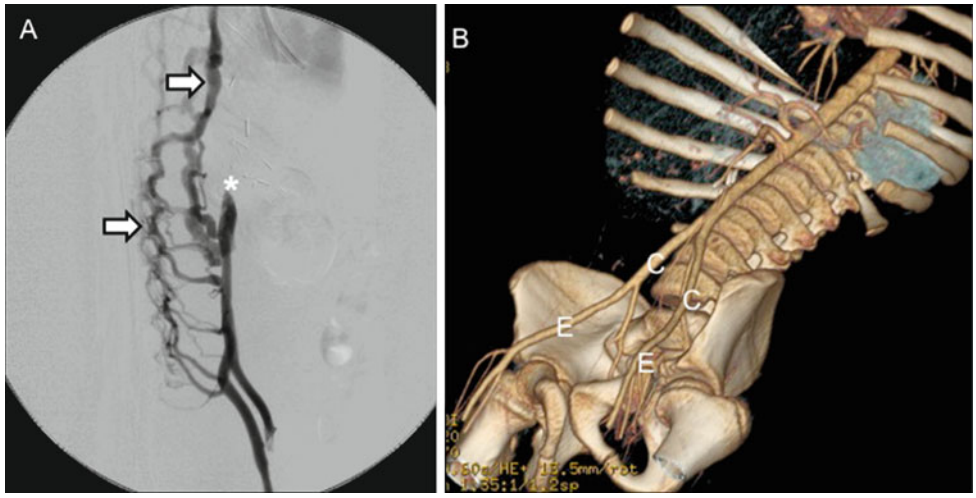

Fig. 8.10 Imaging studies used to further evaluate abdomino-pelvic vascular anatomy following abnormal Doppler ultrasound screening: (**a**) Venogram demonstrating occluded inferior vena cava (*) with prominent collaterals into lumbar veins and the azygos system (*arrows*). (**b**) CT scan reconstruction 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 [66, 69]. This is especially true of patients with underlying voiding dysfunction and those with high-grade reflux (grade IV–V) [55, 69]. Basiri found that preemptive ureteral reimplantation failed to reduce the risk of infection in patients with VUR who underwent transplantation. However, 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 pre-transplant, 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 is able to 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 renal 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 a number of situations in which nephrectomy is indicated (Table 8.6). Renin-dependent hypertension is common to focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome, reflux nephropathy, and cystinosis. Pre-transplant nephrectomy may be indicated in these patients as steroid medication

Table 8.6 Indications for pre-transplant nephrectomy

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

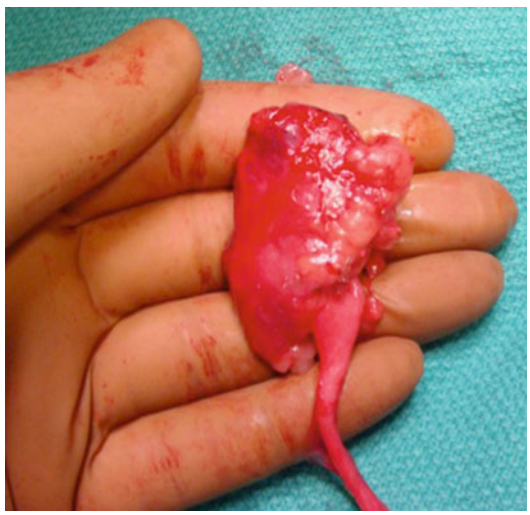

Fig. 8.11 A small atrophic kidney removed laparoscopically in a patient with stage 5 CKD and renin-mediated hypertension. Procedure performed in preparation for renal transplantation, with improvement in blood pressure control

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. 8.11). Additionally, the vaso-active 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 renal tract dysfunction and, if present, is an indication for nephrectomy [123]. Massive 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 suitable 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 renal unit ahead of immunosuppressive therapy. The kidney that is predisposed to symptomatic stone formation should 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 [124]. 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. 8.12).

When nephrectomy is being considered in the child with stage 5 CKD (ESRD) one has to 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.

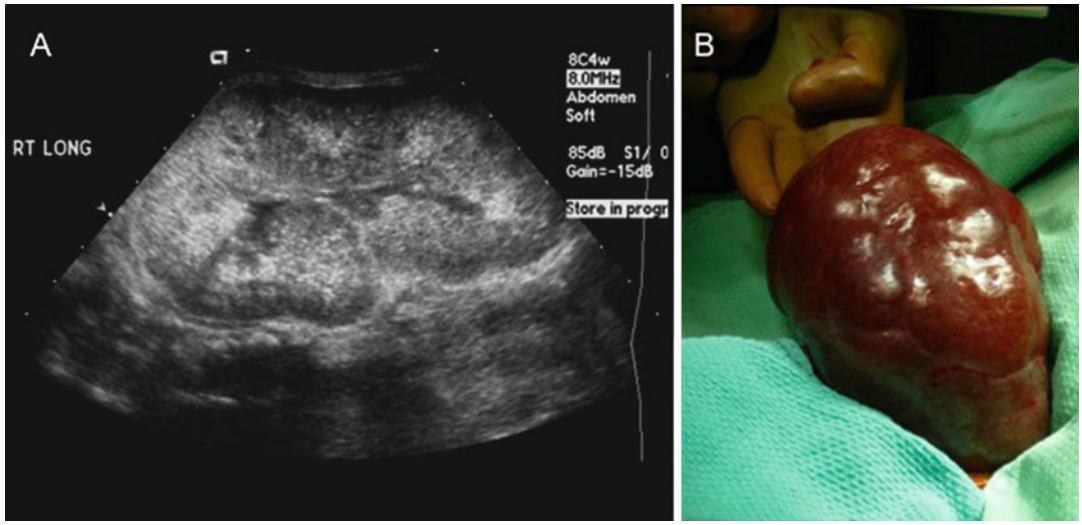

Fig. 8.12 Large kidney removed from patient with autosomal recessive polycystic kidney disease due to inability to effectively carry out peritoneal dialysis. Patient subsequently has been considered for deceased donor renal transplantation. Notice large size of the native kidney on ultrasound (**a**) and at the time of open nephrectomy (**b**, compare size to surgeon's hand in the background)

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 [123, 125, 126].

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 [127, 128].

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 [129].

The persistence of a patent processus vaginalis is found in 90% of neonates and predisposes them to the development of an indirect inguinal hernia [130]. 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 [131]. 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 [132]. 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 [133, 134].

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 (horizontal paramedian incision), hernia repair (inguinal/umbilical incisions), ventriculo-peritoneal shunt placement (horizontal upper quadrant), and renal 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. 8.13). 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.

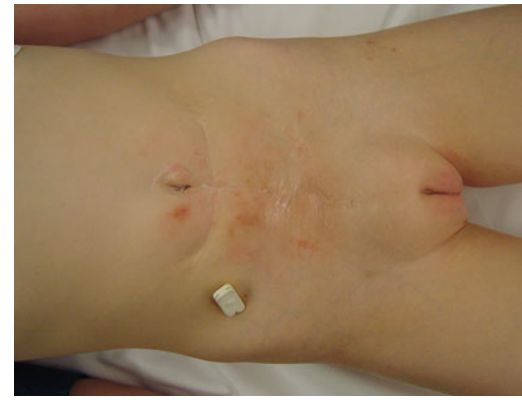

Fig. 8.13 The scarred lower abdomen of a patient with CKD following multiple surgical interventions

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 practice to find urological issues destroying normal kidneys. It is far more common that renal dysfunction preexists as part of, or secondary to, early fetal

urological pathology. Despite fetal interventions, we are unable to alter this congenital renal dysfunction and are therefore restricted to prolonging native function by optimizing the drainage of urine from these kidneys in order to prevent infection and pressure from damaging them further. Additionally, we must be cognizant of the fact that many of these patients will require more than one major surgical intervention, including renal transplantation, during their lifetime and decisions made in their early management will have lifelong implications.

References

1. Orr NI, et al. Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. Pediatr Nephrol. 2009;24(9):1719–26.
2. Deleau J, et al. Chronic renal failure in children: an epidemiological survey in Lorraine (France) 1975–1990. Pediatr Nephrol. 1994;8(4):472–6.
3. Neu AM, et al. Chronic dialysis in children and adolescents: the 2001 NAPRTCS annual report. Pediatr Nephrol. 2002;17(8):656–63.
4. Ardissino G, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003;111(4 Pt 1):e382–7.
5. Chesney RW, et al. Report of an NIH task force on research priorities in chronic kidney disease in children. Pediatr Nephrol. 2006;21(1):14–25.
6. Seikaly MG, et al. Chronic renal insufficiency in children: the 2001 annual report of the NAPRTCS. Pediatr Nephrol. 2003;18(8):796–804.
7. de Jong TP, et al. Treatment of the neurogenic bladder in spina bifida. Pediatr Nephrol. 2008;23(6):889–96.
8. Kari JA. Neuropathic bladder as a cause of chronic renal failure in children in developing countries. Pediatr Nephrol. 2006;21(4):517–20.
9. Kari JA, et al. Renal involvement in children with spina bifida. Saudi J Kidney Dis Transpl. 2009;20(1):102–5.
10. DeFoor W, et al. Risk factors for end stage renal disease in children with posterior urethral valves. J Urol. 2008;180(4 Suppl):1705–8. Discussion 1708.
11. Dik P, et al. Early start to therapy preserves kidney function in spina bifida patients. Eur Urol. 2006;49(5):908–13.
12. Coulthard MG, Keir MJ. Reflux nephropathy in kidney transplants, demonstrated by dimercaptosuccinic acid scanning. Transplantation. 2006;82(2):205–10.
13. Strand WR. Initial management of complex pediatric disorders: prunebelly syndrome, posterior urethral valves. Urol Clin North Am. 2004;31(3):399–415, vii.
14. Marra G, 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.
15. Roth KS, et al. Obstructive uropathy: an important cause of chronic renal failure in children. Clin Pediatr (Phila). 2002;41(5):309–14.
16. 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.
17. Casale AJ. Early ureteral surgery for posterior urethral valves. Urol Clin North Am. 1990;17(2):361–72.
18. Thomas DF, Gordon AC. Management of prenatally diagnosed uropathies. Arch Dis Child. 1989;64(1 Spec No):58–63.
19. 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.
20. Roth KS, Carter Jr WH, Chan JC. Obstructive nephropathy in children: long-term progression after relief of posterior urethral valve. Pediatrics. 2001;107(5):1004–10.
21. 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 1034.
22. Ansari M et al. Risk factors for progression to end-stage renal disease in children with posterior urethral valves. J Pediatr Urol. 2010;6:261–4.
23. Warren J, Pike JG, Leonard MP. Posterior urethral valves in Eastern Ontario – a 30 year perspective. Can J Urol. 2004;11(2):2210–5.
24. Smith GH, et al. The long-term outcome of posterior urethral valves treated with primary valve ablation and observation. J Urol. 1996;155(5):1730–4.
25. Holmes N, Harrison MR, Baskin LS. Fetal surgery for posterior urethral valves: long-term postnatal outcomes. Pediatrics. 2001;108(1):E7.
26. McLorie G, et al. Outcome analysis of vesicoamniotic shunting in a comprehensive population. J Urol. 2001;166(3):1036–40.
27. Salam MA. Posterior urethral valve: outcome of antenatal intervention. Int J Urol. 2006;13(10):1317–22.
28. Freedman AL, et al. Long-term outcome in children after antenatal intervention for obstructive uropathies. Lancet. 1999;354(9176):374–7.
29. Georgieva M, et al. Urinary ascites and perirenal urinoma – a renoprotective "complication" of posterior urethral valves. Aktuelle Urol. 2003;34(6):410–2.
30. Rittenberg MH, et al. Protective factors in posterior urethral valves. J Urol. 1988;140(5):993–6.
31. Oliveira EA, et al. Prognostic factors in prenatally-detected posterior urethral valves: a multivariate analysis. Pediatr Surg Int. 2002;18(8):662–7.
32. Mizra K, Onuora V, Al-Sowailem A. Protective factors in posterior urethral valves in Saudi children. Ann Saudi Med. 1998;18(3):263–5.

33. Kaefer M, et al. Posterior urethral valves, pressure pop-offs and bladder function. J Urol. 1995;154 (2 Pt 2): 708–11.
34. Silveri M, 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.
35. Mukherjee S, et al. 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.
36. De Gennaro M, et al. The changing urodynamic pattern from infancy to adolescence in boys with posterior urethral valves. BJU Int. 2000;85(9):1104–8.
37. Emir H, et al. Urodynamic findings of posterior urethral valve patients. Eur J Pediatr Surg. 2002;12(1): 38–41.
38. Mitchell ME. Valve Bladder syndrome. In: Presented at the annual meeting of the North Central Section, Hamilton: American Urological Association; 1980.
39. Koff S, Mutabagani K, Jayanthi V. The valve bladder syndrome: pathophysiology and treatment with nocturnal bladder emptying. J Urol. 2002;167(1):291–7.
40. De Gennaro M, et al. Detrusor hypocontractility in children with posterior urethral valves arises before puberty. Br J Urol. 1998;81(Suppl 3):81–5.
41. Glassberg KI, et al. Observations on persistently dilated ureter after posterior urethral valve ablation. Urology. 1982;20(1):20–8.
42. Nguyen MT, et al. Overnight catheter drainage in children with poorly compliant bladders improves post-obstructive diuresis and urinary incontinence. J Urol. 2005;174(4 Pt 2):1633–6. Discussion 1636.
43. 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.
44. Hassan JM, et al. Vesicoureteral reflux in patients with posterior urethral valves. J Urol. 2003;170(4 Pt 2): 1677–80. Discussion 1680.
45. Priti K, et al. Posterior urethral valves: incidence and progress of vesicoureteric reflux after primary fulguration. Pediatr Surg Int. 2004;20(2):136–9.
46. Cuckow PM, et al. Long-term renal function in the posterior urethral valves, unilateral reflux and renal dysplasia syndrome. J Urol. 1997;158(3 Pt 2): 1004–7.
47. Parkhouse HF, et al. Long-term outcome of boys with posterior urethral valves. Br J Urol. 1988;62(1): 59–62.
48. Heikkila J, Rintala R, Taskinen S. Vesicoureteral reflux in conjunction with posterior urethral valves. J Urol. 2009;182(4):1555–60.
49. Narasimhan KL, et al. The vesicoureteral reflux dysplasia syndrome in patients with posterior urethral valves. J Urol. 2005;174(4 Pt 1):1433–5. Discussion 1435.
50. Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. Clin Nephrol. 1973;1(3):132–41.
51. Rolleston GL, Shannon FT, Utley WL. Relationship of infantile vesicoureteric reflux to renal damage. Br Med J. 1970;1(5694):460–3.
52. Roberts JA. Pathogenesis of pyelonephritis. J Urol. 1983;129(6):1102–6.
53. Roberts JA. Vesicoureteral reflux in the monkey: a review. Urol Radiol. 1983;5(3):211–7, 219.
54. Fenton S, et al. Renal replacement therapy in Canada: a report from the Canadian organ replacement register. Am J Kidney Dis. 1995;25(1):134–50.
55. Casale P, et al. 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.
56. Ardissino G, 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.
57. Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev. 2001;4: CD001534.
58. Conway PH, et al. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. JAMA. 2007;298(2): 179–86.
59. Pennesi M, 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.
60. Roussey-Kesler G, 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 679.
61. Hadjizadeh N, et al. Association of voiding dysfunction with functional constipation. Indian Pediatr. 2009;46(12):1093–5.
62. Halachmi S, Farhat WA. The impact of constipation on the urinary tract system. Int J Adolesc Med Health. 2008;20(1):17–22.
63. Kasirga E, et al. Evaluation of voiding dysfunctions in children with chronic functional constipation. Turk J Pediatr. 2006;48(4):340–3.
64. Mathew TH, Kincaid-Smith P, Vikraman P. Risks of vesicoureteric reflux in the transplanted kidney. N Engl J Med. 1977;297(8):414–8.
65. Prat V, et al. Urinary tract infection in renal transplant patients. Infection. 1985;13(5):207–10.
66. Ranchin B, et al. Vesicoureteral reflux after kidney transplantation in children. Nephrol Dial Transplant. 2000;15(11):1852–8.
67. Fontana I, et al. Impact of vesicoureteral reflux on graft survival in paediatric kidney transplants. Transplant Proc. 1998;30(5):2000–1.
68. Dunn SP, et al. Pyelonephritis following pediatric renal transplant: increased incidence with vesicoureteral reflux. J Pediatr Surg. 1987;22(12): 1095–9.

69. Basiri A, et al. Does pre-transplantation antireflux surgery eliminate post-renal transplantation pyelonephritis in children? J Urol. 2006;175(4):1490–2.
70. Barrero R, et al. Vesicoureteral reflux after kidney transplantation in children. Pediatr Transplant. 2007; 11(5):498–503.
71. Engelstein D, et al. A critical appraisal of vesicoureteral reflux in long-term renal transplantation recipients: prospective study. Transplant Proc. 1997; 29(1–2):136–7.
72. Neuhaus TJ, et al. Pyelonephritis and vesicoureteral reflux after renal transplantation in young children. J Urol. 1997;157(4):1400–3.
73. Cloix P, et al. Endoscopic treatment of vesicoureteric reflux in transplanted kidneys. Br J Urol. 1993;72(1): 20–2.
74. Williams MA, Giel DW, Hastings MC. Endoscopic Deflux injection for pediatric transplant reflux: a feasible alternative to open ureteral reimplant. J Pediatr Urol. 2008;4(5):341–4.
75. 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.
76. Neveus T, 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.
77. Wein AJ. Classification of neurogenic voiding dysfunction. J Urol. 1981;125(5):605–9.
78. Joseph DB. Current approaches to the urologic care of children with spina bifida. Curr Urol Rep. 2008; 9(2):151–7.
79. 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.
80. Kaefer M, et al. Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. J Urol. 1999;162(3 Pt 2):1068–71.
81. Edelstein RA, 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.
82. Lapides J, et al. Clean, intermittent self-catheterization in the treatment of urinary tract disease. J Urol. 1972;107(3):458–61.
83. Goto M, et al. 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.
84. Thompson IM, Lauvetz R. Oxybutynin in bladder spasm, neurogenic bladder, and enuresis. Urology. 1976;8(5):452–4.
85. Koyanagi T. Further observation on the denervation supersensitivity of the urethra in patients with chronic neurogenic bladders. J Urol. 1979;122(3): 348–51.
86. Takimoto Y, 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.
87. Wan J. The role of urethral dilation in managing pediatric neurogenic bladder dysfunction. Curr Urol Rep. 2009;10(2):153–8.
88. Park JM, et al. External urethral sphincter dilation for the management of high risk myelomeningocele: 15-year experience. J Urol. 2001;165(6 Pt 2): 2383–8.
89. Pan D, et al. Long-term outcomes of external sphincterotomy in a spinal injured population. J Urol. 2009;181(2):705–9.
90. Morrisroe SN, et al. Vesicostomy revisited: the best treatment for the hostile bladder in myelodysplastic children? BJU Int. 2005;96(3):397–400.
91. 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.
92. 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.
93. Gurocak S, et al. Bladder augmentation: Review of the literature and recent advances. Indian J Urol. 2007;23(4):452–7.
94. Churchill BM, et al. Ureteral bladder augmentation. J Urol. 1993;150(2 Pt 2):716–20.
95. Landau EH, et al. Bladder augmentation: ureterocystoplasty versus ileocystoplasty. J Urol. 1994;152 (2 Pt 2):716–9.
96. Capizzi A, et al. Kidney transplantation in children with reconstructed bladder. Transplantation. 2004; 77(7):1113–6.
97. Djakovic N, et al. Intestinal reconstruction of the lower urinary tract as a prerequisite for renal transplantation. BJU Int. 2009;103(11):1555–60.
98. DeFoor W, et al. 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 1500.
99. Basiri A, et al. Kidney transplantation in children with augmentation cystoplasty. J Urol. 2007;178(1): 274–7. Discussion 277.
100. Fontaine E, et al. Renal transplantation in children with augmentation cystoplasty: long-term results. J Urol. 1998;159(6):2110–3.
101. Hatch DA, et al. Kidney transplantation in children with urinary diversion or bladder augmentation. J Urol. 2001;165(6 Pt 2):2265–8.
102. Power RE, et al. Renal transplantation in patients with an augmentation cystoplasty. BJU Int. 2000; 86(1):28–31.
103. Rigamonti W, et al. Kidney transplantation into bladder augmentation or urinary diversion: long-term results. Transplantation. 2005;80(10):1435–40.
104. Koo HP, et al. Renal transplantation in children with severe lower urinary tract dysfunction. J Urol. 1999; 161(1):240–5.

105. Ives EJ. The abdominal muscle deficiency triad syndrome–experience with ten cases. Birth Defects Orig Artic Ser. 1974;10(4):127–35.
106. Williams DI, Burkholder GV. The prune belly syndrome. J Urol. 1967;98(2):244–51.
107. Rabinowitz R, Schillinger JF. Prune belly syndrome in the female subject. J Urol. 1977;118(3):454–6.
108. Aaronson IA, Cremin BJ. Prune belly syndrome in young females. Urol Radiol. 1979;1(3):151–5.
109. Bellah RD, States LJ, Duckett JW. Pseudoprune-belly syndrome: imaging findings and clinical outcome. AJR Am J Roentgenol. 1996;167(6):1389–93.
110. 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.
111. Woods AG, Brandon DH. Prune belly syndrome: a focused physical assessment. Adv Neonatal Care. 2007;7(3):132–43. quiz 144–5.
112. Ashcraft's Pediatric Surgery George Whitfield Holcomb III and J. Patrick Murphy (Editors) Saunders 5th edition Chapter 62: Prune Belly Syndrome by Romano DeMarco Pages 796–804.
113. Woodard JR. Prune belly syndrome. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1985. p. 805–24.
114. Smith CA, et al. Voiding function in patients with the prune-belly syndrome after Monfort abdominoplasty. J Urol. 1998;159(5):1675–9.
115. Diao B, et al. Prune belly syndrome: epidemiologic, clinic and therapeutic aspects. Prog Urol. 2008; 18(7):470–4.
116. Fallat ME, et al. The prune belly syndrome: a comprehensive approach to management. J Urol. 1989; 142(3):802–5.
117. Bukowski TP, Perlmutter AD. Reduction cystoplasty in the prune belly syndrome: a long-term followup. J Urol. 1994;152(6 Pt 1):2113–6.
118. Kinahan TJ, et al. The efficiency of bladder emptying in the prune belly syndrome. J Urol. 1992;148(2 Pt 2):600–3.
119. Hubinois P, Valayer J, Cendron J. A series of 34 cases of prune belly syndrome in children. Sem Hop. 1983;59(40):2769–77.
120. Crompton CH, Balfe JW, Khoury A. Peritoneal dialysis in the prune belly syndrome. Perit Dial Int. 1994;14(1):17–21.
121. Fontaine E, et al. Long-term results of renal transplantation in children with the prune-belly syndrome. J Urol. 1997;158(3 Pt 1):892–4.
122. Reinberg Y, et al. The outcome of renal transplantation in children with the prune belly syndrome. J Urol. 1989;142(6):1541–2.
123. 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.
124. Broyer M. What are the indications for nephrectomy, either bilateral or unilateral, prior to transplantation in children? Pediatr Nephrol. 1991;5(1):11.
125. 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.
126. Doublet JD, et al. Retroperitoneal laparoscopic nephrectomy of native kidneys in renal transplant recipients. Transplantation. 1997;64(1):89–91.
127. 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.
128. Dunn MD, 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.
129. von Lilien T, et al. Hernias: a frequent complication in children treated with continuous peritoneal dialysis. Am J Kidney Dis. 1987;10(5):356–60.
130. White JJ, HaIler JA. Groin hernia in infants and children. In: Nyphus LM, Condon RE, editors. Hernia. Philadelphia: Lippincott; 1978.
131. Aranda RA, et al. Intraperitoneal pressure and hernias in children on peritoneal dialysis. Pediatr Nephrol. 2000;14(1):22–4.
132. Wetherington GM, et al. Abdominal wall and inguinal hernias in continuous ambulatory peritoneal dialysis patients. Am J Surg. 1985;150(3): 357–60.
133. Khoury AE, et al. Hernias associated with CAPD in children. Adv Perit Dial. 1991;7:279–82.
134. Tank ES, Hatch DA. Hernias complicating chronic ambulatory peritoneal dialysis in children. J Pediatr Surg. 1986;21(1):41–2.

Conservation of Residual Renal Function in Children Reaching End-Stage Renal Disease

9

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Keywords
Residual renal function • End-stage renal disease • Children

Introduction

Chronic kidney disease (CKD) progresses at variable rate toward end-stage renal disease (ESRD) (Fig. 9.1) [1], and residual renal function (RRF) continues to decrease gradually after initiation of dialysis which is usually initiated when RRF has underpassed 5–10 mL/min/1.73 m² of glomerular filtration rate.

Once dialysis is commenced, most physicians focus on optimal delivery of dialysis rather than the native kidneys' function, which seems to be negligible and beyond control. However, evidence is accumulating that preservation of RRF may be more important than dialysis prescription to prevent cardiac dysfunction and volume overload, maintain nutritional status, growth, and quality of life, and minimize mortality on dialysis [2, 3]. Hence, careful attention to RRF preservation should be a key component to the management of dialyzed patients, especially when an extended duration of dialysis dependence is expected [4].

Experimental and clinical investigations over the past two decades 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 subset 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 measured as a part of the dialysis adequacy assessment (see chapter 11 and chapter 18). The amount of urine volume, normalized to body surface area, is a useful indicator of RRF. The most practical and sufficiently accurate assessment of residual GFR is the arithmetic mean of the urinary creatinine and the urea clearances. The K/DOQI guidelines recommend measurement of RRF 1 month after start of dialysis and at least every 3 months as long as RRF is maintained.

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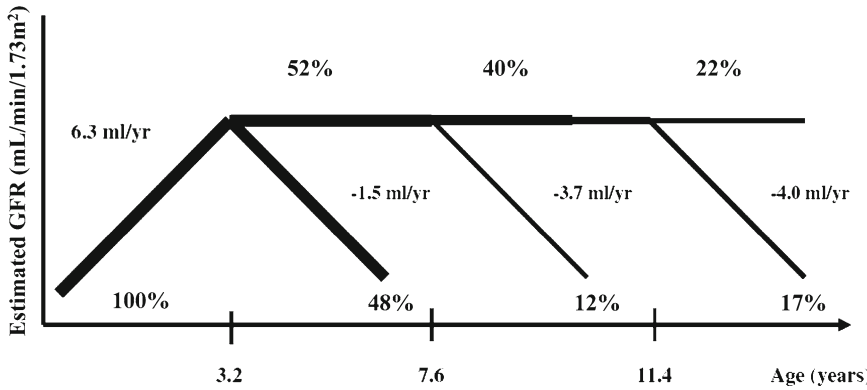

Fig. 9.1 Natural course of renal function in children with renal hypodysplasia. Early postnatal GFR increase followed by progressive deterioration after a stable interim period of variable duration (Source: Reproduced from Ref. [1])

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 defined by small molecule clearance delivery with patient death while on PD [5]. However, later studies separating the effects of renal and peritoneal clearance components revealed that patient survival is correlated with RRF or urine volume, and not with the dose of PD [6–12]. Reanalysis of the CANUSA study also confirmed that patient mortality was associated with renal clearance and urine volume, and not with dialytic clearance [13]. The mortality of adult patients on hemodialysis has also been found to depend on the presence of RRF [14].

Considerable evidence suggests 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 completely attributable to cardiovascular reasons of death [15]. Low urine output has been linked to hypertension, left ventricular hypertrophy, and valvular calcification in chronic PD [16, 17]. In children on PD, RRF is the most important single factor protecting from hypervolemia [18], and its loss predicts diastolic dysfunction [19].

Hyperphosphatemia and hypercalcemia are important mediators of the cardiovascular "toxicity" of ESRD. RRF is an important determinant of serum phosphate levels in PD [20]. As a consequence, anuric PD patients show a high calcium–phosphorus product [21] 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 [22]. In children on PD, beta2-microglobulin, cystatin C, and inulin were shown to be removed mainly by renal clearance [23].

Removal of uremic toxins insufficiently cleared by dialysis may also help to preserve growth and nutrition in dialyzed children. *Statural growth*, expressed as change in height SDS over time, was found to be related with RRF but not with peritoneal solute removal [24]. In a large cohort of PD patients, serum albumin levels correlated positively with RRF [11]. In a recent study of children and adolescents on chronic hemodialysis, RRF positively affected nutritional status independently of dialysis efficacy and rhGH treatment [25]. Also, erythropoietin serum levels tend to be higher in children with RRF [26].

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*.

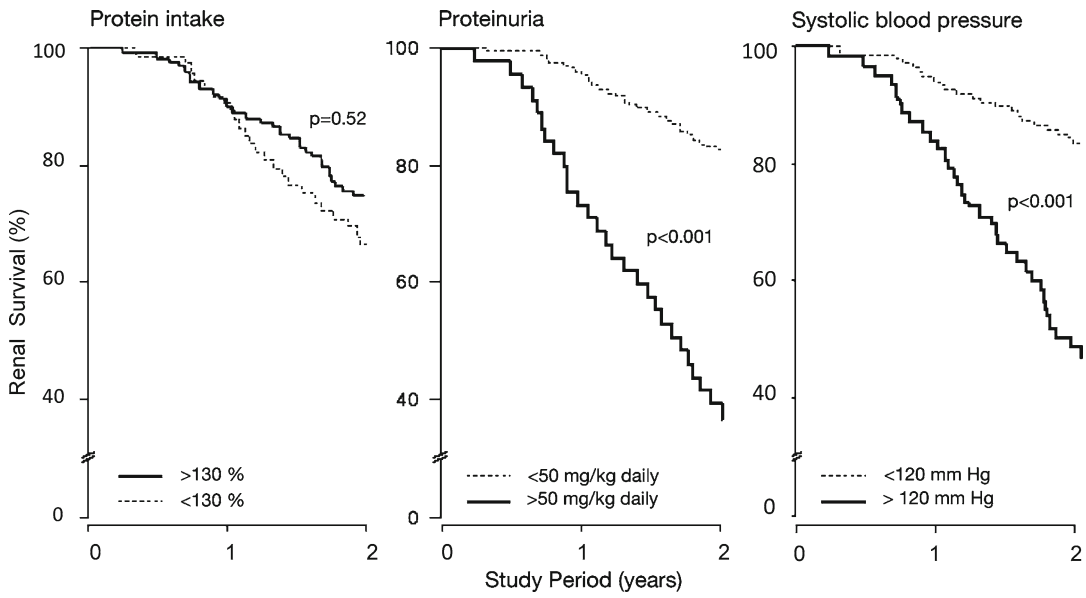

Fig. 9.2 Renal survival in children is associated with proteinuria and hypertension, but not dietary protein intake (Source: Reproduced from Ref. [34])

Observational data unequivocally show an association between the prevailing blood pressure and the rate of CKD progression in adults with CKD [27]. Observations in adults and children suggest that hypertension remains associated with loss of RRF when ESRD is reached [28–30]. Data from the NAPRTCS registry suggested that systolic hypertension predicts CKD progression also in pediatric nephropathies [31]. 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 [32].

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 [32, 33]. The predictive role of proteinuria was also confirmed in studies that included glomerular disorders [1] and in a pediatric prospective multicenter cohort study (Fig. 9.2) [34, 35]. The ESCAPE trial showed an association of proteinuria at baseline, as well as of residual proteinuria during ACE inhibition, with progression [36, 37]. Observational studies in adult patients suggest that the relationship between proteinuria and the rate of loss of RRF persists even after attainment of ESRD [29, 30, 38], providing a rationale for continued antiproteinuric treatment after initiation of dialysis.

The *underlying kidney disorder* is an important predictor of CKD progression. Acquired kidney diseases, usually affecting primarily the glomerulus, generally tend to progress more rapidly than congenitally malformed kidneys [31, 39]. In adult ESRD patients on PD, the diagnosis of a glomerulopathy is a predictor of rapid RRF loss [40, 41], although this difference may not be relevant when HD patients are included [29].

Moreover, progression of pre-end-stage CKD is not linear but depends on *the prevailing degree of renal impairment*: the lower the current GFR, the higher the loss of GFR that can be expected within a given time window. In different pediatric studies, cutoff GFR levels predicting a faster decline of renal function were 30, 40, or 50 mL/min/1.73 m², respectively [1, 31, 42]. In children commencing dialysis, a daily urine volume of less than 1,000 mL/m² was a risk factor for developing anuria [43], and in adult patients, an earlier start of PD was associated with better subsequent preservation of RRF [44]. Conversely, however, other studies that have prospectively monitored the evolution of RRF after start of dialysis suggested faster RRF loss with higher baseline urine

volume or GFR [30, 45]. The exponential decline pattern of RRF observed in adult patients on PD is consistent with these findings [46, 47].

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 CKD [48]. In a recent randomized clinical trial, correction of metabolic acidosis slowed CKD progression in adults [49].

Furthermore, GFR declined more rapidly in adolescent CKD patients with significant *anemia* [50]. In a randomized controlled study in adults, early administration of erythropoietin targeting at a higher hemoglobin level significantly slowed the progression of CKD [51]. 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 [52]. 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 [26].

In adults, *dyslipidemia* (hypertriglyceridemia and low HDL cholesterol) appears to have a small but significant effect on the relative risk of progression [53]. In children with renal malformations, the occurrence of more than two episodes of *febrile UTI* was associated with a faster decline of renal function [1]. GFR declined faster in *hypoalbuminemic* patients, but this may reflect the effect of proteinuria [42, 50].

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 [54]. High serum calcium was also independently associated with a decreased risk of RRF loss in adult dialysis patients [55]. In another study, PD patients with no RRF showed a higher calcium–phosphorus product (Ca×P) [17]. 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 [56].

The role of *genetic factors* in determining the rate of renal failure progression still awaits full exploration. Whereas no gender difference has been noted in cohorts encompassing the pediatric age range [31, 42], GFR appears to decline more rapidly in adult and adolescent males [26, 50], compatible with an adverse impact of androgens (or a protective effect of female sex steroids) on the conservation of RRF in CKD. In adult patients on dialysis, the impact of gender is controversial: Faster loss of RRF was found associated with male [38], female [55], and independent of gender [40, 57].

Furthermore, African American ethnicity is a significant risk factor of progression in pediatric CKD patients [31]. Nonwhite race also predicts rapid loss of RRF in adults on dialysis [55].

The DD genotype, a common variant of the ACE gene, was found overrepresented in pediatric ESRD as compared to the general population [58]. 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 [59]. Other studies suggested an association of the DD genotype with declining renal function also in pediatric glomerular diseases with normal renal function [60, 61]. Furthermore, polymorphisms in the KLK1 and the TGF-beta1 genes were reported as risk factors for renal deterioration in reflux nephropathy [62]. Ongoing large-scale whole genome association studies in large CKD cohorts are hoped to establish the most relevant common genetic variants related to CKD progression in both adult and pediatric populations.

Rapid *somatic growth* and gain in body weight is associated with accelerated deterioration of renal function [32]. Patient age, reflecting body growth, is a general risk factor for progression in children [31, 32, 63]; 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 [64]. 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 [65].

Interestingly, in adult patients on long-term dialysis *obesity* is associated with an accelerated decline of RRF [38, 66, 67].

Specific Risk Factors for Loss of RRF in Patients on Dialysis

RRF decreases with *time on dialysis* [55]. The loss over time is exponential rather than linear [46]. In a study in adult patients on hemodialysis and PD, the decline of RRF was most prominent during the first 3 months after the start of dialysis [29]. Repetitive intravascular volume depletion and hypotensive events are considered important causes of a rapid loss of RRF [66]. Congestive heart failure was also correlated with faster decline of RRF in adults [38, 55, 66].

The choice of *dialysis modality* has a crucial impact on RRF. There is ample evidence both in adults and children that RRF is preserved better in PD than with hemodialysis [43, 55, 68–70]. A more than two times faster decline of RRF was observed in adult patients on HD compared to those on CAPD [55, 68]. 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. 9.3) [43]. 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 [68].

Several studies have suggested that the preservation of RRF may be affected by the PD modality. A more rapid decline was observed in some studies with the more intermittent fluid removal obtained by automated PD than with CAPD [71–73]; however this finding is not unequivocal [40, 74, 75]. Automated PD was still associated with better preservation of RRF than observed even with hemodiafiltration, the hemodynamically least challenging extracorporeal procedure [76]. However, usage of biocompatible high-flux membranes, bicarbonate buffer, and ultrapure water in hemodialysis have improved the preservation of RRF in recent years [4, 77, 78].

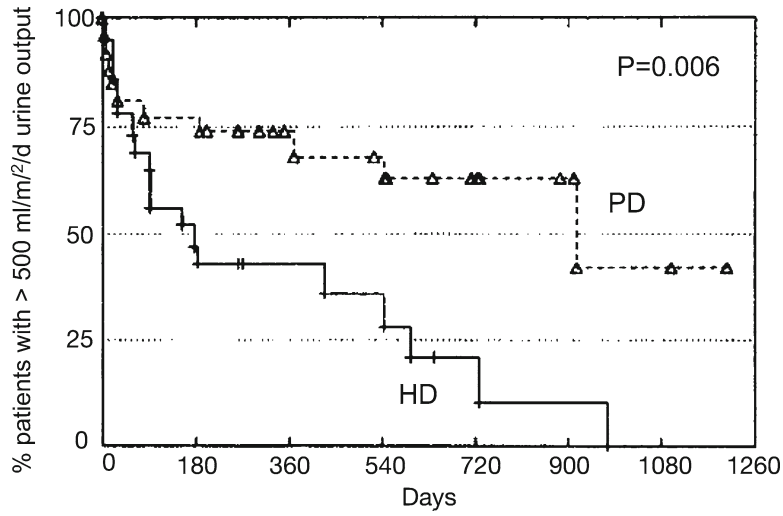

Fig. 9.3 Time to oliguria (daily diuresis <500 mL/m^2) in children with ESRD treated by peritoneal vs. hemodialysis (Source: Reproduced from Ref. [43])

The tidal variant of APD was reported to preserve RRF better than nontidal modalities [79].

Peritonitis frequency was associated with RRF decline in adult patients on PD [38, 46]. This observation may be explained by hypotensive episodes related to systemic infection, but 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 [80], administration of aminoglycoside for at least 3 days was correlated with more rapid decline of RRF [81].

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, hypoalbuminemia, hyperlipidemia, hypocalcemia, and hyperphosphatemia, 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, continuous PD modalities should be preferred to hemodialysis or NIPD under the aspect of preserving RRF. If for some reason an intermittent modality is chosen, careful monitoring of the volume status and avoidance of dehydration and hypotensive events, as well as hypertension 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 in a large number of children 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. 9.4) [36]. The risk of losing 50% GFR or progressing to ESRD was 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 [27]. In pediatric nephropathies, RAS antagonists reliably lower blood pressure and proteinuria [82], 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

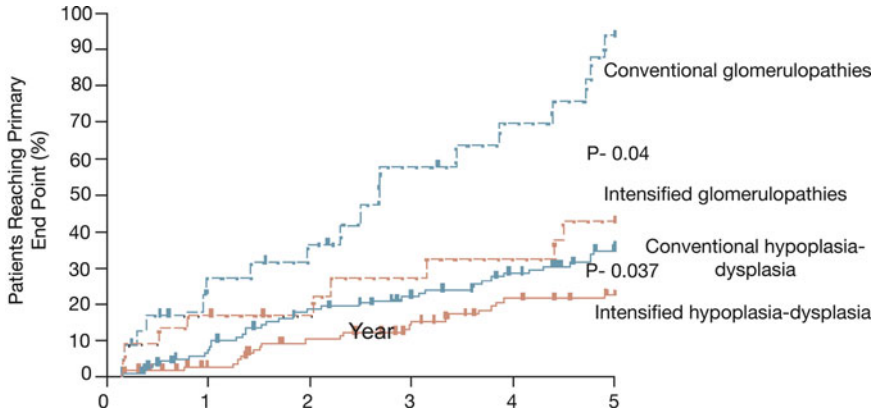

Fig. 9.4 Effect of intensified blood pressure control on renal survival in children with hypo/dysplastic and glomerular disorders receiving fixed-dose ACE inhibition. *Red lines* denote patients randomized to intensified blood pressure target (<50th 24 h MAP percentile), *blue lines* those with conventional target (50–95th 24 h MAP percentile) (Source: Reproduced from Ref. [36])

these agents [37, 83]. As in pre-end-stage CKD, there are reports that ACE inhibitors may protect RRF in adults on dialysis [55, 84]. In a randomized controlled trial in patients on PD, a time-dependent effect of ACE inhibition was observed; RRF declined faster and the risk of 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 [85]. This biphasic effect of ACE inhibition may be explained by hemodynamic mechanisms reducing GFR effective 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 [86]. 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 [87], 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 [88].

In a single report the use of calcium channel blockers was associated with a decreased loss of RRF [55].

Diuretics

There are controversies on the effect of loop diuretics on RRF. It was reported that diuretics can help maintain fluid balance but not RRF [89]. In another study in adults on hemodialysis, patients on diuretics retained RRF after 1 year [90]. In contrast, a study in adults on PD reported that the use of diuretics was associated with more rapid decline of RRF [66].

Biocompatible Dialysis

The 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 [91–93]. 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.

Preliminary results from controlled clinical trials suggest that RRF is indeed better preserved when PD is performed with low-GDP fluids employing either glucose sterilized in multichamber bags or the alternative osmotic agent icodextrin [91–96].

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 [55, 68, 97, 98]. 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 [68, 99, 100]. It has also been reported that the use of ultrapure water and bicarbonate buffer may preserve RRF [4, 101].

Emerging Therapies

Experimental research supports a role for anti-inflammatory and anti-fibrotic agents in pharmacological nephroprotection. Such approaches are currently being tested in early clinical trials. In an uncontrolled pilot study, mycophenolate mofetil was reported to stabilize GFR in childhood CKD due to congenital urinary tract anomalies [102]. In adults, the carbonic adsorbent AST-120 (Kremezin) was reported to suppress the plasma levels of indoxyl sulfate, TGF-beta1, and the progression of CKD [103]. Pentoxifylline and bardoxolone methyl were also reported to slow the decline of GFR in CKD [104, 105].

Administration of erythropoietin in patients without severe anemia was also reported to slow CKD progression [51]. In an animal study a hematologically subtherapeutic low dose of an erythropoietin analogue activated the Akt pathway and reduced apoptotic cell death in glomerular cells ameliorating the progressive renal injury [106].

Special Conditions

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.

In patients returning to dialysis after failed transplant, continued immunosuppression preserves the residual allograft function for some time [68]. Of course, side effects of the immunosuppressive medications have to be weighed against the benefit of RRF in these patients.

References

1. Gonzalez Celedon 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 Suppl. 2008;108:S42–51.
4. 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.
5. Churchill DN, Taylor DW, Keshaviah PR, for the CANUSA Peritoneal Dialysis Study 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.
6. Rocco MV, Frankenfield DL, Prowant B, Frederick P, Flanigan MJ. Risk factors for early mortality in U.S. peritoneal dialysis patients: impact of residual renal function. Perit Dial Int. 2002;22(3):371–9.
7. Davies SJ, Phillips L, Russell GI. Peritoneal solute transport predicts survival on CAPD independently of residual renal function. Nephrol Dial Transplant. 1998;13(4):962–8.
8. Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang SM, Zhu X, Lazarus JM. Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. Am J Kidney Dis. 1999;33(3):523–34.
9. Rocco M, Soucie JM, Pastan S, McClellan WM. Peritoneal dialysis adequacy and risk of death. Kidney Int. 2000;58(1):446–57.
10. Szeto CC, Wong TY, Leung CB, et al. Importance of dialysis adequacy in mortality and morbidity of chinese CAPD patients. Kidney Int. 2000;58(1):400–7.
11. 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.
12. Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT. 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.
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, 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.
15. 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.
16. Menon MK, Naimark DM, Bargman JM, Vas SI, Oreopoulos DG. Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. Nephrol Dial Transplant. 2001;16(11):2207–13.
17. 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.
18. Acar B, Yalcinkaya F, Cakar N, et al. The outcome for pediatric patients on peritoneal dialysis. J Nephrol. 2008;21(3):394–9.
19. Bakkaloglu SA, Saygili A, Sever L, 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.
20. 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.
21. Wang AY, Woo J, Wang M, 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.
22. 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.
23. Montini G, Amici G, Milan S, et al. Middle molecule and small protein removal in children on peritoneal dialysis. Kidney Int. 2002;61(3):1153–9.
24. 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.
25. 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.
26. Erkan E, Moritz M, Kaskel F. Impact of residual renal function in children on hemodialysis. Pediatr Nephrol. 2001;16(11):858–61.
27. Jafar TH, Stark PC, Schmid CH, 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.
28. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, et al. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland – a nationwide survey. Nephrol Dial Transplant. 2006;21(3): 736–42.
29. 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.
30. 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.
31. Mitsnefes M, Ho PL, McEnery PT. 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.
32. Litwin M. Risk factors for renal failure in children with non-glomerular nephropathies. Pediatr Nephrol. 2004;19(2):178–86.
33. 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.
34. 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. II. Adult outcome of pediatric renal disease. Lancet. 1997;349(9059):1117–23.
35. Wong CS, Pierce CB, Cole SR, 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):812–19.
36. Wuhl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361(17):1639–50.
37. 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.
38. 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.
39. Soares CM, Diniz JS, Lima EM, et al. Clinical outcome of children with chronic kidney disease in a pre-dialysis interdisciplinary program. Pediatr Nephrol. 2008;23(11):2039–46.
40. 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;25:110–14.
41. Caravaca F, Dominguez C, Arrobas M. Predictors of loss of residual renal function in peritoneal dialysis patients. Perit Dial Int. 2002;22(3):414–17.
42. Soares CM, Diniz JS, Lima EM, 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.
43. 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.
44. 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.
45. Liao CT, Shiao CC, Huang JW, et al. Predictors of faster decline of residual renal function in Taiwanese peritoneal dialysis patients. Perit Dial Int. 2008;28 (Suppl 3):S191–5.
46. Shin SK, Noh H, Kang SW, 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.
47. 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.
48. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis. 2005;45(6):978–93.
49. 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.
50. Furth SL, Cole SR, Fadrowski JJ, 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.
51. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int. 2004;66(2):753–60.
52. Wang AY, Wang M, Woo J, et al. A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. Kidney Int. 2002;62(2):639–47.
53. 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.
54. Han KH, Lee SH, Lee HK, 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.
55. Moist LM, Port FK, Orzol SM, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol. 2000;11(3):556–64.
56. Noordzij M, Voormolen NM, Boeschoten EW, 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.
57. Johnson DW, Mudge DW, Sturtevant JM, et al. Predictors of decline of residual renal function in new peritoneal dialysis patients. Perit Dial Int. 2003;23(3):276–83.
58. Papp F, Friedman AL, Bereczki C, et al. Renin-angiotensin gene polymorphism in children with uremia and essential hypertension. Pediatr Nephrol. 2003;18(2):150–4.
59. Hohenfellner K, Wingen AM, Nauroth O, Wuhl E, Mehls O, Schaefer F. Impact of ACE I/D gene polymorphism on congenital renal malformations. Pediatr Nephrol. 2001;16(4):356–61.
60. 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.
61. Amoroso A, Danek G, Vatta 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.
62. Lee-Chen GJ, Liu KP, Lai YC, Juang HS, Huang SY, Lin CY. Significance of the tissue kallikrein promoter and transforming growth factor-beta1 polymorphisms with renal progression in children with vesicoureteral reflux. Kidney Int. 2004;65(4): 1467–72.
63. Ardissino G, Testa S, Dacco V, 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.
64. Lane PH. Puberty and chronic kidney disease. Adv Chronic Kidney Dis. 2005;12(4):372–7.
65. Tonshoff B, Fine RN. Recombinant human growth hormone for children with renal failure. Adv Ren Replace Ther. 1996;3(1):37–47.
66. Liao CT, Chen YM, Shiao CC, 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.
67. Drechsler C, de Mutsert R, Grootendorst DC, 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.
68. 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.
69. 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.
70. Lysaght MJ, Vonesh EF, Gotch F, et al. The influence of dialysis treatment modality on the decline of remaining renal function. ASAIO Trans. 1991;37(4): 598–604.
71. 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.
72. 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.
73. Roszkowska-Blaim M, Skrzypczyk P, Drozdz D, Pietrzyk JA. 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.
74. 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.
75. 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.
76. 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.
77. Ng TG, Johnson DW, Hawley CM. Is it time to revisit residual renal function in haemodialysis? Nephrology (Carlton). 2007;12(3):209–17.
78. Chandna SM, Farrington K. Residual renal function: considerations on its importance and preservation in dialysis patients. Semin Dial. 2004;17(3):196–201.
79. 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.
80. 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.
81. 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.
82. Wuhl E, Mehls O, Schaefer F. Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure. Kidney Int. 2004;66(2):768–76.
83. Ardissino G, Vigano S, Testa S, 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.
84. 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.
85. Li PK, Chow KM, Wong TY, Leung CB, Szeto CC. 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.
86. 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.
87. 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.
88. 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.
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. Bragg-Gresham JL, Fissell RB, Mason NA, 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.
91. Haag-Weber M, Kramer R, Haake R, 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.
92. Szeto CC, Chow KM, Lam CW, et al. Clinical biocompatibility of a neutral peritoneal dialysis solution with minimal glucose-degradation products – a 1-year randomized control trial. Nephrol Dial Transplant. 2007;22(2):552–9.
93. Williams JD, Topley N, Craig KJ, 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.
94. Fan SL, Pile T, Punzalan S, Raftery MJ, Yaqoob MM. Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function. Kidney Int. 2008;73(2):200–6.
95. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol. 2003;14(9):2338–44.
96. Adachi Y, Nakagawa Y, Nishio A. Icodextrin preserves residual renal function in patients treated with automated peritoneal dialysis. Perit Dial Int. 2006; 26(3):405–7.

97. 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.
98. 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.
99. 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.
100. Hakim RM, Wingard RL, Husni L, Parker RA, Parker III TF. The effect of membrane biocompatibility on plasma beta 2-microglobulin levels in chronic hemodialysis patients. J Am Soc Nephrol. 1996;7(3):472–8.
101. 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):1814–18.
102. Trachtman H, Christen E, Frank R, et al. Pilot study of mycophenolate mofetil for treatment of kidney disease due to congenital urinary tract disorders in children. Am J Kidney Dis. 2008;52(4):706–15.
103. Iida S, Kohno K, Yoshimura J, et al. Carbonic-adsorbent AST-120 reduces overload of indoxyl sulfate and the plasma level of TGF-beta1 in patients with chronic renal failure. Clin Exp Nephrol. 2006;10(4):262–7.
104. Perkins RM, Aboudara MC, Uy AL, Olson SW, Cushner HM, Yuan CM. Effect of pentoxifylline on GFR decline in CKD: a pilot, double-blind, randomized, placebo-controlled trial. Am J Kidney Dis. 2009;53(4):606–16.
105. Pergola PE, Raskin P, Toto R, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med. 2011;365:327–36.
106. Bahlmann FH, Kielstein JT, Haller H, Fliser D. Erythropoietin and progression of CKD. Kidney Int Suppl. 2007;107:S21–5.

Part III

Peritoneal Dialysis

Peritoneal Access in Children Receiving Dialysis

10

Bradley A. Warady and Walter S. Andrews

Keywords
Peritoneal access • Children dialysis • Pediatric dialysis • PD

Peritoneal Dialysis Access

Peritoneal dialysis (PD) is the initial dialytic modality for many children with end-stage renal disease (ESRD). This is especially true for children who have acquired ESRD during their first decade of life [1]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reveals that of the 6,491 dialysis initiations entered into the dialysis registry between 1992 and 2008, more than 60% were for PD [2]. 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 to attend school on a regular basis.

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

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Table 10.1 Peritoneal dialysis access characteristics

Catheter	Cuffs	Tunnel	Exit-site	N (4112)[a]	% (100.0)
Curled	One	Straight	Lateral	593	14.4
Curled	Two	Swan necked/curved	Down	385	9.4
Curled	Two	Straight	Lateral	313	7.6
Straight	One	Straight	Lateral	301	7.3
Curled	Two	Straight	Down	270	6.6
Curled	One	Straight	Down	256	6.2
Curled	One	Straight	Up	194	4.7
Straight	One	Straight	Up	135	3.3
Presternal	Two	Swan necked/curved	Down	128	3.1
Straight	One	Straight	Unknown	122	3.0
Curled	Two	Swan necked/curved	Lateral	117	2.8
Curled	Two	Swan necked/curved	Unknown	107	2.6
Straight	One	Swan necked/curved	Lateral	104	2.5
Straight	Two	Straight	Lateral	101	2.5
Straight	One	Straight	Down	99	2.4
Curled	One	Straight	Unknown	74	1.8
Curled	One	Swan necked/curved	Down	73	1.8
Curled	One	Swan necked/curved	Lateral	63	1.5
Curled	Two	Straight	Unknown	56	1.4
Straight	Two	Straight	Up	50	1.2
Straight	Two	Swan necked/curved	Lateral	43	1.0
Curled	Two	Straight	Up	42	1.0
All other combination (<1% each)				486	11.8

[a]Cases with missing elements are excluded

variable, more than 25 different combinations of catheter characteristics are possible, as documented in the 2008 annual report of the NAPRTCS (Table 10.1) [2]. As noted above, the most common catheter with these characteristics used by pediatric patients is the Tenckhoff catheter.

A review of the 2008 NAPRTCS dialysis registry catheter data reveals that most of the catheters that were placed were of the Tenckhoff curled (61.5%) or Tenckhoff straight (26.9%) variety [2] (Table 10.2). The curled Tenckhoff catheter was previously noted as being the most commonly used pediatric catheter (88% usage) in the 1995 survey of the Pediatric Peritoneal Dialysis Study Consortium (PPDSC) [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

Table 10.2 Peritoneal dialysis access

	N	%
Peritoneal dialysis courses	4352	100.0
Catheter		
Tenckhoff straight	1170	26.9
Tenckhoff curled	2677	61.5
Toronto western	26	0.6
Presternal	272	6.3
Other	88	2.0
Unknown/missing	119	2.7
Cuffs		
One	2263	52.0
Two	1951	44.8
Unknown/missing	138	3.2
Tunnel		
Swan neck/curved	1397	32.1
Straight	2801	64.4
Unknown/missing	154	3.5
Exit-site orientation		
Up	535	12.3
Down	1425	32.7
Lateral	1735	39.9
Unknown/missing	657	15.1

omental wrapping, and (6) potentially less trauma to bowel [5]. In contrast to the NAPRTCS data, the Italian PD registry reflects a predominance of straight catheters [4]. Currently, there is no definitive data that supports using a curled catheter over a straight catheter and there is some published data to the contrary [4, 8, 9]. Noteworthy is the fact that neither the NAPRTCS data nor a formal review of the few available prospective studies provides evidence for any association between the intraperitoneal configuration and the development of peritonitis or exit-site/tunnel infection [2, 10].

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 [11, 12]. 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]. Cuff extrusion may lead to the development of an exit-site/tunnel infection and the subsequent need for shaving of the cuff off the catheter [13–15]. While there are very few reports describing the incidence of distal cuff extrusion with double-cuff catheters in children, two series from 1986 to 2004 reported outer cuff extrusion rates of 8% and 4.8%, respectively [4, 16]. It may be, in part, for this reason that 52% 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

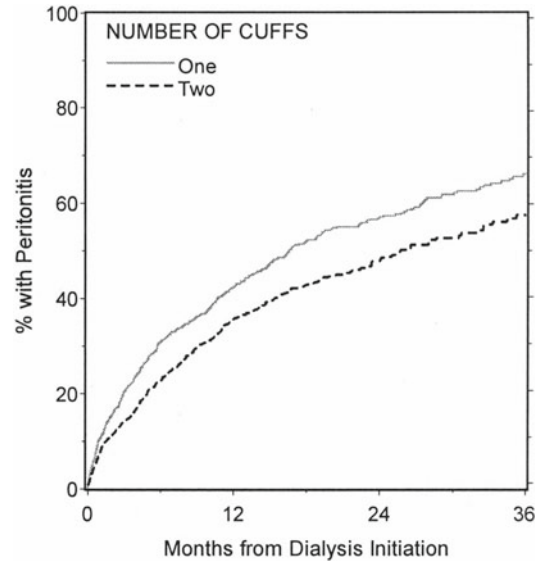

Fig. 10.1 Comparison between one cuff and two cuff catheters and the time to the first episode of peritonitis (Source: Adapted from Ref. [2])

catheters and found a significantly lower incidence of infections in the double-cuff group [17]. The National CAPD Registry also documented that double-cuff catheters were less likely to require removal secondary to an exit-site/tunnel infection [18]. A similar conclusion can be drawn from the NAPRTCS registry data that reports a significantly lower incidence of peritonitis in association with double-cuff catheters (1/21.0 patient months) compared to single-cuff catheters (1/15.7 patient months) [2]. In addition, the NAPRTCS data shows a longer time to first peritonitis episode in the double-cuff catheter group [2, 19] (Fig. 10.1). This information seems to have made an impact worldwide, as recent (2005–2008) data from the International Pediatric Peritonitis Registry (IPPR) revealed that 86% of catheters reported by participating centers were of the double-cuffed variety. Unfortunately, there has only been a single prospective randomized trial addressing the issue of single versus double-cuff catheters, and this study showed no significant difference in the risk of peritonitis or exit-site/tunnel infection [19].

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-shape

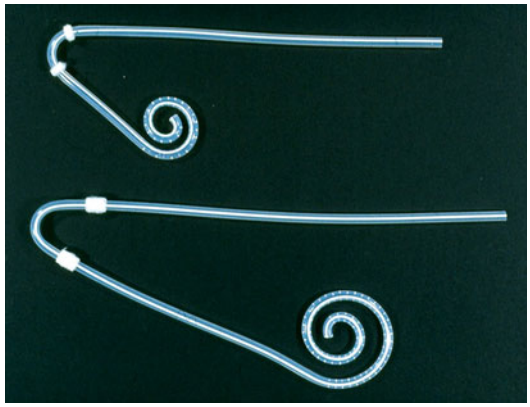

Fig. 10.2 Picture of a Tenckhoff, double-cuff curled catheter with Swan neck bend

arc (170–180°) between the deep and the superficial cuffs (Fig. 10.2). 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 [20, 21]. While the cumulative NAPRTCS data reports a swan neck/curved tunnel in only 32.1% of catheters (identical to the results of the North American survey by Washburn et al.), data collected by the IPPR and the International Pediatric Peritoneal Dialysis Network (IPPN) revealed that 53.5% and 74% of the catheters, respectively, were of the "swan neck" variety [22, 23]. 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 [24–26]. 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 patients with stomas. Recently, Crabtree et al. reported their experience with remote exit-sites in adults [27]. 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.

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 [28]. More recently, the 2008 NAPRTCS data revealed that a straight catheter tunnel was associated with a peritonitis rate of 1/15.8 patient-months, while the rate associated with a swan neck/curved tunnel was only 1/23.1 patient-months [2]. Likewise, the peritonitis rates associated with an upward and downward oriented exit-site were 1/14.2 patient-months and 1/21.6 patient-months, respectively [2]. A study from Network 9 in the U.S. has also highlighted a significantly lower peritonitis rate with permanent bent catheters. With a downward pointing exit-site, Golper et al. noted a 38% decrease in the incidence of peritonitis associated with an exit-site and/or tunnel infection [29]. 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 [30–32].

A recently reported alternative to the swan neck catheter has been reported by several authors from China [33–35]. 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) so they would have 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

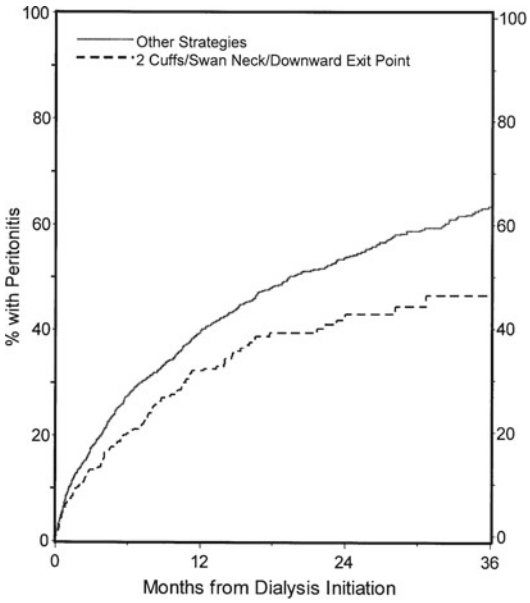

Fig. 10.3 Comparison between catheter with downward facing exit-site, Swan Neck and two cuffs versus all other strategies and the time to first episode of peritonitis (Source: Adapted from Ref. [2])

the latter catheter is related to its significantly lower cost than the swan neck catheter in China.

In summary, the lack of prospective studies designed to evaluate PD catheter characteristics makes it impossible to conclude that one catheter characteristic is superior to another based upon definitive evidence. However, quite convincing is the NAPRTCS registry data which 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. 10.3) [2]. This information has prompted an increase in the percentage of patients using the double-cuff/swan neck /downward pointed exit-site configuration from 5% in 1992–1995 (NAPRTCS) to 23.2% in 2005–2009 [2]. The continued collection of catheter information in registries such as the NAPRTCS 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 the literature as being associated with an increased risk for post placement PD catheter migration is constipation [36]. 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 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 11.8–53.0% [37–39]. The highest frequency of inguinal hernias occur within the first year of life; they are often bilateral and most 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 [40, 41]. If detected, the hernias can then be fixed at the same time the PD catheter is inserted [42–44]. Forehand knowledge of the need for a 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. The exit-site must be planned so that it is either on the opposite side of the abdomen from the 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 [45–48].

Preoperative antibiotic usage has been shown, in several studies, to decrease the incidence of peritonitis after the placement of a PD catheter in both children and adults. Interestingly, these studies have shown that any class of antibiotic will be beneficial [10, 49–53]. Currently, we utilize a first or second-generation cephalosporin unless the patient is known to be colonized with methicillin-resistant *Staphylococcus aureus*. This recommendation comes from the pediatric and adult guidelines of the International Society for Peritoneal Dialysis (ISPD), as well as from the European guidelines [51, 54–56]. 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 catheter placement. If positive, a course of intranasal mupirocin (twice daily for 5 days) is recommended [56].

Omentectomy

The data recommending the performance of an omentectomy/omentopexy at the time of catheter placement to prevent PD catheter occlusion is compelling [58, 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 [43, 60]. A survey conducted by the 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 [7, 22]. An omentectomy was performed with the insertion of 82.4% of catheters in the Italian PD registry [4]. 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. In practical terms, the omentectomy does not have to be complete. Enough of the omentum is removed so that its remnant will not reach to the catheter which is positioned in the pelvis.

An omentopexy can be considered as an alternative to omentectomy. 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 [61–63]. Our experience with fibrin glue would support both of these assertions. Typically, the fibrin glue is applied around the internal cuff and down the tunnel between the inner and outer cuffs.

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 the implantation of

the PD catheter [22, 64, 65]. The complications of dialysate leakage, dislocation of the catheter, erosion/extrusion of the cuffs, exit-site/tunnel infections, 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 [36].

Over the last few years, several authors have reviewed their experience with peritoneal catheter insertion and they have concluded that a laparoscopic approach is superior to the open approach [66–68]. 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. In a recent 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% [66]. The low incidence of catheter flow problems in the laparoscopic group was attributed to a combination of rectus sheath tunneling of the catheter (allowing the 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 [69]. 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 [70]. 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 can be corrected at the time of catheter placement. We currently use a modification of the technique first described by Daschner et al. [71] and recently by Crabtree et al. [66].

The catheter insertion site is chosen with consideration of the patient's size and the need for the catheter to exit in a downward direction. Consideration must also to 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 belt line 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- and exit-sites are marked on the patient's skin.

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 depending on the size of the child, either a 3 mm or a 5 mm port is placed. A corresponding 3 mm or 5 mm laparoscope is then inserted and the abdomen is insufflated. The peritoneal entrance site is positioned so that the inner catheter cuff will be located between both sheaths of the rectus muscle and the tip of the catheter will lie in the pelvis. At this point, a 3 mm instrument is inserted through a stab wound at the marked catheter exit-site. A second 3–5 mm port is inserted at the marked entrance site of the catheter. This port is then tunneled under the anterior rectus sheath and along the posterior rectus sheath for a distance of between 4 and 7 cm (depending on the size of the patient) and then popped into the abdomen. The omentum can then either be partially removed with the use of electrocautery or it can be plicated using a technique reported by Crabtree et al. [66]. We feel that a complete omentectomy is not necessary as long as the omentum is prevented from entering the pelvis.

After the omentum has been addressed, a guide wire is inserted into the abdomen via the

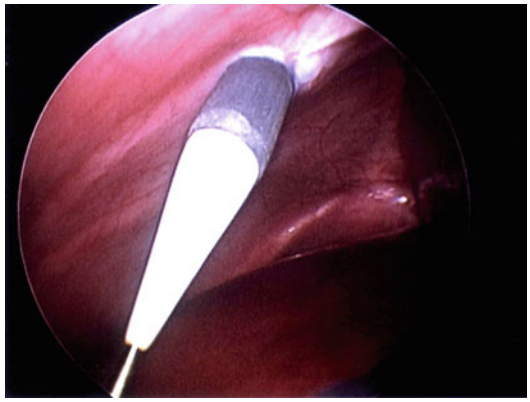

Fig. 10.4 A laparoscopic view of the 20 French peel-away sheath being inserted into the peritoneum over a guide wire (From Chapter #45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

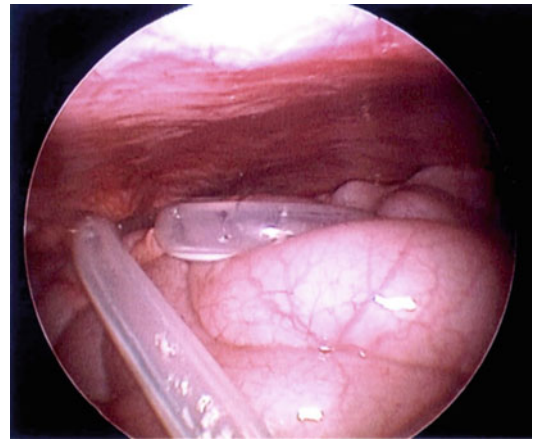

Fig. 10.5 A laparoscopic view of the PD catheter which lies positioned in the pelvis. The catheter is sitting between the bowel and the anterior abdominal wall (From Chapter #45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

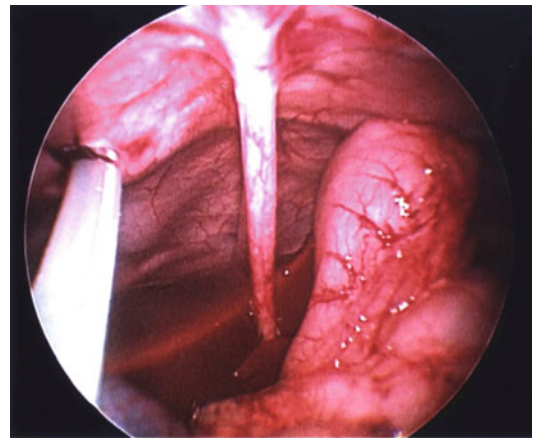

Fig. 10.6 A laparoscopic view of the PD catheter (*left*) showing it leaving the peritoneal cavity. Note that the inner cuff is not visible within the peritoneal cavity (From Chapter #45, Surgical Issues in Pediatric Peritoneal Dialysis, by Walter S. Andrews. In: Clinical Dialysis, 4th Edition, Nissenson AR, Fine RN, eds. McGraw-Hill Companies, Inc., 2005)

entrance site port. The port is then removed and the skin incision is enlarged to approximately 1 cm. Using a peel-away sheath technique, a 20 French sheath is then inserted into the abdomen over the guide wire (Fig. 10.4). The PD catheter is then placed on a stiffener and inserted into the pelvis under direct vision. The pneumoperitoneum is maintained by pushing the proximal cuff of the PD catheter into the sheath, thereby preventing gas loss. Once the catheter has been positioned into the pelvis, the sheath is removed (Fig. 10.5). 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. Care is taken to make sure that the innermost portion of the cuff does not project into the peritoneum (Fig. 10.6). The peritoneum is also carefully inspected for evidence of any inguinal hernias. If a hernia is discovered, it is fixed after completion of the PD catheter insertion. The camera and all ports are then removed and the umbilical fascia is repaired.

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 catheter is then pulled through the tunnel, positioning the outer cuff so that it is approximately 2.0 cm from the exit-site. Shorter distances between the exit-site and outer cuff predispose 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 [36, 44]. At this point, fibrin sealant may be injected in the subcutaneous tissue around the entrance site of the catheter through the anterior rectus sheath and also down the tunnel between the outer and inner cuffs. 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 [51].

Open Technique

Catheter location is determined using the same methods as noted with the laparoscopic approach. The most frequent open technique utilizes an incision over the mid portion of the rectus muscle. The rectus muscle is split in the direction of its fibers and the posterior sheath is then opened longitudinally. The catheter is threaded over a stiffening wire to allow its placement deep in the pelvis, a few degrees to the right of 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 of 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. 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 [44]. 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 [10].

One advantage of the open technique is the ability to directly visualize the 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 [56, 72]. 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 has 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 [73]. After this time period, an exit-site is created over the subcutaneous pocket and the catheter is exteriorized. While successful in its application, prospective trials comparing initial exteriorization of the catheter versus implantation and subcutaneous burying of the catheter for 6 weeks have not demonstrated a significant difference in the rate of either peritonitis or exit-site/tunnel infections or on long-term catheter survival [53, 74, 75]. Twardowski, et al., on the other hand, has merely recommended that initially, the exit-site should only be covered with several layers of sterile gauze and should be kept dry [76, 77]. 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 which decreases the risk for bacterial colonization [78, 79]. 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 [78].

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 European guidelines recommend at least 2 weeks, whenever possible [5, 56]. This is supported by a study conducted by Patel et al. in which immediate versus delayed (an average of 20 days) catheter use was compared [80]. The authors noted an increased incidence of dialysate leakage in the immediate use group, but a disconcerting increase in exit-site/tunnel infections, 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 that there was no difference in the risk of infection [72]. Finally, 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]. Accordingly, while the available data might suggest a preference for delayed catheter usage if possible, there is no definitive evidence for any particular rest period and a prospective, randomized trial is clearly needed to address this issue [8]. Of course, when early usage is necessary, efforts should be made to minimize any increase in the intraperitoneal pressure by using small exchange volumes, possibly in the supine position with a cycling device.

Chronic Exit-Site Care

The goal of chronic exit-site care is to prevent the development of exit-site/tunnel infections. 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 [76, 77, 81]. 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 and care givers. Centers that have initiated a program to prophylatically treat carriers have noted a decreased incidence of catheter associated infections [52, 82–85]. It is, however, generally agreed upon that the use of a non-cytotoxic cleansing agent (e.g. 20% poloxamer 188, soap, sodium hypochlorite) and a dressing is associated with fewer infections in the pediatric patient [56, 86]. In addition, the application of either mupirocin or gentamicin creams to the catheter exit-sites has also been efficacious in decreasing exit-site/tunnel infections [86–91].

Finally, a survey of exit-site care practices in 22 pediatric sites and 125 adults sites found that significantly fewer pediatric programs conducted daily care and used tap water or antibacterial soap, while a greater percentage "air dried" the cleaned exit-site and used a semi-permeable dressing over an absorbent layer, compared to adult programs (B. Warady, Personal Communication).

Mechanical Complications

Mechanical complications are generally felt to be the second most common reason (after infection) for catheter failure. 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. 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 had an early catheter malposition (less than 30 days) and a durable patency rate of 82% with late malpositions (greater than 30 days) [92]. 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 [67].

Our center has used a laparoscopic approach to reposition 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 is then manipulated under direct vision and is repositioned back into the pelvis. Any adhesions that are encountered during the repositioning of the catheter are lysed at the same time. In addition, we have used this technique to free catheters that have become encased in adhesions or obstructed by omentum. 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 [93–95].

Exit-Site Infection, Tunnel Infection, and Peritonitis

Catheter exit-site/tunnel infections, and peritonitis are a significant cause of catheter failure. In a review of the NAPRTCS data from 1992 to 1997, the incidence of exit-site/tunnel infections increased from 11% at 30 days post catheter insertion to 30% by 1 year after catheter insertion [28]. 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]. 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 [55]. If, however, an infection does occur, medical management is typically successful [55, 96]. One approach to the treatment of exit-site/tunnel infections in children is described in Table 10.3 [97]. In situations in which antibiotic therapy of an exit-site/tunnel infection was unsuccessful, surgical salvage by unroofing/cuff shaving has been conducted [13–15]. 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 [98]. In another report, 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 [99]. 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.

Table 10.3 Management of exit-site/tunnel infections [97]

Therapeutics		
0 hour		
Obtain Culture and Gram Stain of Exudate and/or Drainage If clinical appearance mandates immediate therapy prior to culture result, initiate empiric therapy with either 1st generation cephalosporin or ciprofloxacin PO		
Gram positive organism	Gram negative organism	
Penicillinase resistant penicillin PO or 1st generation cephalosporin PO	Ciprofloxacin 20 mg/kg/day in divided doses (>12 years; maximum 1.0 gm/day) or Ceftazidime load: 500 mg/L IP Maintenance: 125 mg/L IP in each bag	
48–72 hours		
Adjust antibiotics to culture and sensitivity	Adjust antibiotics to culture and sensitivity	
If no improvement, add rifampin 10–20 mg/kg/day PO in divided doses (maximum 600 mg/day)	If *Pseudomonas* and receiving ciprofloxacin without improvement, consider adding ceftazidime load: 500 mg/LIP; Maintenance: 125 mg/L IP in each bag	
2 weeks		
Re-evaluate		
Infection resolved: stop therapy	Infection improved: Continue therapy for 2 weeks and re-evaluate	After adequate and prolonged antibiotic treatment, if no improvement: consider catheter revision (cuff shaving) or removal

Glycopeptides (e.g., vancomycin or teicoplanin) should be avoided for the routine treatment of exit-site infections secondary to staphylococcus species due to concerns of emerging bacterial resistance

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 [4, 55]. 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 [4, 100–102]. 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

It has been recommended that dressing care occur weekly during the post transplant period. In most cases, catheters are removed 4–8 weeks following successful renal transplantation. It is not necessary to obtain routine PD cultures. While two studies noted an absence of catheter infections after kidney 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 [103, 104]. 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 [105]. In their series of 40 catheter removals, ten

(25%) of the procedures were associated with complications, and eight 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 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" and the regular evaluation of treatment results are initiatives designed to optimize the function of this important component of PD.

References

1. Warady BA, Bunchman TE. An update on peritoneal dialysis and hemodialysis in the pediatric population. Curr Opin Pediatr. 1996;8(2):135–40.
2. North American Pediatric Renal Trials & Collaborative Studies (NAPRTCS) 2008. Annual Report 2009, Rockville.
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. 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.
6. Twardowski ZJ. Peritoneal access: the past, present, and the future. Contrib Nephrol. 2006;150:195–201.
7. 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.
8. 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.
9. Stegmayr BG, Wikdahl AM, Bergstrom M, et al. A randomized clinical trial comparing the function of straight and coiled Tenckhoff catheters for peritoneal dialysis. Perit Dial Int. 2005;25(1):85–8.
10. 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;18(4): CD004680.
11. Alexander SR, Tank ES. Surgical aspects of continuous ambulatory peritoneal dialysis in infants, children and adolescents. J Urol. 1982;127(3):501–4.
12. Vigneau A, Hardy B, Balfe JA. Chronic peritoneal catheter in children: one or two dacroncuffs? (Letter). Perit Dial Bull. 1981;1:151.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. Lindblad AS, Novak JW, Nolph KD, Stablein DM, Cutler SJ. The 1987 USA National CAPD Registry report. ASAIO Trans. 1988;34(2):150–6.
19. Eklund B, Honkanen E, Kyllonen L, Salmela K, Kala AR. Peritoneal dialysis access: prospective randomized comparison of single-cuff and double-cuff straight Tenckhoff catheters. Nephrol Dial Transplant. 1997;12(12):2664–6.
20. 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.
21. Auron A, Simon S, Andrews W, et al. Prevention of peritonitis in children receiving peritoneal dialysis. Pediatr Nephrol. 2007;22(4):578–85.

22. 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.
23. 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.
24. 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.
25. Moreiras P, Cuina L, Goyanes G, Lavoratti G, Gonzalez L. Mechanical complications in chronic peritoneal dialysis. Clin Nephrol. 1999;52(2):124–30.
26. 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.
27. 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.
28. 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.
29. Golper TA, Brier ME, Bunke M, et al. Risk factors for peritonitis in long-term peritoneal dialysis: the Network 9 peritonitis and catheter survival studies. Academic Subcommittee of the Steering Committee of the Network 9 Peritonitis and Catheter Survival Studies. Am J Kidney Dis. 1996;28(3):428–36.
30. Eklund BH, Honkanen EO, Kala AR, Kyllonen LE. Catheter configuration and outcome in patients on continuous ambulatory peritoneal dialysis: a prospective comparison of two catheters. Perit Dial Int. 1994;14(1):70–4.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. van Asseldonk JP, Schroder CH, Severijnen RS, de Jong MC, Monnens LA. Infectious and surgical complications of childhood continuous ambulatory peritoneal dialysis. Eur J Pediatr. 1992;151(5): 377–80.
39. Holtta TM, Ronnholm KA, Jalanko H, Ala-Houhala M, Antikainen M, Holmberg C. Peritoneal dialysis in children under 5 years of age. Perit Dial Int. 1997;17(6):573–80.
40. Khoury AE, Charendoff J, Balfe JW, McLorie GA, Churchill BM. Hernias associated with CAPD in children. Adv Perit Dial. 1991;7:279–82.
41. Tank ES, Hatch DA. Hernias complicating chronic ambulatory peritoneal dialysis in children. J Pediatr Surg. 1986;21(1):41–2.
42. Remes J, Peeters J, Coosemans W, et al. Five years of surgical experience with peritoneal dialysis. Acta Chir Belg. 1998;98(2):66–70.
43. Conlin MJ, Tank ES. Minimizing surgical problems of peritoneal dialysis in children. J Urol. 1995;154(2 Pt 2):917–19.
44. Brandt M, Brewer E. Peritoneal dialysis access in children. Dordrecht: Kluwer Academic Publishers; 2004.
45. Twardowski ZJ. Presternal peritoneal catheter. Adv Ren Replace Ther. 2002;9(2):125–32.
46. 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.
47. 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.
48. 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.
49. Sardegna KM, Beck AM, Strife CF. Evaluation of perioperative antibiotics at the time of dialysis catheter placement. Pediatr Nephrol. 1998;12(2): 149–52.
50. Harvey EA. Peritoneal access in children. Perit Dial Int. 2001;21(Suppl 3):S218–22.
51. Piraino B, Bailie GR, Bernardini J, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005;25(2):107–31.
52. 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.

53. 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.
54. Warady BA. Peritoneal dialysis catheter related infections in children. Pediatr Infect Dis J. 1998; 17(12):1165–6.
55. Warady BA, Schaefer F, Holloway M, et al. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int. 2000;20(6):610–24.
56. 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.
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):1014–19.
58. 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.
59. Pumford N, Cassey J, Uttley WS. Omentectomy with peritoneal catheter placement in acute renal failure. Nephron. 1994;68(3):327–8.
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. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. Crabtree JH, Burchette RJ. Effective use of laparoscopy for long-term peritoneal dialysis access. Am J Surg. 2009;198(1):135–41.
67. 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.
68. 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.
69. 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.
70. Wang JY, Chen FM, Huang TJ, et al. Laparoscopic assisted placement of peritoneal dialysis catheters for selected patients with previous abdominal operation. J Invest Surg. 2005;18(2):59–62.
71. Daschner M, Gfrorer S, Zachariou Z, Mehls O, Schaefer F. Laparoscopic Tenckhoff catheter implantation in children. Perit Dial Int. 2002;22(1):22–6.
72. Rahim KA, Seidel K, McDonald RA. Risk factors for catheter-related complications in pediatric peritoneal dialysis. Pediatr Nephrol. 2004;19(9):1021–8.
73. Moncrief JW, Popovich RP. Moncrief-Popovich catheter: implantation technique and clinical results. Perit Dial Int. 1994;14(Suppl 3):S56–8.
74. 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):211–19.
75. 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.
76. Twardowski ZJ, Prowant BF. Exit-site healing post catheter implantation. Perit Dial Int. 1996;16(Suppl 3):S51–70.
77. Twardowski ZJ, Prowant BF. Exit-site study methods and results. Perit Dial Int. 1996;16(Suppl 3): S6–31.
78. 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.
79. 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.
80. 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.
81. Twardowski ZJ, Prowant BF. Classification of normal and diseased exit sites. Perit Dial Int. 1996;16(Suppl 3):S32–50.
82. Kopriva-Altfahrt G, Konig P, Mundle M, et al. Exit-site care in Austrian peritoneal dialysis centers – a nationwide survey. Perit Dial Int. 2009;29(3):330–9.
83. Mupirocin Study Group. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infection during peritoneal dialysis. J Am Soc Nephrol. 1996;7(11): 2403–8.
84. Lobbedez T, Gardam M, Dedier H, et al. Routine use of mupirocin at the peritoneal catheter exit site and mupirocin resistance: still low after 7 years. Nephrol Dial Transplant. 2004;19(12):3140–3.

85. Perez-Fontan M, Rosales M, Rodriguez-Carmona A, Falcon TG, Valdes F. Mupirocin resistance after long-term use for Staphylococcus aureus colonization in patients undergoing chronic peritoneal dialysis. Am J Kidney Dis. 2002;39(2):337–41.
86. 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.
87. 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.
88. 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.
89. 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.
90. 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.
91. 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.
92. 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.
93. 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.
94. Sakarcan A, Stallworth JR. Tissue plasminogen activator for occluded peritoneal dialysis catheter. Pediatr Nephrol. 2002;17(3):155–6.
95. Krishnan RG, Moghal NE. Tissue plasminogen activator for blocked peritoneal dialysis catheters. Pediatr Nephrol. 2006;21(2):300.
96. 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;10(1):136–45.
97. Warady B, Alexander S, Firanek C. Peritoneal dialysis catheter and complications management for children. Deerfield: Baxter Healthcare Corporation; 2001.
98. 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.
99. 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.
100. Swartz RD, Messana JM. Simultaneous catheter removal and replacement in peritoneal dialysis infections: update and current recommendations. Adv Perit Dial. 1999;15:205–8.
101. 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.
102. Majkowski NL, Mendley SR. Simultaneous removal and replacement of infected peritoneal dialysis catheters. Am J Kidney Dis. 1997;29(5): 706–11.
103. 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.
104. 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.
105. 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

11

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Keywords
Peritoneal dialysis • Children • Continuous ambulatory peritoneal dialysis (CAPD)

Introduction

Since 1978, when continuous ambulatory peritoneal dialysis (CAPD) was first introduced for the treatment of pediatric patients with end-stage renal disease (ESRD), 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. More recently, a revolution in the fields of electronics and computer science has generated a series of automated delivery systems called "cyclers" that allow great prescription flexibility, as well as the monitoring of therapy results and of 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 over night. Both CAPD and APD are currently widely used in children around the world.

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 CAPD Connection Technology

In CAPD, 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.

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Catheter-to-Transfer Set Connectors

A special Luer-lock catheter adapter made of titanium was developed to prevent cracking of the plastic connector or accidental disconnection, problems that had frequently occurred with the old plastic plug-in connectors. Titanium was chosen for its light weight and resistance to electrolyte-containing PD solutions. More recently, catheter-to-transfer set connectors made of more durable plastics have also been developed.

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, and failure to mate the spike with the port correctly can result in contamination and 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.

CAPD 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 on-line 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. However, the major drawbacks of this system were that the PD fluid was infused into the abdominal cavity immediately after the connection (and potential bacterial contamination), and 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 to 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]. However, care must be taken 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; in this case, 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^{R}, 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 potentially affected are primarily limited to 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^{R}, 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^{R}, Laboratoire Aguettant, Lyon, France); in this system, when the cap is positioned, the catheter has already been automatically closed.

In a further development, a polyolefine-made plasticizer-free system (stay-safe^{R}, 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 partner training, and has been associated with a reduction of the rate of peritonitis episodes due to touch contamination both in adult [7, 8] and in pediatric patients [9].

Peritoneal Dialysis Prescription

The aim of the process of PD prescription for pediatric patients with ESRD is tailoring the treatment schedule to the needs of each individual subject, according to a series of parameters including patient's age, body size, associated non-renal diseases, residual renal function (RRF), clinical conditions, 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 burden of PD treatment should be compatible with a satisfactory level of psychological and social rehabilitation of the patient and of his/her family. During the last 10–15 years several technical improvements in PD materials and devices, the development of more biocompatible PD solutions, and the increased use of computer technology have provided dialysis staff with valuable tools to improve the efficacy and tolerability of chronic PD treatment.

The selection of chronic PD modality, as well as the prescription of the optimal treatment schedule, should be based on knowledge of PM physiology and on 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 (See Also Chap. 2)

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 suggested to vary between 50 and 100 mL/min. However, the effective amount of this flow that is involved in peritoneal exchanges is unknown, and is the subject of controversy. 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 bowel (visceral peritoneum) [13].

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 [14]. 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 [15].
– *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 [16].
– *The layer of mesothelial cells.* These cells have a system of tight and gap junctions, microvillous 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 [17, 18].

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 [18].

Diffusive Transport

Diffusion consists of 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 changing 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," low MW proteins). Therefore, low MW compounds such as urea are preferentially removed by diffusion, and each compound is characterized by a specific PM permeability coefficient.
– 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 [19, 20]. This area can be estimated by means of the so-called three-pore permeability model [21]. According to this model, the peritoneum is characterized as a heteroporous three-pore membrane with few (~1–2%) water-exclusive ultra-small 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. 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 1,400 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 [22–25]. The impact of dialysate volume is felt to rest on the principle of geometry of diffusion [26], 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 disease, increasing during acute peritonitis, while it can be progressively impaired by peritoneal fibrosis. 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 [27].

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 [28]. 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 [29]:

$$J_F = K_f([P_c + s_f] - [p_c + P_f])$$

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; 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. 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 [30]. Fluid is believed to move primarily into interstices in the peritoneal cavity and to be driven by intraperitoneal hydraulic pressure [31]. The limited data on lymphatic absorption in children are conflicting [30, 32].

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) [33].

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 [34]. Conversely,

PD solutions containing a polymer of glucose with an average MW of 16,200 Dalton (Icodextrin[R] Baxter, Deerfield, IL), which exerts a sustained colloid osmotic effect through the small pores, have been shown to sustain UF over a prolonged exchange dwell time [35–38].

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). 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 [39, 40].

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 PM to PD solutions and materials. 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, and in case of recurrent or particularly severe peritonitis episodes, or of any other clinical event that may cause changes in PM transport capacity [39, 41]. 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 [42]. 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 [43, 44]. BSA can be calculated by means of mathematical formulas from the patient's weight and height. An exchange volume of 1,100 mL/m^2 BSA approximates the standard 2,000 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 dialysis prescription, and can be performed with the help of computer technology that gives reliable results also 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 [27, 45]. 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 [27].

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) remains the most widely employed means of characterizing PM transport capacity in adult as well as in pediatric patients [27, 41, 46, 47]. The PET measures the rate at which solutes, usually creatinine (Cr), urea, and glucose, come to equilibration between the blood and the dialysate. To reach a satisfactory level of reproducibility of PET results, a standard PET in children can be performed with a dwell volume of 1,100 mL/m^2 BSA using a 2.5% dextrose PD solution. In pediatric patients, comparable results have been obtained by using 2.5% dextrose [27] and 2.27% anhydrous glucose PD solutions. Dialysate to plasma (D/P) ratio 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. Dialysate Cr concentration must be corrected for the interference of the high glucose levels in the dialysate by the formula:

$$\text{Corrected Cr (mg/dL)} = \text{measured Cr (mg/dL)} - \text{correction factor} \times \text{dialysate glucose (mg/dL)}$$

The correction factor should be determined in the laboratory of each dialysis center, by dividing measured Cr of a fresh PD solution by glucose concentration.

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 [48, 49]. 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 study in which the same PET procedure was adopted (Figs. 11.1 and 11.2) [27]. Thus, patients will be characterized as having a high, high average, low average, or low solute transport capacity (Table 11.1). 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 [50], and low-turnover bone disease [51]. 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 [48, 49]. On the other hand, 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, 49]. Therefore, the same PD solution should be used for the PET and for the dwell of the preceding night.

Recently, 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 [52]. Therefore, these 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 by Twardowski in the original PET publication [46]. 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. However, further study with a larger patient cohort is required to confirm the accuracy of the short PET in the characterization of membrane transport capacity in this setting [53].

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 as well as in pediatric patients, but are less frequently employed than the PET in the clinical

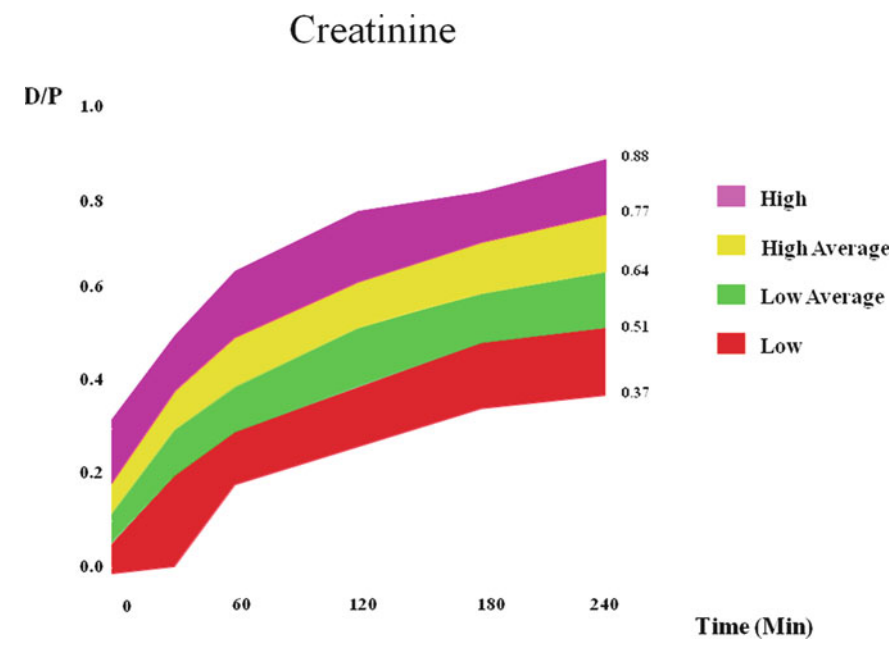

Fig. 11.1 Peritoneal equilibration test results for creatinine. *Colored* areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population (From Ref. [27], with permission)

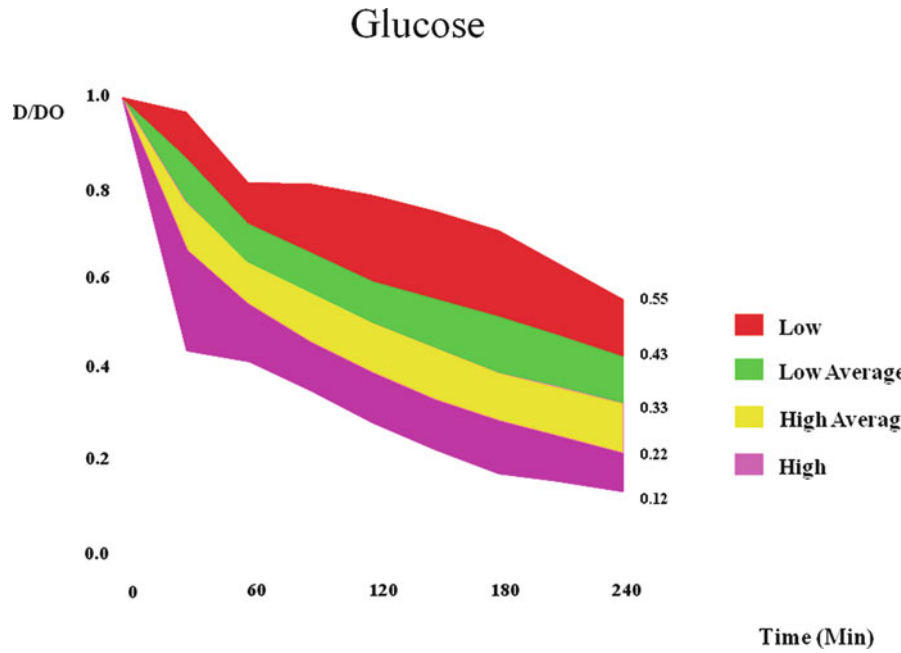

Fig. 11.2 Peritoneal equilibration test results for glucose. *Colored* areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population (From Ref. [27], with permission)

Table 11.1 Classification of peritoneal transport capacity according to the results of urea and creatinine dialysate to plasma ratio (D/P), and of dialysate glucose to initial dialysate glucose concentration ratio (D/D0) at 4 h dwell of a peritoneal equilibration test performed with 1,100 mL/m² body surface area of a 2.5% dextrose dialysis solution [27]

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. [27], used with permission)

setting. 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, and intraperitoneal volume (IPV). SPA conducted with a test IPV of 1,200 mL/m² and a 1.36% or 3.86% glucose PD solution gave comparable results in adult and pediatric patients [54, 55].

Personal Dialysis Capacity Test

The personal dialysis capacity (PDC) test [21] 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 [33]. The following three parameters are calculated:

1. The effective peritoneal surface area, or unrestricted pore area over diffusion distance ($A_0/\Delta X$), corresponding to the diffusion capacity for solutes and comparable to the D/P value of the PET.
2. Absorption, that is, the final rate of fluid reabsorption from the abdominal cavity, primarily representing the lymphatic flow.
3. The large pore flow, which represents the rate of protein-rich fluid passing through the large pores from blood to dialysate. A large pore flow that is higher than expected according to the total vascular surface area is a sign of an inflamed PM [56].

The PDC test has been successfully employed in children to model individual PM function [33]. In one pediatric study, D/P or D/D_0 ratios derived from PET analysis were used to estimate $A_0/\Delta X$ by using a specific computer program [22].

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 [20, 39, 41]. 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 [21, 22]. Raising IPV from 800 to 1,400 mL/m² BSA leads to maximization of peritoneal vascular surface area [22]. On the other hand, a too large IPV may cause patient discomfort, pain, dyspnoea, hydrothorax, hernia, 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 to evaluate fill volume tolerance in the individual patient [28]. Fill volume leading to an IPP of 18 cm H_2O in the supine position is considered the maximum tolerable IPV, above which abdominal pain and a decrease in respiratory vital capacity may occur [20];

increasing IPV above this peak volume can result in reduced PD efficiency. An IPV of 1,400 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, fill volume prescription should be 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 limit of 1,400 mL/m^2 BSA 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 [20]. Bedside measurement of IPP can be performed following the procedure described by Fischbach et al. [28]; measured IPP levels can be compared with reference values obtained in a group of pediatric patients [22].

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 [20, 39, 41]. 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 would benefit from short exchanges, due to the dissipation of the osmotic gradient by fast glucose absorption. 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, 28, 57]. On the other hand, a long dwell time exchange can be associated with the risk of impaired UF, or even with dialysate re-absorption while using glucose-based solutions. Icodextrin-based solution is more appropriate for such long dwells [35, 58].

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 [57].

The above mentioned 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

Following the resurgence of interest in PD as a maintenance dialysis modality that occurred in the 1970s, chronic PD was primarily performed as CAPD in adult as well as in pediatric patients. During the last 20 years, thanks to the development of new automatic machines (cyclers), APD has rapidly expanded as an answer to the demands for higher dialysis doses and better quality of life [59]. Children with ESRD were the population of patients where APD had the widest application.

The PD regimen can be either continuous, with dialysis solution present in the peritoneal cavity evenly throughout 24 h, or intermittent, with empty abdomen for part of the day, usually during daytime (Fig. 11.3). Continuous regimens allow complete equilibration of small solutes as well as removal of middle-sized molecules. However, 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. 11.3). The short interruptions at the time of

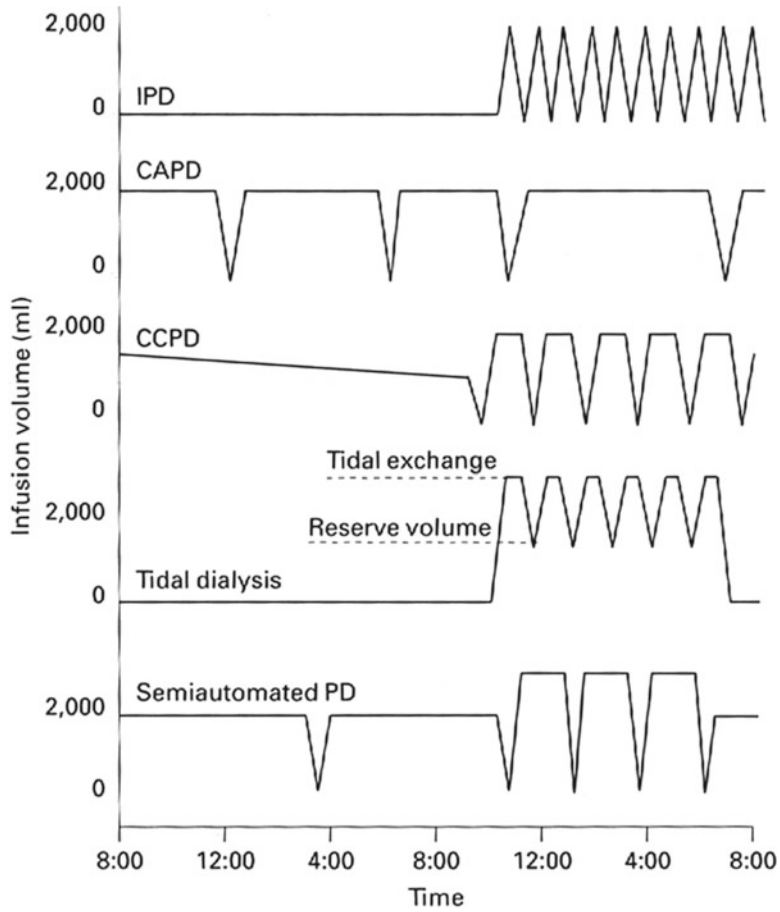

Fig. 11.3 Schematic representation of various peritoneal dialysis (PD) regimens based on a standard fill volume of 2,000 mL of dialysis fluid. *IPD* nightly intermittent PD; *CAPD* continuous ambulatory PD; *CCPD* continuous cyclic PD

the 3–5 daily exchanges do not disqualify the regimen as continuous if they do not exceed 10% of total dialysis time [60].

In the CAPD exchange, a double bag PD solution container with a Y set disconnectable 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. Moreover, CAPD has the undoubted advantage of a limited cost of the equipment.

As already said, 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 [39], the initial fill volume can be 600–800 mL/m^2 during the day, and 800–1,000 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 [28]. When there is inadequate UF overnight due to rapid glucose absorption, an icodextrin-based PD solution can be employed for the prolonged night-time exchange.

CAPD is usually effective in patients who still have RRF, but this should be closely monitored, together with the UF capacity and the patient's dry BW [39]. Patients with a low-average or high-average peritoneal transport status as per the PET [27] 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. However, if increasing the number of exchanges to obtain adequate UF and solute removal represents an excessive burden upon the patient and the family, a shift of 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 [61–64]. 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, night time 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 [65]. 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 night-time 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 1,400 mL/m^2 BSA was not associated with an unsafe increase of IPP. Such a high fill volume is infrequently prescribed, due to problems of patient tolerance [66, 67]. 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) [22, 68]. 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 offers a wide selection of treatment schedules that have in common the use of automated machines for fluid exchanges and the high efficiency obtained through short dwell times, high dialysate flows, and large IPV [59].

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 [69]. 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 [33, 45, 70]. Both of these software programs have an 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 [71, 72]. 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 "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 application control by direct measurement of solute clearances and UF remains necessary.

Finally, the choice of the proper APD regimen through which the individual dialytic prescription

Table 11.2 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	Not adequate small solute clearance in patients with low- and low-average transport
Preservation of body image (for adolescents mainly)	Not adequate middle-sized molecule clearance
Reduced loss of proteins and AA Better preservation of the peritoneal membrane integrity	No flush of the catheter and lines at the start of the night session

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. 11.3). 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 11.2. The reduced exposure of the PM to glucose and glucose degradation products, together with the reduced deposition of advanced glycosylation end products (AGE), have been reported to be beneficial for long term PM preservation [73]. However, the prescription of a small fill volume during the daytime is frequently adopted in an attempt to lessen 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 [74].

The major limitation of NIPD may be that the absence of a daytime dwell reduces small 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. Therefore, NIPD frequently represents the initial mode of PD employed in children with RRF [39]. A typical initial prescription can be formulated as follows:

- Nine to twelve hours of total treatment time.
- A fill volume of 800–1,000 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% 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 [72, 75, 76]. An increase of the efficiency of NIPD can be obtained by:

- Maximizing the dwell volume, according to patient tolerance and IPP limits [20, 22, 28].
- 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% [75].

When with these adjustments of the NIPD schedule, a sufficient increase of solute and water removal is not achieved, the patient may be at risk for inadequate treatment, and would be better off using a different APD regimen.

Continuous Cyclic Peritoneal Dialysis (CCPD)

CCPD, just like CAPD, represents a continuous regimen of PD (Fig. 11.3). 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% 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 if external occlusion is used. The 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 [77]. Since complete saturation of the dialysate with small solutes over a long dwell exchange is often achieved, daytime clearances are 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 IPP), and the membrane transport status. 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. However, phosphate removal by PD can be improved by increasing dwell volume [78], and by optimizing exchange duration through the calculation of the so-called phosphate purification dwell time (PPT) from a PET [57].

A continuous PD regimen is recommended when RRF has become negligible, and/or 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 [79, 80]. Patients with high-average transport rates often do best on CCPD (Table 11.1).

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% glucose solution, and significantly greater than that reached with a 1.36% glucose solution both in adult and pediatric patients [35, 81, 82]. 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 [36]. 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 [83]. By comparing the results of two 4-h PETs, performed in nine pediatric patients using 3.86% glucose and 7.5% icodextrin as a test solution, Rusthoven et al. [38] found that the two solutions had different effects on the change in IPP. During the PET performed with a 3.86% glucose solution the increase in IPP was positively correlated with transcapillary UF and inversely correlated with patients' BSA,

while by using an icodextrin solution IPP hardly increased during the 4-h dwell and no correlation was found with fluid kinetics or patient BSA.

If a further increase in solute clearances 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 mid-day or after school, using the cycler in a disconnectable manner (Fig. 11.3), and the length of each dwell is optimized according to the patient's peritoneal transport rate and the type of osmotic agent employed [39, 77]. This modality requires more patient participation, but allows one to achieve small solute dialysate-to-plasma equilibration during both of the two daytime exchanges.

Tidal Peritoneal Dialysis (TPD)

TPD is an automated PD technique in which an initial infusion of solution into the peritoneal cavity is followed, after an usually short dwell time, by drainage of only a portion of the dialysate, leaving an intra-abdominal reserve volume (Fig. 11.3). 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

Moreover, TPD may be indicated in patients experiencing pain during the drainage phase.

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 used larger total session dialysate volumes [84, 85].

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 [86]. 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 the critical point (also called 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 the drainage the peritoneal cavity is almost empty, and solute clearance is significantly reduced [67, 87]. 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.

Continuous Flow Peritoneal Dialysis (CFPD)

The limitation of significant fill and drain times while performing high-flux APD regimens could be circumvented by maintaining a continuous flow of dialytic solution obtained with two peritoneal catheters or a double-lumen catheter. In such a system, a continuous dwell at a predetermined

dwell volume is attained, and the dialysate flow rate is only dependent on the function of the catheter(s). These are the mechanical principles of CFPD [79, 88], one of the first PD techniques performed, but that was soon abandoned owing to a series of technical problems, as well as high costs.

When applied to adult patients, CFPD relies on a 2–3 L dwell volume and a continuous dialysate flow at 100–300 mL/min. This high flow rate requires a highly efficient double-lumen peritoneal catheter, or two catheters with their intraperitoneal tips separated as distantly as possible. Moreover, CFPD requires the facility to generate or regenerate large volumes of PD fluid. The theoretical advantages of CFPD would be an enhanced small solute clearance and UF permitting a shorter dialysis session and intermittent treatment, the use of reduced dialysate glucose concentration and bicarbonate solutions, and a reduction in protein loss, since proteins which have diffused into the dialysate are returned to the patient. Online preparation of PD fluids allows customization of their composition with respect to glucose, buffer, sodium, and calcium content [89].

More recently, a renewed interest in CFPD has arisen, since new technologies have made possible the development of appropriate equipment for accurate fluid handling, reliable monitoring of pressures and flows in the circuit, and the possibility of generating PD fluid online or regenerating a batch for recirculation, either with a hemodialysis filter or by absorption. Moreover, a double-lumen catheter with adequate flow characteristics has been developed [90].

Potential problems and disadvantages that will require consideration in the further development of CFPD include:

- The unknown, long-term effects of high dialysate flow rate on peritoneal cells and host defense mechanisms
- The unknown effects of exposure of PD fluid to hemodialysis synthetic membranes or sorbents
- The risks of peritoneal infection associated with the procedure (multiple connections)
- The potential for abdominal over-distension
- The cost of equipment and disposables

Another technical challenge is represented by the need for UF control, with a means to accurately balance transperitoneal fluid flow with external UF [90]. Indeed, one of the main concerns about the utilization of CFPD is the variable and unpredictable UF rate. The observed disparate UF results may be due to streaming and recirculation, which require new catheters with better separation of the fluid streams [91].

CFPD holds promise to become an attractive modality for daily home dialysis in the future, provided the remaining technical problems can be solved and the technology offered at an affordable price. Further technological advances and long-term clinical experience are still needed before recommending this technique for the routine treatment of children with ESRD.

Conclusive Remarks

For each regimen of chronic PD delivered to pediatric patients with ESRD, the prescription of the dialysis dose should be adjusted and monitored following the guidelines of the European Pediatric Peritoneal Dialysis Working Group [39] and the 2006 update of the NKF-KDOQI clinical practice recommendations for pediatric PD adequacy [41]. 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. In general, regular assessment of the results 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 [39, 41, 50]. 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 outcome among pediatric patients. (For an in-depth discussion of this topic, please see Chap. 14.) A number of factors can make the diagnosis of peritonitis more difficult in APD than in CAPD: (1) peritoneal effluent is not readily available to inspection, owing to the use of a non-transparent 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; (3) the abdomen is frequently (although not necessarily) dry during the day. For these reasons, the presence of a cloudy effluent, that 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 [92]. In view of these issues, the use of a reactive strip-test, which is sensitive to granulocyte peroxidase, can be helpful for the early diagnosis of peritonitis. In our center, 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 (approximately 1,100 mL/m^2 BSA) 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 outcome 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 was associated with higher clearances of low MW molecules, such as urea and creatinine [93, 94]. Small solute clearance was considered the key criterion of PD adequacy in the clinical practice guidelines developed in the year 2000 by the Kidney Disease Outcomes Quality Initiative (KDOQI), which defined dialysis adequacy by certain minimum urea and creatinine clearance values [95]. 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 increasing peritoneal small solute clearances, but showed that RRF is a much stronger predictor of survival than peritoneal clearance [96–98]. 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 [99]. Moreover,

Table 11.3 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

some recommendations 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 comprehensively take into consideration also a series of clinical, metabolic, and psychosocial aspects, the most important of which are listed in Table 11.3.

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 [41] 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 not less than 1.8 per week. Data from pediatric and adult studies found 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 [41, 100]. 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's outcome (96–99), 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 progressive 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 [41].

The 2006 KDOQI guidelines [41] 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, and it was proposed that the ratio of these two parameters should be 1:30 [11, 39]. A discrepancy between urea and creatinine-based PD adequacy parameters was often reported [101–104], also in children [39]. 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, 105]. 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 the presence of RRF. The finding of adequate values of Kt/V_{urea} associated with inadequate values of CrCl can be related to a hyper-permeable PM state, or a too low IPV, since both of these conditions are associated with a greater removal of urea than creatinine [11, 50, 105]. 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 [39]. 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} [41, 101, 104]. However, in children on APD we continue to target a 1:30 urea over creatinine purification ratio in our program [11, 39, 102, 106].

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 [107] systematically overestimate TBW in pediatric patients receiving PD. Recently, a new set of anthropometric TBW prediction equations have been developed in this patient population and validated by comparison with the determination of TBW by means of a heavy water (H_2O^{18} or D_2O) dilution technique [108]. These formulae are based on a new anthropometric parameter called *height times weight*, which correlates linearly with TBW when both values are log-transformed, and are as follows:

$$\text{Boys: TBW} = 0.10 \times (\text{HtWt})^{0.68} - 0.37 \times \text{weight}$$

$$\text{Girls: TBW} = 0.14 \times (\text{HtWt})^{0.65} - 0.35 \times \text{weight}$$

Hyperphosphatemia and elevated calcium times phosphorus product are associated with calcifying large-vessel arteriopathy, which develops even in young patients with childhood onset ESRD [109, 110]. Recently, Schmitt and coworkers [111] 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. Phosphate elimination by an APD regimen can be modified by the number of cycles, dwell time, and total dialysate volume used [111].

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 Kt/V_{urea} nor CrCl is the perfect index to predict outcome in PD patients; however, they can be considered two potentially 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 5,000 Daltons MW) is one of the possible explanations for the failure of increased dialysis dose to improve patient survival [99, 112]. Small solute and middle-sized molecule clearances respond differently to changes in the PD prescription, since the former is mainly determined by the frequency and volume of dialysate dwell, while the latter depends more on the dialysate/PM contact time [113, 114]. 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 [115]. In practice, the removal of middle-sized molecules and low-MW proteins, such as $\beta(\text{beta})_2$-microglobulin and leptin, mainly depends on RRF [116, 117]. 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 [55]. Hence, particular attention should be paid to middle molecule clearance, especially in children on NIPD, and as RRF is declining. In these cases, a continuous PD regimen (CCPD or CAPD) should be adopted even if small solute clearance is above target without the longer dwell [41]. Increased β(beta)$_2$-microglobulin and leptin clearance have been reported in patients receiving a long dwell with icodextrin solution [118].

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 total body volume and offers better homeostatic stability than intermittent therapies. Nevertheless, PD population surveys show a high prevalence of hypertension and cardiovascular mortality with adequacy of UF a significant predictor of mortality in anuric adult PD patients [76, 119]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [120] showed that 57% of nearly 4,000 pediatric patients on dialysis had blood pressure 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. Left ventricular hypertrophy was documented by echocardiography in 68% of 38 long-term pediatric patients on PD therapy [121]. Hypertension and cardiac impairment were most frequently found in the younger and nephrectomized PD patients [122]. 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 [41]. Overhydration 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 PD [39, 41]. In the absence of validated, readily applicable indicators of volume status, the assessment of patient target weight mainly relies on clinical judgment. 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 is 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 [71, 72]. 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; night-time dwell on CAPD) may enhance their UF capacity [11]. La Milia and coworkers [123] suggested calculation of the exact volume of free water transport by measuring the amount of sodium transported through the small pores over an 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 [49]. Smit and coworkers [124] 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 [49].

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 [72]; an increase of dextrose tonicity is associated with enhanced UF, but the osmotic gradient dissipates over time; therefore, dextrose solutions are indicated for short dwells, while for the night-time dwell in CAPD and the daytime dwell in APD, icodextrin solution may be more appropriate; as already said, icodextrin is also effective in maintaining adequate UF rate during peritonitis episodes [125]; the observation that icodextrin may behave differently in young children, in whom UF may not be as successful as in older patients, requires further confirmation [37]. 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 [57]. APD cycle length should be equivalent to the APEX time.

Lymphatic absorption. A high effective lymphatic absorption rate may be the consequence of a marked elevation in IPP [126]. A reduction of the fill volume may help to 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. Compliance with dietary recommendations should be regularly assessed.

Residual diuresis. The use of loop diuretics can be considered 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 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; replace single long exchange with two or more exchanges.

The Role of Residual Renal Function in Treatment Adequacy (see also Chap. 9)

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 [96–98, 127, 128]. RRF plays an even more important role for patients in whom targets of solute and fluid removal cannot be achieved by means of the PD regimen alone [96]. In pediatrics, no data from large-scale trials on the correlation between RRF and patient outcome are currently available. However, a single-center observational study on PD pediatric patients by Chada et al. [129] reported that growth velocity

was higher in a group of children with RRF than in another group of 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 reported by Tkaczyk and coworkers [130], residual urine output was higher in normotensive patients. In a study of the assessment of cardiovascular risk in a group of 59 pediatric PD patients, residual diuresis was an independent predictor of diastolic dysfunction [131].

The rate of RRF decline in pediatric patients on PD was reported to be slower than in patients on HD [132, 133]. 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 [134, 135]. 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 [136].

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 [41, 133]. Loop diuretics can be used to increase urinary water and salt excretion.

Efforts to preserve RRF also involve the prevention of such nephrotoxic insults as [41]:

- 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 [137, 138]. A recently published 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 [139]. Minimal experience on the effect of these agents on RRF in children on chronic dialysis is available; 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 [140]. Adult PD patients with RRF and on ACE-I therapy were found to have significantly lower 24-h urine and peritoneal dialysate potassium excretion than those not on ACE-I; patients on ACE-I therapy with no RRF displayed not only a significantly lower dialysate potassium loss, but also a significant increase in the mean serum potassium concentration [141].

In summary, interventions that may contribute to the preservation of RRF in the course of chronic PD treatment should be adopted whenever possible [41]. 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 the occurrence of signs and/or symptoms of 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 [50] 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 [142]. As already mentioned, Chada et al. [129] presented data showing 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.

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 [143]. 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 [143, 144]. In these patients, dietary protein intake is inconsistently correlated with delivered Kt/V_{urea} [145–147]. 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 [148]. 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), owing to an increased loss of albumin in the peritoneal effluents [149].

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 [150]. 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 [131].

Monitoring PD Adequacy in the Clinical Setting

Regular assessment of the delivered dialysis dose can be performed following the NKF-DOQI clinical practice guidelines [41], with some adaptations to specific problems of childhood, and the European guidelines on adequacy of the pediatric PD prescription [39]. 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 [151]:

$$(\text{24 - hour D/P urea} \times \text{24 - hour dialysate volume} \times 7) / \text{V}$$

where D/P represents the dialysate to plasma urea concentration ratio.

In patients with RRF, renal Kt/V_{urea} corresponds to:

$$(\text{mL/min urea clearance} \times 1{,}440\ \text{min/day} \times 7) / (1{,}000\ \text{mL} \times \text{V}).$$

CrCl calculation is normalized to BSA, which can be calculated from weight and height by use of the Gehan and George formula [152]:

$$\text{BSA}(\text{m}^2) = 0.0235 \times (\text{height,cm})^{0.42246} \times (\text{weight,kg})^{0.51456}$$

The following formula can be employed to calculate dialytic CrCl per week [151]:

$$(\text{24 - hour D/P Cr} \times \text{24 - hour dialysate volume} \times 7 \times 1.73\ \text{m}^2) / \text{BSA}(\text{m}^2)$$

Residual renal clearance is better expressed as the average of CrCl and urea clearance, each of which can be calculated by the standard formula:

$$\text{Solute clearance (mL/min)} = \frac{(\text{24 - h urine volume in mL} \times \text{urine solute concentration})}{(1{,}440\ \text{min/day} \times \text{serum solute concentration})}$$

This calculation is then normalized to patient's BSA.

PD dose assessment should be coupled with an evaluation of nutritional status, including anthropometric measurements (skin fold thickness, mid-arm circumference), a 3-day dietary record (to be evaluated by a renal dietitian), and the determination of normalized protein equivalent 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 [153]:

$$\text{FFM [kg]} = 0.65 \times (\text{height}^2/\text{impedance})\ [\text{ohms/cm}^2] + 0.68 \times \text{age (years)} + 0.15$$
$$\text{TBW [L]} = 0.144 \times (\text{impedance/height}^2)\ [\text{ohms/cm}^2] + 40 \times \text{weight [kg]} + 1.99.$$

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 4 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
- Weight
- Head circumference (in infants)
- Blood pressure
- Blood urea nitrogen and creatinine
- Serum electrolytes
- Acid–base status
- Hemoglobin/hematocrit
- Serum albumin
- Daily urine volume and UF

Every 3 Months

- Serum ferritin
- Serum iron
- Total iron binding capacity
- Alkaline phosphatase
- Intact parathyroid hormone
- Kt/V_{urea} and CrCl from 24-h dialysate and urine collection

Every 12 Months

- Ambulatory blood pressure monitoring
- Echocardiography
- Hand and wrist x-ray for bone age
- Neurodevelopment assessment

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
- Arterial hypertension
- 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.

In conclusion, it should be stressed once again that numerical targets of small solute removal should be interpreted cautiously and in the context of patient clinical assessment; failure to reach these targets should be regarded as a warning sign, leading to careful reevaluation of each constituent of the therapeutic program. The contribution of RRF to the adequacy of PD treatment 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 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 above mentioned signs and/or symptoms of inadequate treatment.

Machines for Automated Peritoneal Dialysis

The rapid evolution that APD has experienced over the last decade has been closely linked to the development of new automatic machines, which are currently referred to as cyclers.

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 smaller, lighter, more user friendly, less expensive, and more reliable machines [59]. Since APD is performed by the patient or his or her 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 [154]. 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 most recent 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 ensuring 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.

The machine interface is typically characterized by an easy and clear display with unequivocal 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; thus only scheduled changes can be programmed 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, 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 drainage at low flow rates, 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.

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 [155]. The cycler could use the recorded information of the patient response to a given treatment schedule 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 feed-back on the PD fluid composition in the following cycle (profiling of glucose concentration throughout the dialysis session). Bedside production of dialysis solution could individualize PD treatment with respect to osmotic agent, buffer, sodium and calcium contents [89, 155].

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, as well as a means of monitoring patient compliance, and creates a 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 it can be retrieved via modem as often as needed.

One example of the potential utilization of this recording system is the evaluation of the functioning of the peritoneal catheter. 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 of 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 [86, 87].

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 patients and parents [156]. Tube kinking or catheter malfunction are the most frequent causes of drain alarms. In some cases, unsuitable setting of alarm limits (such as leaving the default setting of the cycler) 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 modem connection between the home cycler and the dialysis unit makes 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 through the modem connection from the cycler's memory card to the personal computer of the dialysis unit on a regular basis (e.g., every 7–10 days), and in case of any problem observed by the patient or the caregiver, or of any doubt they may have on cycler or peritoneal catheter function. Information stored in the file of each patient is examined and evaluated by the physician and dialysis nurse according to a scheduled program. Data can be organized in charts and graphs, and statistically elaborated. Modem connection allows an early detection of a series of therapy problems and may reduce the feeling of isolation and detachment that the patient and family may experience in the course of long-term home PD, especially if they live a distance from the dialysis center.

The results reported on the use of telemedicine in a pediatric PD program [156] showed 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 might be represented 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. Moreover, the awareness of routine data recording and transmission can help the patient to be more confident of treatment control, and the dialysis doctors and nurses to more rapidly update the PD prescription. The tele dialysis system can also be integrated by videoconferencing equipment (digital camera; ISDN 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 [157, 158]. However, in a recent report on the use of telecare

in a pediatric program, the employed videophone equipment still showed technical limitations and was considered not cost-effective [159]; therefore, this technology deserves further evaluation in pediatric home PD. In general, whether telePD is able to significantly reduce the need for patient hospitalization or the incidence of technique failure in a population of home APD children should be evaluated in large-scale studies.

Monitoring of Patient Adherence to the Prescribed APD Treatment

Non-adherence is an important obstacle to achieving adequate PD therapy, as well as a significant cause of morbidity, patient hospitalization and dialysis technique failure. Several methods to assess patient adherence to the PD prescription have been proposed, based on comparison of measured versus predicted creatinine excretion [160]; home visits to check dialysis solution supply inventories [161]; patient self-report confidential questionnaires [162]; or the comparison of self-reports of compliance with the rate of predicted versus measured Kt/V_{urea} and CrCl [163]. However, because no single method is able to provide a complete assessment of non-adherence in patients on home PD, they 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. More frequent changes made by the patients or caregivers include:

- 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 to 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. Strategies should be targeted both on patient and family, and on the dialysis staff, and accomplished through a structured comprehensive program.

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.

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 life-style
- 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 [164] should:

- Start well before dialysis initiation.
- Involve a multidisciplinary team: nephrologist, renal nurse, renal dietitian, psychologist, social worker, school teacher, play 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 can be completed in the home environment.

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 outcome

Once PD treatment has started, regular telephone contact 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 PD prescription and evaluate its 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

Over the last 15 years, PD has experienced a rapid evolution, which has been mostly linked to the development of safe and simple to use connecting devices, more biocompatible materials and solutions, and new automatic machines for PD delivery, with the employment of computer technology. All these achievements have provided dialysis staff valuable tools to improve the overall efficacy and tolerability of PD treatment in children.

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 of 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 now 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.

Children represent a patient category that would greatly benefit from the use of new more physiological and biocompatible PD solutions, especially if one considers their long-term dependence on a functioning PM in case of a kidney transplant failure and the fact that in APD frequent short cycles continuously expose the PM to a non physiological and bio-incompatible milieu. Combined use of glucose, amino acids, and icodextrin as part of a glucose-sparing APD regimen, together with the adoption of pH-neutral solutions, may represent a strategy to adequately manage solute removal and UF, while preserving PM integrity over time.

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, and UF failure is an important cause of abandonment of the technique.

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. Therefore, 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 insults and the use of loop diuretics, while the potential role of angiotensin-converting enzyme inhibitors and ARB needs to be further investigated in children on PD. As RRF declines over time, PD prescription should be adjusted to its decline in a timely fashion.

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, their interactivity with the patient and their ability to record patient medical data could still be improved. Teledialysis may help in significantly reducing the need for patient hospitalization and the incidence of technique failure.

The ultimate goal of the whole process 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 the amount of dialysis above which the additional expected benefit does not justify the increase of the burden on patient and family and of financial costs.

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. Twardowski ZJ. Physiology of peritoneal dialysis. In: Nissenson AR, Fine RN, Gentile DE, editors. Clinical dialysis. Norwalk: Appleton & Lange; 1990.
14. Gotloib L, Shostak A, Bar-Sella P, et al. Fenestrated capillaries in human parietal and rabbit diaphragmatic peritoneum. Nephron. 1985;41:200–2.
15. Pecoits-Filho R. The peritoneal cavity: a room with a view to the endothelium. Perit Dial Int. 2005; 25:432–4.
16. Krediet RT, Lindholm B, Rippe B. Pathophysiology of peritoneal membrane failure. Perit Dial Int. 2000;20(Suppl 4):22–42.
17. Flessner M, Henegar J, Bigler S, et al. Is the peritoneum a significant barrier in peritoneal dialysis? Perit Dial Int. 2003;23:542–9.
18. 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.
19. Flessner MF. The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol. 2005;288: 433–42.
20. 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.
21. 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.
22. Fischbach M, Haraldsson B. Dynamic changes of total pore area available for peritoneal exchange in children. J Am Soc Nephrol. 2001;12:1524–9.
23. 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.
24. 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.
25. 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.
26. Morgenstern BZ. Equilibration testing: close, but not quite right. Pediatr Nephrol. 1993;7:1309–12.
27. Warady BA, Alexander SR, Hossli S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol. 1996;7: 2385–2391.
28. 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.
29. Ahmad S. Peritoneal dialysis. In: Ahmad S, editor. Manual of clinical dialysis. London: Science Press; 1999. p. 65–8.
30. Rippe B. Is lymphatic absorption important for ultrafiltration? Perit Dial Int. 1995;15:203–4.
31. Flessner MF. Transport kinetics during peritoneal dialysis. In: Leypoldt JK, Austin RG, editors. The artificial kidney: physiological modelling and tissue engineering. Texas: Landes; 1999.
32. Mactier RA, Khanna R, Moore H, et al. Kinetics of peritoneal dialysis in children: role of lymphatics. Kidney Int. 1988;34:82–8.
33. 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.
34. Schroeder CH. Optimal peritoneal dialysis: choice of volume and solution. Nephrol Dial Transplant. 2004;19:782–4.
35. De Boer AW, Schröder CH, Van Vliet R, et al. Clinical experience with icodextrin in children: ultrafiltration profiles and metabolism. Pediatr Nephrol. 2000;15:21–4.
36. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int. 2008;108:S137–44.
37. Dart A, Feber J, Wong H, et al. Icodextrin re-absorption varies with age in children on automated peritoneal dialysis. Pediatr Nephrol. 2005;20:683–5.
38. 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.
39. 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.
40. Goldstein SL. Adequacy of dialysis in children: does small solute clearance really matter ? Pediatr Nephrol. 2004;19:1–5.
41. 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.
42. Geary DF, Harvey EA, MacMillan JH, et al. The peritoneal equilibration test in children. Kidney Int. 1992;42:102–5.
43. 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.
44. 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.
45. 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.
46. Twardowski ZJ, Nolph KD, Khanna R, et al. Peritoneal equilibration test. Perit Dial Bull. 1987;7: 138–47.
47. 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.
48. 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.
49. Smit W. Estimates of peritoneal membrane function – new insights. Nephrol Dial Transplant. 2006;21(Suppl 2):ii16–9.
50. 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.
51. 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.
52. Warady BA, Jennings J. The short PET in pediatrics. Perit Dial Int. 2007;27:441–5.
53. Schaefer F. The PET-iatrics of peritoneal solute transport: is short also good for the young ones ? Perit Dial Int. 2007;27:413–4.
54. 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.
55. Bouts AHM, Davin JC, Groothoff JW, et al. Standard peritoneal permeability analysis in children. J Am Soc Nephrol. 2000;11:943–50.
56. 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.
57. 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.
58. Schröder CH. The choice of dialysis solutions in pediatric chronic peritoneal dialysis: guidelines by

an ad hoc European Committee. Perit Dial Int. 2001;21:568–74.
59. Diaz-Buxo JA. Automated peritoneal dialysis. A therapy in evolution. In: Ronco C, Amici G, Feriani M, Virga G, editors. Automated peritoneal dialysis. Basel: Karger; 1999. p. 1–14.
60. Twardowski ZJ. Peritoneal dialysis glossary III. Adv Perit Dial. 1992;8:47–9.
61. 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.
62. Mujais S, Childers RW. Profiles of automated peritoneal dialysis prescription in the US 1997–2003. Kidney Int. 2006;103:S84–90.
63. 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.
64. North American Pediatric Renal Trials and Collaborative One Students (NAPRTCS). 2008. NAPRTCS Annual Report. http://www.emmes.com/study/ped/annlrept/annlrept.html.
65. Chiu M-C, Fai-Ngor Ng C, Lee L-P, Suppl 29, 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.
66. 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.
67. 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.
68. 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.
69. 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.
70. Warady BA, Watkins SL, Fivush BA, et al. Validation of PD Adequest 2.0 for pediatric dialysis patients. Pediatr Nephrol. 2001;16:205–11.
71. 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.
72. 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.
73. Holmes CJ, Shockley TR. Strategies to reduce glucose exposure in peritoneal dialysis patients. Perit Dial Int. 2000;20:S37–41.
74. Warady BA, Ellis EN, Fivush BA, et al. Flush before fill in children receiving automated peritoneal dialysis. Perit Dial Int. 2003;23:493–8.
75. 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.
76. Jansen MAM, Termorshuizen F, Korevaar JC, et al. Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 2005;68:1199–205.
77. 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.
78. Fischbach M, Terzic J, Menouer S, et al. Optimal volume prescription for children on peritoneal dialysis. Perit Dial Int. 2000;20:603–6.
79. 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.
80. Amici G. Solute kinetics in automated peritoneal dialysis. Perit Dial Int. 2000;20(Suppl. 2):S77–82.
81. 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.
82. 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.
83. Mujais S, Vonesh E. Profiling of peritoneal ultrafiltration. Kidney Int. 2002;62(Suppl 81):S17–22.
84. 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.
85. 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.
86. 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.
87. 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.
88. Ronco C, Dell'Aquila R. Continuous flow peritoneal dialysis. Perit Dial Int. 2001;21(Suppl3):S138–43.
89. Brunkhorst R, Fromm S, Wrenger E, et al. Automated peritoneal dialysis with "online"-prepared bicarbonate-buffered dialysate: technique and first clinical experiences. Nephrol Dial Transplant. 1998;13:3189–92.
90. Ronco C, Amerling R. Continuous flow peritoneal dialysis: current state-of-the-art and obstacles to further development. Contrib Nephrol. 2006;150:310–20.
91. Diaz-Buzo JA. Continuous-flow peritoneal dialysis: update. Adv Perit Dial. 2004;20:18–22.
92. 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.

93. 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.
94. 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.
95. National Kidney Foundation. K/DOQI clinical practice guidelines for peritoneal dialysis adequacy. Am J Kidney Dis. 2000;37(Suppl 1):S65–136.
96. 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.
97. 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.
98. 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.
99. Churchill DN. Impact of peritoneal dialysis dose guidelines on clinical outcome. Perit Dial Int. 2005;25(Suppl 3):S95–8.
100. 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.
101. Chen HH, Shetty A, Afthentopoulos IF, et al. Discrepancy between weekly Kt/V and weekly creatinine clearance in patients on CAPD. Adv Perit Dial. 1995;11:83–7.
102. 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.
103. Wang T, Heimburger O, Cheng HH, et al. Effect of increased dialysate fill volume on peritoneal fluid and solute transport. Kidney Int. 1997;52:1068–76.
104. 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.
105. 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.
106. Durand PY, Freida P, Issad B, et al. How to reach optimal creatinine clearances in automated peritoneal dialysis. Perit Dial Int. 1996;16(Suppl 1): S167–70.
107. Mellits ED, Cheek DB. The assessment of body water and fatness from infancy to adulthood. Monogr Soc Res Child Dev. 1970;35:12–26.
108. 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.
109. 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.
110. 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.
111. 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.
112. van den Wall Blake AWL, Kooman JP, Lange JM, et al. Adequacy of peritoneal dialysis and the importance of preserving residual renal function. Nephrol Dial Transplant. 2006;21(Suppl 2):ii34–7.
113. Kim DJ DOJH, Huh WS, et al. Dissociation between clearances of small and middle molecules in incremental peritoneal dialysis. Perit Dial Int. 2001;21:462–6.
114. 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.
115. 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.
116. 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.
117. 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.
118. 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.
119. Brown EA, Davies SJ, Ruthford P, et al. Survival of functionally anuric patients on automated peritoneal dialysis: The European APD Outcome Study. J Am Soc Nephrol. 2003;14:2948–57.
120. 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.
121. Mitsnefes MM, Daniels SR, Schwartz SM, et al. Severe left ventricular hypertrophy in pediatric patients: prevalence and predictors. Pediatr Nephrol. 2000;14:898–902.
122. 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.
123. 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.
124. Smit W, Struijk DG, Ho-dac MM, et al. Quantification of free water transport in peritoneal dialysis. Kidney Int. 2004;66:849–54.
125. Posthuma N, ter Wee PM, Donker AJM, et al. Icodextrin use in CCPD patients during peritonitis: ultrafiltration and serum disaccharide concentrations. Nephrol Dial Transplant. 1998;13:2341–4.
126. 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.
127. 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.
128. 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.
129. 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.
130. 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.
131. 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.
132. 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.
133. 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.
134. 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.
135. 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.
136. 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.
137. 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.
138. 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.
139. 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.
140. 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.
141. Garthwaite E, Bhandari S. The effects of angiotensin converting enzyme inhibitors on potassium homeostasis in dialysis patients with and without residual renal function. Artif Organs. 2009;33:641–7.
142. 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.
143. Paglialonga F, Edefonti A. Nutrition assessment and management in children on peritoneal dialysis. Pediatr Nephrol. 2009;24:721–30.
144. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22:1689–702.
145. 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.
146. Aranda RA, Pecoits-Filho RFS, Romao Jr JE, et al. Kt/V in children on CAPD: how much is enough? Perit Dial Int. 1999;19:588–9.
147. 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.
148. 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.
149. 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.
150. 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.
151. 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, pp. 84–85.
152. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemoter Rep. 1970;54:225–35.

153. 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.
154. 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.
155. Ronco C, Amerling R, Dell' Aquila R, et al. Evolution of technology for automated peritoneal dialysis. Contrib Nephrol. 2006;150:291–309.
156. Edefonti A, Boccola S, Picca M, et al. Treatment data during pediatric home peritoneal dialysis. Pediatr Nephrol. 2003;18:560–4.
157. 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.
158. Nakamoto H. Telemedicine system for patients on continuous ambulatory peritoneal dialysis. Perit Dial Int. 2007;27(Suppl 2):S21–6.
159. Cargill A, Watson AR. Telecare support for patients undergoing chronic peritoneal dialysis. Perit Dial Int. 2003;23:91–4.
160. 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.
161. 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.
162. 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.
163. 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.
164. 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

12

Claus Peter Schmitt

Keywords
Peritoneal dialysis solution • Fluid composition • Biocompatible PD

Introduction

PD has traditionally been performed with acidic solutions containing glucose as osmotic and lactate as buffer agent. These solutions confer marked local and systemic toxicity (Fig. 12.1). Within few years, the peritoneal membrane undergoes profound morphological transformations including progressive mesothelial denudation, submesothelial fibrosis, hyaline vasculopathy, and neoangiogenesis [1]. Hypervascularization of the peritoneal membrane results in increased solute clearance, but also in rapid glucose uptake and thus ultrafiltration loss and eventually PD failure [2]. Peritonitis episodes, chronic inflammation, and a persistently elevated calcium* phosphate product further accelerate membrane transformation, which in severe cases results in life-threatening, encapsulating peritoneal sclerosis. Even though most patients will not develop these complications if early transplantation is available, they still represent a major clinical problem on a global scale as reflected by the limited long-term technique and patient survival [3]. In recent years, PD solutions with a markedly improved biocompatibility profile have been developed to remedy this problem. They which are gradually becoming available for routine patient care around the globe. These "biocompatible" solutions allow for a refined and individualized therapy with a significantly reduced toxin load. Knowledge of the specific features of each solution is necessary to provide a most efficient and biocompatible PD regimen.

*The askerik denotes the calcium -phosphate product, i.e. the multiplication of both serum concentrations. This product is highly relevant and often used in nephrology publications

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PD Fluid Composition

Peritoneal dialysis fluids are composed of an osmotic agent, a buffer substance, and electrolytes, which determine their purification and ultrafiltration capacity as well as clinical tolerability.

Osmotic Agents

The standard osmotic agent is glucose at supraphysiological concentrations (1,500–4,250 mg/dL). The high dialysate glucose concentration creates an osmotic gradient via the peritoneal mem-

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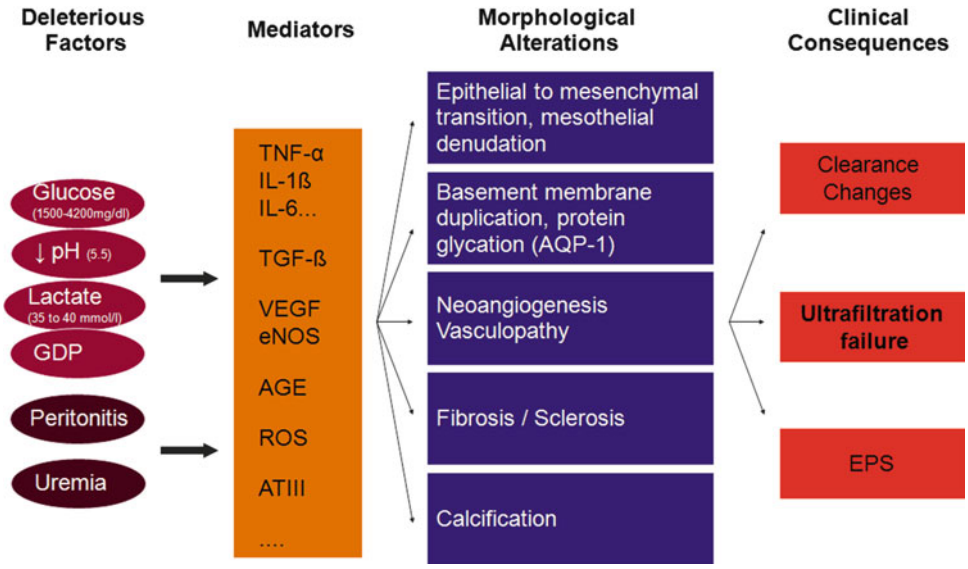

Fig. 12.1 PD fluid toxicity and associated morphological and functional alterations. *AGE* advanced glycated endproducts; *ROS* reactive oxygen species; *AQP-1* Aquaporin 1; *EPS* encapsulating peritoneal sclerosis; *GDP* glucose degardation product

brane to achieve ultrafiltration. On the other hand, the hyperosmolar and hyperglycemic milieu, is also a major driving force for the peritoneal membrane transformation and progressive increase in peritoneal solute transport rates [4]. Depending on the transporter status, from low to high, 45–88% of the intraperitoneal glucose is absorbed within 4 h. While providing some usually welcome additional calorie supply, glucose resorption is the rate-limiting factor for ultrafiltration capacity.

Moreover, sterilization of the glucose at high temperature and a relatively high pH (5.5) as well as prolonged storage promotes the generation of numerous glucose degradation products (GDP), such as formaldehyde, acetaldehyde, 3-deoxyglucosone (3-DG), 3,4-dideoxyglucosone (3,4-DGE), and 5-hydroxymethyl furaldehyde (5-HMF). GDP impair peritoneal mesothelial cell function [5], induce pro-angiogenetic factors such as VEGF [6] and impair local host defense mechanisms [7]. They are rapidly absorbed via the peritoneal membrane [8] and contribute to inflammation, fibrosis, and vasculopathy. GDP are potent precursors for advanced glycation endproduct (AGE) formation. AGE accumulate in the PD membrane but also in the entire body [9], and further accelerate the process of vascular and tissue aging (Fig. 12.2).

Based on these deleterious effects of glucose, three alternative technological measures have been realized to improve PD fluid biocompatibility: the separation of glucose at a very low pH from the buffer in double- and triple-chamber bag systems; the replacement of glucose by icodextrin, a glucose polymer derived from stark; and the replacement of glucose by amino acids. All these solutions contain significantly less GDP than conventional dextrose-based fluids (Tables 12.1 and 12.2) [10, 11].

Buffer Substances

Lactate has been the only buffer available for PD fluids until recently. It is added to PD solutions at concentrations far above the physiological range (Table 12.1), is rapidly absorbed via the peritoneal membrane and is metabolized to bicarbonate in the liver. The net buffer gain is counterbalanced by the simultaneous loss of blood bicarbonate into the dialysate [12]. In vitro and animal studies have provided ample evidence that the high amounts of lactate, present in conventional PD solutions at a low pH, have detrimental effects on peritoneal mesothelial cells. Lactate alters specific cytokine release [13], reduces the avail-

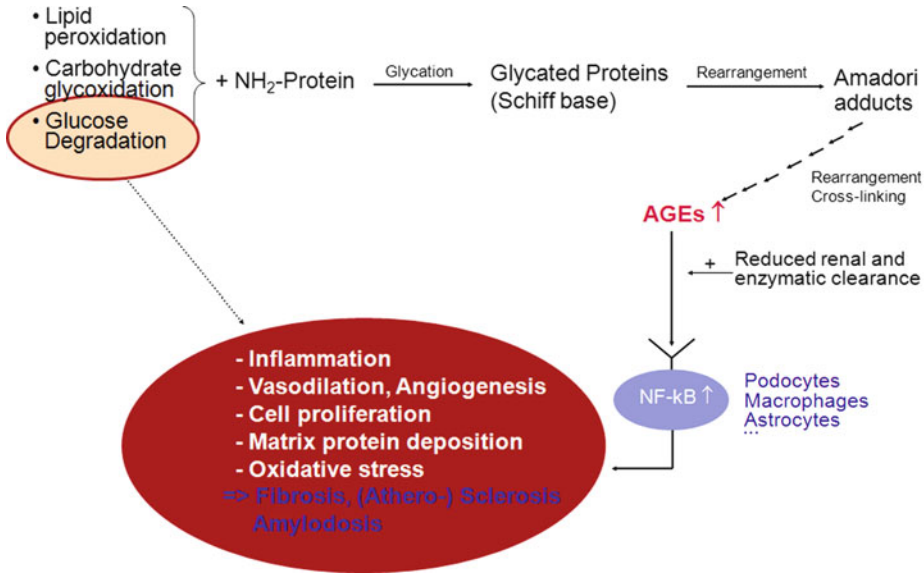

Fig. 12.2 Deleterious effects of glucose degradation products (GDP) and advanced glycation endproducts (AGE) in PD patients. PD fluids accelerate the aging process by delivery of glucose degradation products, which act directly and indirectly via enhanced generation of AGE on the peritoneum membrane but also systemically

Table 12.1 Composition of conventional, single-chamber PD solutions

	CAPD 2/3/4 17/18/19	Dianeal PD 1, PD2[a], PD4	Gambrosol 10/40
Sodium (mmol/L)	134	132	132
Chloride (mmol/L)	102.5	102/96/95	96/95
Calcium (mmol/L)	1.25/1.75	1.75/1.75/1.25	1.75/1.35
Magnesium (mmol/L)	0.5	0.75/0.75/0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.36/2.27/3.86	1.5/2.5/4.0
Osmolarity (mosmol/L)	356–509	344–486	353–492
Lactate (mmol/L)	35	35/40/40	40
pH	5.5	5.5	5.5
Formaldehyde (μmol/L)[b]	5.4 ± 0.4	6.8 ± 0.2	6.4 ± 0.5
3,4 DGE (μmol/L)[b]	16.2 ± 0.8	11.3 ± 0.5	13.1 ± 1.1
Bag size (L)	1.5/2/2.5	1.5/2/2.5/3/5 (APD)	0.5/1/1.5/2/2.5/3 (G40)/4.5/5

GDP concentrations taken from Ref. [10], for Gambrosol 10/40 from Ref. [11]
[a]Not available in all countries
[b]At medium glucose concentration

ability of antioxidants such as gluthatione [14] and induces neoangiogenesis [15]. Adjustment to a physiological pH markedly improves but does not normalize the ex vivo viability and function of mesothelial cells [16, 17]. In patients with acute renal failure, especially when in poor tissue perfusion states such as shock, lactate acidosis and multiorgan dysfunction, lactate inadequately buffers metabolic acidosis. This is especially true in patients with impaired hepatic metabolism.

Dialysis fluids containing bicarbonate, the physiological buffer of the blood, have been demonstrated to improve the outcome of patients who require acute dialysis [18, 19]. Bicarbonate-based PD solutions used to require local manufacturing and rapid consumption due to the ready dissociation of HCO_3 to gaseous CO_2 [20]. In recent years, advances in foil technology have made it possible to produce industrially manufactured, stable PD fluid bags containing either pure bicarbonate or a mixture of bicarbonate and lactate buffer (Table 12.2). Superior control of metabolic acidosis has been demonstrated for the pure 34 mmolar bicarbonate solution and

Table 12.2 Composition of biocompatible PD solutions

	BicaVera	Balance	Gambrosol trio 10/40	Physioneal 35/40	Extraneal (7.5% Icodextrin)	Nutrineal (1.1%AS)
Sodium (mmol/L)	132	134	132[b]	132	132	132
Chloride (mmol/L)	104.5	100.5	96[b]	101/95	96	105
Calcium (mmol/L)	1.75	1.25/1.75	1.75/1.35[b]	1.75/1.25	1.75	1.25
Magnesium (mmol/L)	0.5	0.5	0.25[b]	0.25	0.25	0.25
Glucose (%)	1.5/2.3/4.25	1.5/2.3/4.25	1.5/2.5/3.9	1.36/2.27/3.86	0	0
Osmolarity (mosmol/L)[a]	358–511	358–511	356–483	344–484	284	365
Lactate (mmol/L)	0	35	40[b]	10/15	40	40
Bicarbonate (mmol/L)	34	0	0	25/25	0	0
pH	7.4	7.0	5.5–6.5[a]	7.4	5.5	6.7
Formaldehyde (μmol/L)[b]	<3.3	<3.3	<3.3	3.4±0	3.6±0.7	n.d.
3,4 DGE[b] (μmol/L)	<2.4	<2.4	<2.4	14.3±2.5	<2.4	n.d.
Bag size (L)	2/2.5/3 (APD)	2/2.5/3 and 5 (APD)	2/2.5/5 (APD)	1.5/2/2.5/5 (APD)	2.0 and 2.5	2.0

GDP concentrations taken from Ref. [10]
n.d. not done
[a]Low to high glucose concentration
[b]Medium glucose concentration

the 25/10 mmolar bicarbonate/lactate solution as compared to single-chamber, 35 mmolar lactate PD fluid [21, 22]. Overcorrection to metabolic acidosis may occur with very frequent cycles and with higher dialysate buffer content [23]. *Pyruvate*, a natural radical scavenger with buffer capacity, might be an attractive alternative buffer agent but thus far has only been investigated in experimental settings [24].

Electrolytes

Sodium, chloride, calcium, and magnesium are added to the PD solutions to maintain mineral homeostasis. *Sodium chloride* balance is closely related to the ultrafiltration rate. Depending on dwell time and the relative contribution of free water transport via aquaporin-1 in the early phase of a dwell, more than 100 mmol of sodium per liter ultrafiltrate can be lost. In infants, the relatively higher ultrafiltration rates may therefore result in reduced total body sodium chloride content, hypovolemia, and hypotension. Since the losses are isotonic, sodium depletion is commonly not associated with hyponatremia; rather, nocturnal hypotension and tachycardia may be the first symptoms of sodium chloride deficiency. Sodium chloride supplementation is mandatory in these patients. Only if dwell time is very short and dialysate glucose concentration is high, as for example required in severely volume overloaded patients, aquaporin-1 mediated free water transport predominates. Since the drained dialysate sodium mass is low in these cases ("sodium sieving"), relative body sodium concentrations increase and results in third. The third scenario usually affects older children and adults who are typically salt and thus water overloaded due to poor dietary adherence, especially if anuric. In these patients, the complementary use of icodextrin solution has proven beneficial (see below). Sodium balance, hydration status, and blood pressure might also be improved by low sodium dialysate solutions, which have shown promising results in clinical studies [25, 26] but have not yet been admitted to the market.

Optimal *calcium* control, i.e., serum levels in the lower normal range, is crucial for bone and vascular health. Dialysate calcium concentrations range from the physiological 1.25 mmol/L, which usually allows for a calcium neutral dialysis, unless ultrafiltration occurs, to 1.75 mmol/L, which results in a positive calcium balance. The net dialytic calcium balance can be estimated from the dialysate turnover and the difference between PD fluid and effluent calcium concentrations and the calcium losses via the ultrafiltrate. It adds to the total body calcium balance determined by urine losses and intestinal absorption from nutrients and phosphate binders and modified by vitamin D treatment. While calcium balance should be mildly positive to meet the mineral requirements of a growing child, routine administration of 1.75 millimolar PD fluid will result in calcium overload in most children. The use of solutions containing 1.0 mmol/L calcium leads to aggravated secondary hyperparathyroidism and have become dispensible with the advent of calcium-free phosphate binders [27]. Since *magnesium* accumulates in advanced CKD, dialysate magnesium concentrations are low to low normal relative to serum concentrations (Tables 12.1 and 12.2). Harmful effects of increased serum magnesium levels include altered nerve conduction velocity, pruritus, and altered bone and parathyroid gland function. On the other hand, hypermagnesemia may also slow vascular calcification rate. An inverse relationship between serum Mg, hyperparathyroidism, and vascular calcification has been demonstrated in adult dialysis patients [28, 29].

PD Fluid Types

Conventional PD Solutions

Single-chamber PD solutions allow for efficient ultrafiltration, transperitoneal solute transport, and, thus, blood purification. They, however, contain high amounts of toxic GDP and expose the patient to supraphysiological lactate concentrations at an unphysiologically low pH (Table 12.1). They impair peritoneal mesothelial cell function, local host defense [13, 14, 30, 31], and lead to largely irreversible alterations of PD membrane morphology and function within a few years of usage [1, 2, 15].

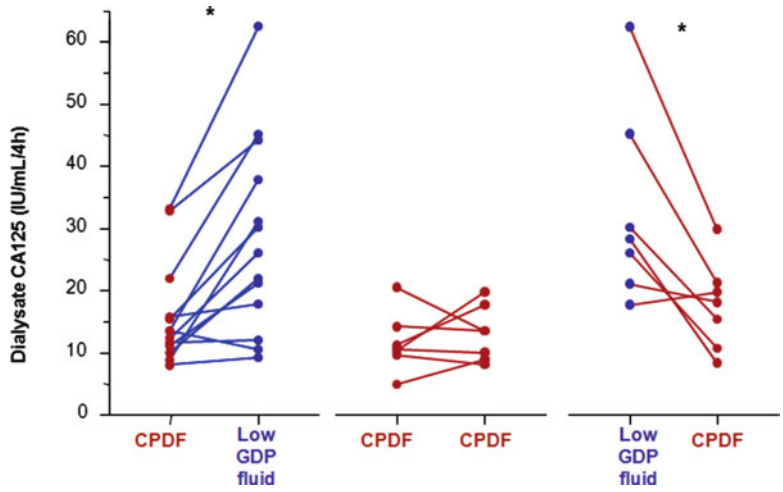

Fig. 12.3 CA125 effluent concentration in children treated with conventional (CPDF) and low GDP solution (BicaVera®). Twenty-eight children were randomly assigned to undergo 12 week treatment periods with low GDP solution followed by CPDF or vice versa. CA125 effluent concentrations, a marker of peritoneal mesothelial cell mass, increase with low GDP solution (*left*), remain low in patients who continue to receive CPDF, and decrease in children switched from low GDP fluid to CPDF (*right*) (With permission from Ref. [21])

Multi-Chamber PD Fluids

By separating the glucose at a very low pH in double- and triple-chamber bags, formation of GDP is markedly reduced. Most, albeit not all, of the solutions are buffered at neutral or even physiological pH with lactate, bicarbonate, or a mixture of both. Numerous experimental and clinical studies have demonstrated an improved biocompatibility profile of multi-chamber PD solutions.

In vitro, multi-chamber PD fluids improve mesothelial cell viability and function, preserve innate peritoneal immune defense mechanisms, and reduce the synthesis and secretion of cytokines related to inflammation, fibrosis, and angiogenesis [31–34].

Animal studies confirmed improved in vivo peritoneal host defense [35, 36], reduced peritoneal TGF-ß and VEGF expression, reduced deposition of AGE, preservation of the mesothelial cell layer, and markedly reduced fibrosis, vasculopathy and neoangiogenesis [37]. The acute peritoneal hyperperfusion observed with conventional solutions is largely prevented when perfusion is performed with multi-chamber PD fluid [38]. Finally, multi-chamber fluids have been associated with preserved ultrafiltration capacity in an experimental long-term dialysis model [39].

In humans, effluent CA125 concentration, a surrogate parameter of peritoneal mesothelial cell mass increases (Fig. 12.3), whereas the inflammation markers IL-6 and hyaluronic acid decrease [21, 40–43]. The effluent concentration of VEGF, a putative marker of peritoneal neoangiogenesis, decreased in some but not all studies [34, 42, 43]. Several prospective randomized trials demonstrate similar solute transport and ultrafiltration capacity in children and adults treated with multi-chamber as compared to conventional PD solutions [8, 21, 23, 44]. In case of reduced ultrafiltration rate, this was compensated by improved residual renal urine output [40, 45]. Indeed, residual renal function appears to be better preserved with multi-chamber PD fluids [46, 47], most likely due to reduced GDP resorption. GDP are toxic to podocytes and tubular cells [48]. Switch from conventional to low GDP solutions results in a peritoneal washout of AGE [49, 50] and a 15% decline in systemic AGE levels in children [8] and adults [41].

A relevant clinical benefit of multi-chamber PD fluids is likely but difficult to ascertain. An immediate advantage is the reduction of abdominal discomfort due to reduced inflow pain and intraperitoneal pressure [51, 52]. Some but not all groups observed a reduced overall peritonitis

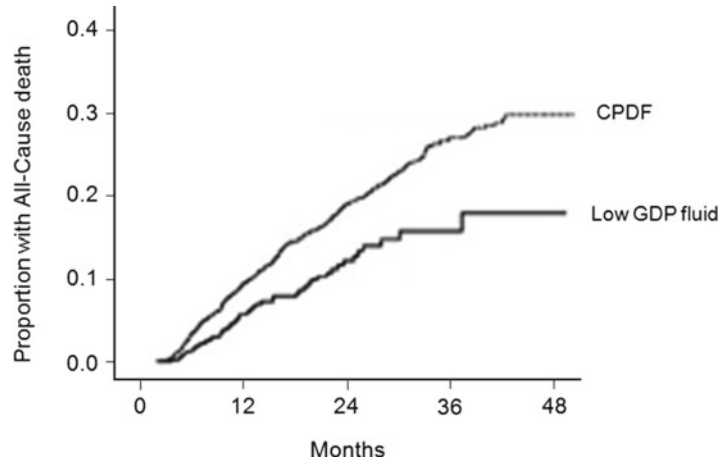

Fig. 12.4 Observational data on all-cause mortality in adult PD patients on low GDP solution (n = 1,621) and patients on conventional PD solution (CPDF, n = 542) suggesting improved patient survival with the low GDP solution ($p < 0.01$, With permission from Ref. [55]). This association is currently validated in prospective clinical trials

incidence in patients treated with PD solutions with reduced GDP content, new cyclers, and improved connection devices [53, 54]. Two large-scale registries demonstrate significant improvement of patient morbidity and mortality in adults using multi-chamber as compared to conventional fluids [55, 56] (Fig. 12.4). These promising findings have stimulated large-scale randomized comparative trials which are currently underway.

An interesting side note related to triple-chamber systems is the option to mix a hypoosmolar solution with 0.75% dextrose, which may be used for rehydration of dehydrated children.

Taken together, a plethora of beneficial effects has been demonstrated experimentally for low-GDP multi-chamber PD solutions, and evidence for relevant clinical benefits is beginning to emerge. It should be noted though that the different currently available solutions still differ considerably with respect to their GDP contents and final pH, obviously due to differences in the manufacturing process. Some manufactures reduced total GDP content by 50%, others by more than 90% compared to single-chamber PD fluid (Table 12.2) [10, 11]. The clinical impact of these differences has not yet been delineated.

Icodextrin Solution

Exposure to glucose at high concentrations confers some degree of toxicity to the peritoneum even in the absence of GDP. Therefore, a complementary research strategy besides minimization of GDP formation has been the search for alternative, less toxic osmotic agents. Icodextrin is derived from starch and consists of a mixture of glucose polymers with an 85% molecular weight range of 1.7–45 kD. The GDP content of the icodextrin solution is low, lactate concentration is 40 mmol/L at a pH of 5.5 (Table 12.2). Although the transperitoneal absorption rate is much lower than that of glucose, 40% of the icodextrin molecules are absorbed within 12 h [57]. Icodextrin is metabolized to maltose and its derivatives, which accumulate in the human body and increase serum osmolality by 5 mosmol/L [58]. A clinical impact of chronic maltose accumulation has not yet been discerned. After icodextrin discontinuation, the plasma levels of its metabolites return to baseline within 3–7 days [57].

Unlike the hyperosmolar, crystalloid osmotic gradient of glucose solutions, icodextrin solution is characterized by iso-osmotic, colloid osmotic ultrafiltration. This type of ultrafiltration is aquaporin-1 independent, i.e., sodium sieving does not occur. The ultrafiltration pattern is delayed as compared to glucose-containing PD fluids, with sustained net fluid withdrawal for more than 12 h (Fig. 12.5). Icodextrin should therefore be administered once daily during the long dwell.

Once daily administration of icodextrin increases sodium removal and improves the daily ultrafiltration rate and hydration status [58, 59],

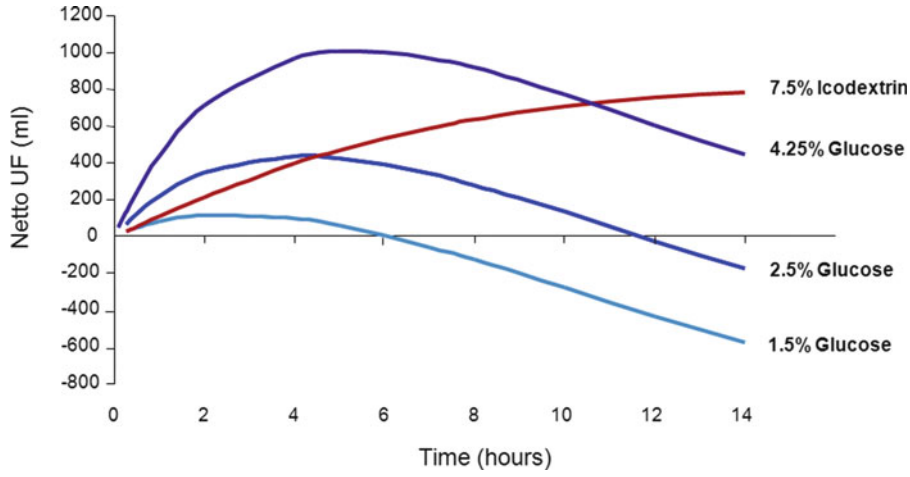

Fig. 12.5 Scheme of icodextrin and glucose-dependent ultrafiltration kinetics. Icodextrin induces relative slow, AQP-1 independent, but sustained ultrafiltration and should be used for a single long dwell

independent of the prevailing peritoneal transporter status [60]; blood pressure and left ventricular mass are improved within 3–6 months [61, 62].

The local and systemic glucose load is significantly reduced and the plasma lipid profile improves with icodextrin usage [63, 64]. In anuric APD patients, icodextrin administration during the daytime dwell preserves peritoneal membrane function as compared to patients receiving conventional, high GDP solution only [65].

In many centers, icodextrin is combined with conventional single-chamber PD solution. Whether long-term results are comparable to prescription of pH neutral, low GDP solutions only is yet unknown. Twice daily administration of icodextrin has been proposed in seriously hypervolemic patients [66]. Caution, however, is mandatory, since the metabolic impact of the additional icodextrin and oligosaccharide load is yet unknown.

Disadvantages of icodextrin solution concern the high lactate concentration and the low pH (Table 12.2). Allergic skin reactions to icodextrin and exfoliative dermatitis have been reported in up to 10% of the patients. Discontinuation of icodextrin usually is curative. In the past, aseptic peritonitis outbreaks were repeatedly noted with icodextrin fluid; these were mainly due to transient contamination with peptidoglycan, a bacterial membrane compound inducing local inflammation, which had escaped endotoxin testing [67]. The last published outbreak occurred in 2006 [68]. The reduced GDP content improves peritoneal host defense mechanisms in an ex vivo model, but not to a similar extent as double-chamber PD fluids [36].

Glucose-specific assays are required to measure serum glucose levels in patients treated with icodextrin since falsely increased plasma glucose determinations are obtained when glucose dehydrogenase-based (GDH PQQ) or glucose-dye-oxidoreductase-based methods are used. Total alpha-amylase activity is 75% lower in the serum of patients treated with icodextrin than in patients only treated with glucose solutions and 66% lower as compared to healthy subjects, for unknown reasons [69]. This needs to be considered if a pancreatic disease is suspected. Mild increases in serum GOT, GPT, and AP have been observed in 1–10% of the patients.

In summary, icodextrin solution has important advantages over conventional PD solutions with respect to sodium removal and ultrafiltration, which are particularly relevant in anuric subjects and those with a high peritoneal transporter status. In the future, the emergence of a high transporter status, and consequently the need for icodextrin treatment, is hoped to decline with the administration of biocompatible PD solutions from the very beginning.

Amino Acid Solutions

Amino acids are another alternative to glucose as osmotic agent. Amino acid–based PD solutions contain very low amounts of GDP [70] and allow for a phosphate-free amino acid supply. The solution is only slightly hyperosmolar, similar to 1.5% glucose solution, and contains 40 mmol/L of lactate at a slightly acidic pH of 6.7. Experimental studies, however, do not unequivocally support the notion of improved biocompatibility [37, 71]. Amino acids induce mesothelial NO production, a factor involved in neoangiogenesis [72], increase effluent IL-6 concentrations, a potential surrogate marker of inflammation [73], and suppress leukocyte recruitment in rats [36]. Long-term dialysis in rats, however, revealed only minor peritoneal changes and preserved ultrafiltration capacity, similar to double-chamber PD fluid [37]. In children and adults, solute and water transport is similar as compared to conventional, high GDP fluids [74, 75].

With respect to the nutritional effect of amino acid solutions, early studies yielded disappointing results with no improvement in anthropometric indices, increased serum nitrogen levels, and metabolic acidosis [76]. More recent stable isotope studies in adult CAPD patients using amino acid and glucose PD fluid exposure at a ratio of 1:4 yielded increased protein anabolism [77] and a 4% higher protein synthesis rate as compared to patients treated with a double-chamber PD solution only. Increases in serum nitrogen levels and metabolic acidosis were not observed, protein breakdown was not affected [78]. The anabolic effect was most pronounced in malnourished patients. This is in line with clinical observations in four malnourished patients followed over 3 years [75]. Outcome data from appropriately sized randomized controlled trials, however, are not yet available.

The limited anabolic effects of the relatively expensive solutions, concerns regarding their biocompatibility, and the usual achievement of adequate nutrition with enteral feeding thus far have prevented wider administration of amino acid–based PD fluids in children, although the concept is intriguing. The few pediatric reports available comprise ten patients or less and suggest good clinical tolerance and similar transport kinetics as compared to other solutions [74, 79–81].

Combination Therapies

Different combinations of biocompatible PD solutions are feasible, and the concept appears intriguing. Icodextrin can be administered together with multi-chamber PD fluids. Combination of icodextrin with multi-chamber PD and amino acid-based fluid has been advocated to substantially reduce glucose and GDP exposure, e.g., by 40–50% in patients on CAPD. While results from prospective, randomized controlled trials are not yet available, observational clinical reports suggest that the triple combination is safe and effective [82, 83] and may improve metabolic acidosis control [84]. The anecdotally reported overcorrection of metabolic acidosis [85] may be related to intensive PD protocols with frequent cycles and could probably be mitigated by choosing PD solutions with lower buffer content.

Perspectives

Biocompatible PD fluids and the new cycler systems are increasingly used in children with end-stage renal disease. According to the International Pediatric PD Network Registry, 60% of the PD children in Europe were treated with multi-chamber PD solutions with reduced GDP content in 2010, 15% with icodextrin solution (www.pedpd.org). Lower numbers have been reported for Asia (25% and 15%) and North America (10% and 17%). In face of the increasing scientific and clinical evidence of local and systemic benefits of these solutions, the associated increase in costs should be offset by reduced infectious complications [53, 54], improved long-term preservation of the PD membrane [37, 39, 65], improved cardiovascular health [61, 65, 66], and ultimately improved long-term patient survival (Fig. 12.6). Registry data support this assumption [55, 56] which is currently being tested in randomized clinical trials.

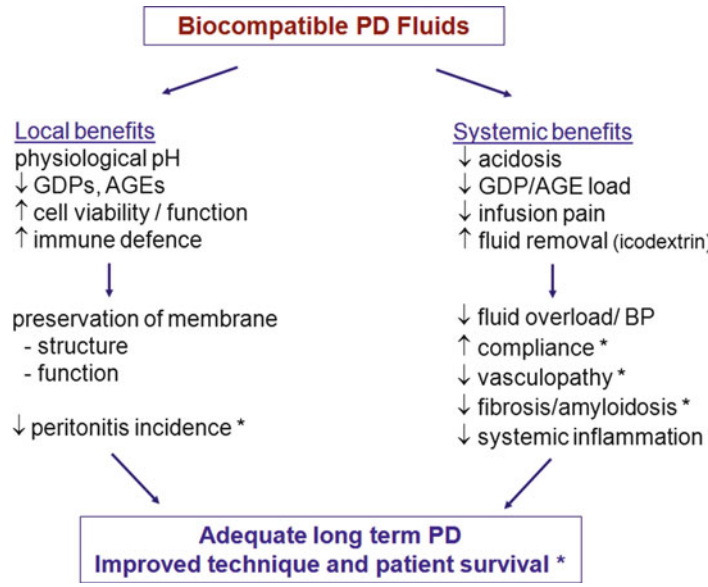

Fig. 12.6 Local and systemic benefits of biocompatible PD solutions. *Asterisks* indicate that only limited scientific evidence is available

Future prospects should include the complete replacement of glucose by a nontoxic (and thus GDP free), nonabsorbable osmotic agent. Several such agents are currently under investigation. To optimize mineral and acid base balance and thus to reduce CKD-MBD and cardiovascular sequelae, novel PD systems should furthermore allow for a more refined, continuous adaptation of electrolyte and buffer supply according to individual needs.

References

1. Williams JD, Craig KJ, Topley N, Von Ruhland C, Fallon M, Newman GR, Mackenzie RK, GT Williams, Peritoneal Biopsy Study Group. Morphologic changes in the peritoneal membrane of patients with renal disease. J Am Soc Nephrol. 2002;13(2):470–9.
2. 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(2):180–5.
3. Schaefer F, Klaus G, Müller-Wiefel DE, Mehls O, Mid European Pediatric Peritoneal Dialysis Study Group (MEPPS). Current practice of peritoneal dialysis in children: results of a longitudinal survey. Perit Dial Int. 1999;19(Suppl 2):S445–9.
4. Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. J Am Soc Nephrol. 2001;12(5):1046–51.
5. Witowski J, Korybalska K, Wisniewska J, Breborowicz A, Gahl GM, Frei U, Passlick-Deetjen J, Jörres A. Effect of glucose degradation products on human peritoneal mesothelial cell function. J Am Soc Nephrol. 2000;11(4):729–39.
6. Inagi R, Miyata T, Yamamoto T, Suzuki D, Urakami K, Saito A, Van de Ypersele Strihou C, Kurokawa K. Glucose degradation product methylglyoxal enhances the production of vascular endothelial growth factor in peritoneal cells: role in the functional and morphological alterations of peritoneal membranes in peritoneal dialysis. FEBS Lett. 1999;463(3):260–4.
7. Jonasson P, Braide M. Kinetics and dose response of the effects of heated glucose peritoneal dialysis fluids on the respiratory burst of rat peritoneal leukocytes. ASAIO J. 2000;46(4):469–73.
8. Schmitt CP, von Heyl D, Rieger S, Arbeiter K, Bonzel KE, Fischbach M, Misselwitz J, Pieper AK, Schaefer F, Mid European Pediatric Peritoneal Dialysis Study Group (MEPPS). 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.
9. Shaw S, Akyol M, Bell J, Briggs JD, Dominiczak MH. Effects of continuous ambulatory peritoneal dialysis and kidney transplantation on advanced glycation endproducts in the skin and peritoneum. Cell Mol Biol (Noisy-le-grand). 1998;44(7):1061–8.
10. Frischmann M, Spitzer J, Fünfrocken M, Mittelmaier S, Deckert M, Fichert T, Pischetsrieder M. Development and validation of an HPLC method to quantify 3,4-dideoxyglucosone-3-ene in peritoneal dialysis fluids. Biomed Chromatogr. 2009;23(8):843–51.
11. Erixon M, Wieslander A, Lindén T, Carlsson O, Forsbäck G, Svensson E, Jönsson JA, Kjellstrand P. How to avoid glucose degradation products in peritoneal dialysis fluids. Perit Dial Int. 2006;26(4):490–7.

12. Schmitt CP, Haraldsson B, Doetschmann R, Zimmering M, Greiner C, Böswald M, Klaus G, Passlick-Deetjen J, Schaefer F. Effects of pH-neutral, bicarbonate-buffered dialysis fluid on peritoneal transport kinetics in children. Kidney Int. 2002;61(4): 1527–36.
13. Witowski J, Topley N, Jorres A, Liberek T, Coles GA, Williams JD. Effect of lactate-buffered peritoneal dialysis fluids on human peritoneal mesothelial cell interleukin-6 and prostaglandin synthesis. Kidney Int. 1995;47:282–93.
14. Breborowicz A, Rodela H, Martis L, Oreopoulos DG. Intracellular glutathione in human peritoneal mesothelial cells exposed in vitro to dialysis fluid. Int J Artif Organs. 1996;19:268–75.
15. Zareie M, Hekking LH, Welten AG, Driesprong BA, Schadee-Eestermans IL, Faict D, Leyssens A, Schalkwijk CG, Beelen RH, Ter Wee PM, Van Den Born J. Contribution of lactate buffer, glucose and glucose degradation products to peritoneal injury in vivo. Nephrol Dial Transplant. 2003;18: 2629–37.
16. Plum J, Razeghi P, Lordnejad RM, Perniok A, Fleisch M, Fussholler A, Schneider M, Grabensee B. Peritoneal dialysis fluids with a physiologic pH based on either lactate or bicarbonate buffer-effects on human mesothelial cells. Am J Kidney Dis. 2001;38(4): 867–75.
17. Ogata S, Mori M, Tatsukawa Y, Kiribayashi K, Yorioka N. Expression of vascular endothelial growth factor, fibroblast growth factor, and lactate dehydrogenase by human peritoneal mesothelial cells in solutions with lactate or bicarbonate or both. Adv Perit Dial. 2006;22:37–40.
18. Thongboonkerd V, Lumlertgul D, Supajatura V. Better correction of metabolic acidosis, blood pressure control, and phagocytosis with bicarbonate compared to lactate solution in acute peritoneal dialysis. Artif Organs. 2001;25(2):99–108.
19. Kierdorf HP, Leue C, Arns S. Lactate- or bicarbonate-buffered solutions in continuous extracorporeal renal replacement therapies. Kidney Int Suppl. 1999;72: S32–6.
20. Dorval M, Legault L, Lessard F, Roy L. Practical aspects of the addition of sodium bicarbonate to peritoneal dialysate. Perit Dial Int. 2000;20(6):791–3.
21. 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.
22. Otte K, Gonzalez MT, Bajo MA, del Peso G, Heaf J, Garcia Erauzkin G, Sanchez Tomero JA, Dieperink H, Povlsen J, Hopwood AM, Divino Filho JC, Faict D. Clinical experience with a new bicarbonate (25 mmol/L)/lactate (10 mmol/L) peritoneal dialysis solution. Perit Dial Int. 2003;23(2):138–45.
23. 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.
24. van Westrhenen R, Zweers MM, Kunne C, de Waart DR, van der Wal AC, Krediet RT. A pyruvate-buffered dialysis fluid induces less peritoneal angiogenesis and fibrosis than a conventional solution. Perit Dial Int. 2008;28(5):487–96.
25. Nakayama M, Kasai K, Imai H, TRM-280 Study Group. Novel low Na peritoneal dialysis solutions designed to optimize Na gap of effluent: kinetics of Na and water removal. Perit Dial Int. 2009;29(5): 528–35.
26. Davies S, Carlsson O, Simonsen O, Johansson AC, Venturoli D, Ledebo I, Wieslander A, Chan C, Rippe B. The effects of low-sodium peritoneal dialysis fluids on blood pressure, thirst and volume status. Nephrol Dial Transplant. 2009;24(5):1609–17. Epub 2009 Jan 14.
27. Weinreich T, Passlick-Deetjen J, Ritz E, The Peritoneal Dialysis Multicenter Study Group. Low dialysate calcium in continuous ambulatory peritoneal dialysis: a randomized controlled multicenter trial. Am J Kidney Dis. 1995;25(3):452–60.
28. Wei M, Esbaei K, Bargman J, Oreopoulos DG. Relationship between serum magnesium, parathyroid hormone, and vascular calcification in patients on dialysis: a literature review. Perit Dial Int. 2006;26(3): 366–73.
29. Navarro-González JF, Mora-Fernández C, García-Pérez J. Clinical implications of disordered magnesium homeostasis in chronic renal failure and dialysis. Semin Dial. 2009;22(1):37–44.
30. Witowski J, Jorres A. Peritoneal dialysis: a biological membrane with a nonbiological fluid. Contrib Nephrol. 2009;163:27–34.
31. Kazancioglu R. Peritoneal defense mechanisms – the effects of new peritoneal dialysis solutions. Perit Dial Int. 2009;29(Suppl 2):S198–201.
32. Topley N, Kaur D, Petersen MM, Jörres A, Passlick-Deetjen J, Coles GA, Williams JD. Biocompatibility of bicarbonate buffered peritoneal dialysis fluids: influence on mesothelial cell and neutrophil function. Kidney Int. 1996;49(5):1447–56.
33. 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.
34. Cooker LA, Luneburg P, Holmes CJ, Jones S, Topley N, Bicarbonate/Lactate Study Group. Interleukin-6 levels decrease in effluent from patients dialyzed with bicarbonate/lactate-based peritoneal dialysis solutions. Perit Dial Int. 2001;21(Suppl. 3):102–7.
35. Mortier S, Lameire NH, De Vriese AS. The effects of peritoneal dialysis solutions on peritoneal host defense. Perit Dial Int. 2004;24(2):123–38.
36. Mortier S, Faict D, Gericke M, Lameire N, De Vriese A. Effects of new peritoneal dialysis solutions on leukocyte recruitment in the rat peritoneal membrane. Nephron Exp Nephrol. 2005;101(4):e139–45.

37. Mortier S, Faict D, Schalkwijk CG, Lameire NH, De Vriese AS. Long-term exposure to new peritoneal dialysis solutions: effects on the peritoneal membrane. Kidney Int. 2004;66(3):1257–65.
38. Mortier S, De Vriese AS, Van de Voorde J, Schaub TP, Passlick-Deetjen J, Lameire NH. Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. J Am Soc Nephrol. 2002;13(2):480–9.
39. Mortier S, Faict D, De Lameire NH, Vriese AS. Benefits of switching from a conventional to a low-GDP bicarbonate/lactate-buffered dialysis solution in a rat model. Kidney Int. 2005;67(4):1559–65.
40. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, Passlick-Deetjen J, Euro Balance Trial Group. 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.
41. Zeier M, Schwenger V, Deppisch R, Haug U, Weigel K, Bahner U, Wanner C, Schneider H, Henle T, Ritz E. Glucose degradation products in PD fluids: do they disappear from the peritoneal cavity and enter the systemic circulation? Kidney Int. 2003;63(1):298–305.
42. Weiss L, Stegmayr B, Malmsten G, Tejde M, Hadimeri H, Siegert CE, Ahlmén J, Larsson R, Ingman B, Simonsen O, van Hamersvelt HW, Johansson AC, Hylander B, Mayr M, Nilsson PH, Andersson PO, De los Ríos T. Biocompatibility and tolerability of a purely bicarbonate-buffered peritoneal dialysis solution. Perit Dial Int. 2009;29(6):647–55.
43. Rippe B, Simonsen O, Heimbürger O, Christensson A, Haraldsson B, Stelin G, Weiss L, Nielsen FD, Bro S, Friedberg M, Wieslander A. Long-term clinical effects of a peritoneal dialysis fluid with less glucose degradation products. Kidney Int. 2001;59(1):348–57.
44. Tranaeus A, The Bicarbonate/Lactate Study Group. A long-term study of a bicarbonate/lactate-based peritoneal dialysis solution – clinical benefits. Perit Dial Int. 2000;20(5):516–23.
45. Montenegro J, Saracho RM, Martínez IM, Muñoz RI, Ocharan JJ, Valladares E. Long-term clinical experience with pure bicarbonate peritoneal dialysis solutions. Perit Dial Int. 2006;26(1):89–94.
46. Kim SG, Kim S, Hwang YH, Kim K, Oh JE, Chung W, Oh KH, Kim HJ, Ahn C, Korean Balnet Study Group. Could solutions low in glucose degradation products preserve residual renal function in incident peritoneal dialysis patients? A 1-year multicenter prospective randomized controlled trial (Balnet Study). Perit Dial Int. 2008;28(Suppl 3):S117–22.
47. Haag-Weber M, Krämer R, Haake R, Islam MS, Prischl F, Haug U, Nabut JL, Deppisch R, DIUREST Study Group. Low-GDP fluid (Gambrosol trio(R)) attenuates decline of residual renal function in PD patients: a prospective randomized study. Nephrol Dial Transplant. 2010;25:2288–96.
48. Müller-Krebs S, Kihm LP, Zeier B, Gross ML, Deppisch R, Wieslander A, Henle T, Penndorf I, Oh J, Reiser J, Nawroth PP, Zeier M. Schwenger V. Eur J Clin Invest: Renal toxicity mediated by glucose degradation products in a rat model of advanced renal failure; 2008.
49. Ho-dac-Pannekeet MM, Weiss MF, de Waart DR, Erhard P, Hiralall JK, Krediet RT. Analysis of non enzymatic glycosylation in vivo: impact of different dialysis solutions. Perit Dial Int. 1999;19(Suppl 2): 68–74.
50. Posthuma N, ter Wee PM, Niessen H, Donker AJ, Verbrugh HA, Schalkwijk CG. Amadori albumin and advanced glycation end-product formation in peritoneal dialysis using icodextrin. Perit Dial Int. 2001;21: 43–51.
51. Mactier RA, Sprosen TS, Gokal R, Williams PF, Lindbergh M, Naik RB, Wrege U, Gröntoft KC, Larsson R, Berglund J, Tranaeus AP, Faict D. Bicarbonate and bicarbonate/lactate peritoneal dialysis solutions for the treatment of infusion pain. Kidney Int. 1998;53(4):1061–7.
52. 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.
53. Montenegro J, Saracho R, Gallardo I, Martínez I, Muñoz R, Quintanilla N. Use of pure bicarbonate-buffered peritoneal dialysis fluid reduces the incidence of CAPD peritonitis. Nephrol Dial Transplant. 2007;22(6):1703–8.
54. Furkert J, Zeier M, Schwenger V. Effects of peritoneal dialysis solutions low in GDPs on peritonitis and exit-site infection rates. Perit Dial Int. 2008;28(6):637–40.
55. Han SH, Ahn SV, Yun JY, Tranaeus A, Han DS. Mortality and technique failure in peritoneal dialysis patients using advanced peritoneal dialysis solutions. Am J Kidney Dis. 2009;54(4):711–20.
56. Lee HY, Choi HY, Park HC, Seo BJ, Do JY, Yun SR, Song HY, Kim YH, Kim YL, Kim DJ, Kim YS, Kim MJ, Shin SK. Changing prescribing practice in CAPD patients in Korea: increased utilization of low GDP solutions improves patient outcome. Nephrol Dial Transplant. 2006;21(10):2893–9.
57. Moberly JB, Mujais S, Gehr T, Hamburger R, Sprague S, Kucharski A, Reynolds R, Ogrinc F, Martis L, Wolfson M. Pharmacokinetics of icodextrin in peritoneal dialysis patients. Kidney Int Suppl. 2002;81:S23–33.
58. Posthuma N, ter Wee PM, Donker AJ, Oe PL, Peers EM, Verbrugh HA, The Dextrin in APD in Amsterdam (DIANA) Group. Assessment of the effectiveness, safety, and biocompatibility of icodextrin in automated peritoneal dialysis. Perit Dial Int. 2000;20(Suppl 2): S106–13.
59. Davies SJ, Woodrow G, Donovan K, Plum J, Williams P, Johansson AC, Bosselmann HP, Heimbürger O, Simonsen O, Davenport A, Tranaeus A, Divino Filho JC. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol. 2003;14(9):2338–44.
60. Finkelstein F, Healy H, Abu-Alfa A, Ahmad S, Brown F, Gehr T, Nash K, Sorkin M, Mujais S. Superiority of

icodextrin compared with 4.25% dextrose for peritoneal ultrafiltration. J Am Soc Nephrol. 2005;16(2):546–54.
61. Konings CJ, Kooman JP, Schonck M, Gladziwa U, Wirtz J, van den Wall Bake AW, Gerlag PG, Hoorntje SJ, Wolters J, van der Sande FM, Leunissen KM. Effect of icodextrin on volume status, blood pressure and echocardiographic parameters: a randomized study. Kidney Int. 2003;63(4):1556–63.
62. Woodrow G, Oldroyd B, Stables G, Gibson J, Turney JH, Brownjohn AM. Effects of icodextrin in automated peritoneal dialysis on blood pressure and bioelectrical impedance analysis. Nephrol Dial Transplant. 2000;15(6):862–6.
63. Bredie SJ, Bosch FH, Demacker PN, Stalenhoef AF, van Leusen R. Effects of peritoneal dialysis with an overnight icodextrin dwell on parameters of glucose and lipid metabolism. Perit Dial Int. 2001;21(3):275–81.
64. Babazono T, Nakamoto H, Kasai K, Kuriyama S, Sugimoto T, Nakayama M, Hamada C, Furuya R, Hasegawa H, Kasahara M, Moriishi M, Tomo T, Miyazaki M, Sato M, Yorioka N, Kawaguchi Y, Japanese Extraneal Collaborated Study Group. Effects of icodextrin on glycemic and lipid profiles in diabetic patients undergoing peritoneal dialysis. Am J Nephrol. 2007;27(4):409–15.
65. Davies SJ, Brown EA, Frandsen NE, Rodrigues AS, Rodriguez-Carmona A, Vychytil A, Macnamara E, Ekstrand A, Tranaeus A, Filho JC, EAPOS Group. Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. Kidney Int. 2005;67(4):1609–15.
66. Say T, Oymak O, Inanc MT, Dogan A, Tokgoz B, Utas C. Effects of twice-daily icodextrin administration on blood pressure and left ventricular mass in patients on continuous ambulatory peritoneal dialysis. Perit Dial Int. 2009;29(4):443–9.
67. Martis L, Patel M, Giertych J, Mongoven J, Taminne M, Perrier MA, Mendoza O, Goud N, Costigan A, Denjoy N, Verger C, Owen Jr WF. Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. Lancet. 2005;365(9459):588–94.
68. Adam FU, Singan M, Ozelsancak R, Torun D, Ozdemir FN, Haberal M. Icodextrin-associated sterile peritonitis: a recent outbreak in Turkey. Perit Dial Int. 2007;27(5):598–9.
69. Anderstam B, García-López E, Heimbürger O, Lindholm B. Determination of alpha-amylase activity in serum and dialysate from patients using icodextrin-based peritoneal dialysis fluid. Perit Dial Int. 2003;23(2):146–50.
70. Schalkwijk CG, ter Wee PM, Teerlink T. Reduced 1,2-dicarbonyl compounds in bicarbonate/lactate-buffered peritoneal dialysis (PD) fluids and PD fluids based on glucose polymers or amino acids. Perit Dial Int. 2000;20(6):796–8.
71. Bender TO, Witowski J, Aufricht C, Endemann M, Frei U, Passlick-Deetjen J, Jörres A. A Biocompatibility of a bicarbonate-buffered amino-acid-based solution for peritoneal dialysis. Pediatr Nephrol. 2008;23(9):1537–43.
72. Reimann D, Dachs D, Meye C, Gross P. Amino acid-based peritoneal dialysis solution stimulates mesothelial nitric oxide production. Perit Dial Int. 2004;24(4):378–84.
73. Tjiong HL, Zijlstra FJ, Rietveld T, Wattimena JL, Huijmans JG, Swart GR, Fieren MW. Peritoneal protein losses and cytokine generation in automated peritoneal dialysis with combined amino acids and glucose solutions. Mediators Inflamm. 2007;2007:97272.
74. Qamar IU, Secker D, Levin L, Balfe JA, Zlotkin S, Balfe JW. Effects of amino acid dialysis compared to dextrose dialysis in children on continuous cycling peritoneal dialysis. Perit Dial Int. 1999;19(3):237–47.
75. Li FK, Chan LY, Woo JC, Ho SK, Lo WK, Lai KN, Chan TM. A 3-year, prospective, randomized, controlled study on amino acid dialysate in patients on CAPD. Am J Kidney Dis. 2003;42(1):173–83.
76. Dombros NV, Prutis K, Tong M, Anderson GH, Harrison J, Sombolos K, Digenis G, Pettit J, Oreopoulos DG. Six-month overnight intraperitoneal amino-acid infusion in continuous ambulatory peritoneal dialysis (CAPD) patients – no effect on nutritional status. Perit Dial Int. 1990;10(1):79–84.
77. Tjiong HL, van den Berg JW, Wattimena JL, Rietveld T, van Dijk LJ, van der Wiel AM, van Egmond AM, Fieren MW, Swart R. 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.
78. Tjiong HL, Rietveld T, Wattimena JL, van den Berg JW, Kahriman D, van der Steen J, Hop WC, Swart R, Fieren MW. 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.
79. Vande Walle J, Raes A, Dehoorne J, Mauel R, Dejaeghere A, Matthys D. Combined amino-acid and glucose peritoneal dialysis solution for children with acute renal failure. Adv Perit Dial. 2004;20:226–30.
80. 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.
81. Canepa A, Carrea A, Menoni S, Verrina E, Trivelli A, Gusmano R, Perfumo F. Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. Kidney Int. 2001;59(5):1967–73. s.o.: Qamar IU et al PDI1999.
82. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int Suppl. 2008;108:S137–44.
83. le Poole CY, Welten AG, Weijmer MC, Valentijn RM, van Ittersum FJ, ter Wee PM. Initiating CAPD with a regimen low in glucose and glucose degradation products, with icodextrin and amino acids (NEPP) is safe and efficacious. Perit Dial Int. 2005;25(Suppl 3):S64–8.

84. le Poole CY, van Ittersum FJ, Weijmer MC, Valentijn RM, ter Wee PM. Clinical effects of a peritoneal dialysis regimen low in glucose in new peritoneal dialysis patients: a randomized crossover study. Adv Perit Dial. 2004;20:170–6.

85. Vande Walle JG, 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. 2004;20:222–5.

Peritoneal Dialysis During Infancy

13

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Keywords
Peritoneal dialysis • Infants • Continuous ambulatory peritoneal dialysis (CAPD) • Automated peritoneal dialysis (APD) • Tidal peritoneal dialysis (TPD) • Dialysis solutions

Introduction

In the early years of renal replacement therapy, there has been doubt if it would be ethically justified to treat end-stage renal disease (ESRD) in newborns and infants with maintenance peritoneal dialysis due to their higher technical complication rates, morbidity, and mortality in comparison to older children [1, 2]. At the end of the 1990s, only 50% of pediatric nephrologists offered dialysis to patients under 1 year of age, and only 40% offered this treatment to neonates [3]. However, during recent years, an increasing number of publications have reported satisfactory outcomes with respect to morbidity, mortality, growth, and development [4–11]. Thus, in experienced centers, results comparable to those achieved in older children can be achieved and most countries with available resources offer treatment to the majority of infants.

Peritoneal dialysis in an infant is demanding to the child, the family, and the medical personnel. Thus, the decision to initiate therapy should be made after thorough discussion with the family and the treatment team with respect of the long-term prognosis of the child. The decision is a particular issue for infants in which coexisting congenital abnormalities are additional risk factors for survival and quality of life [5, 9–12]. However, as more and more infants are successfully treated with peritoneal dialysis and early renal transplantation, it is considered increasingly difficult ethically to withhold active treatment even from children with significant comorbidity.

Diagnosis

The true incidence of ESRD in infants is not known since some infants with serious comorbidity are not referred for renal replacement therapy (RRT). In Europe, the annual incidence of children aged 0–4 years accepted for RRT is 7–8 per million age-related population [13]. In North America, the incidence for RRT in neonates according to the NAPRTCS registry was 0.045 cases per million population per year [14].

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The most common diagnoses leading to terminal renal failure in infancy are renal hypoplasia/dysplasia with or without obstructive uropathy, autosomal recessive polycystic kidney disease (ARPKD), cortical necrosis usually due to perinatal asphyxia, and oxalosis [10, 15]. The spread of diagnoses is affected by race and sometimes by country. For example, in Finland, congenital nephrotic syndrome of the Finnish type represents 56% of infants starting peritoneal dialysis [8].

At our center, we have treated 98 children less than 2 years of age with peritoneal dialysis during the last 23 years. The recommendations in this chapter are based on the literature, and our own experience with this age group.

Initiation of Peritoneal Dialysis

Even in advanced chronic kidney disease (CKD), conservative treatment can usually be continued in infants as long as the child grows and develops normally, quality of life is acceptable, and no absolute indications for dialysis are present. In severe cases of congenital nephrosis not responding to ACE inhibition and indomethacin and requiring daily albumin infusions for sufficient protein balance and growth, we recommend bilateral nephrectomy and peritoneal dialysis when the child is about 6–7 months old (weight > 7 kg) [16]. To avoid dialysate leakage, we recommend to insert the catheter and leave it for 2–3 weeks before starting dialysis. We start dialysis with increasing volumes and perform bilateral nephrectomy to severely nephrotic children after checking the function of dialysis. In severely nephrotic children, warfarin therapy should be stopped 2–3 days prior to nephrectomy and AT III given intravenously (50 IU/kg) immediately prior to the operation. In children with ARPKD, it is advisable to take out both kidneys at the time of catheter insertion to give more space for dialysis volume and pulmonary function. In children with oxalosis, we do not remove the kidneys when combined liver–kidney transplantation is performed, as they may partly recover after liver transplantation.

Peritoneal Access

Both in acute situations, when the need for dialysis is more than a few days, and in cases of ESRD, it is important that a permanent peritoneal access is implanted surgically by an experienced surgeon [17]. Laparoscopic techniques for catheter implantation can also be used in infants in centers experienced with this technique [18].

The catheters most commonly used in infants are coiled Flex-Neck® and coiled or straight infant Tenckhoff® catheters. Since straight catheters may be associated with infusion pain and with a higher rate of mechanical failure, coiled catheters have become the standard choice in the majority of centers. At our center, we use coiled single-cuff infant Flex-Neck® catheters for infants weighing less than 6 kg and pediatric Flex-Neck® in older children. The catheter should be positioned in the lower pelvis, in an unobstructed location, with the deep cuff buried in the rectus muscle in a paramedian position. The exit site should be directed upward laterally in infants, outside the diaper area and away from sites for a gastrostomy tube or an ureterocutaneostomy. If a catheter with two cuffs is used, the superficial cuff should be placed at least 2 cm from the exit site. Some studies report a significantly higher incidence of exit-site infections and peritonitis episodes with single cuff as compared with double-cuff catheters [14]. On the other hand, the incidence of distal cuff extrusion with double-cuff catheters in children is about 8% [19]. In coiled Tenckhoff® catheters for infants, the intraperitoneal part is often too long for very small infants and there may be a tendency for migration of the catheter. It is also thick for small newborn babies with sparse subcutaneous tissue and its pressure can lead to necrosis of the skin. The Flex-Neck® catheter is made of a special silicone blend allowing variable tunnel and exit-site configurations. This catheter has also a shorter intraperitoneal part. We have experienced clearly less migration of the PD catheter while using Flex-Neck® catheters.

We routinely perform partial omentectomy in infants, though its usefulness has been debated in children [20, 21]. Unless colonization with a

methicillin-resistant *Staphylococcus aureus* has been documented, first-generation cephalosporins are recommended as prophylactic antibiotics at catheter insertion [22]. If the infant has severe hypoproteinemia, antithrombin III should be given before catheter insertion to minimize the risk for thrombosis [23].

Our starting regimen involves exchanges with 10 mL/kg dialysate with heparin 500 IU/L, flushed in and out until the effluent is clear, for a maximum of 2 h. Catheter immobilization is imperative to prevent trauma to the healing exit site [17]. We keep the exit site covered with non-occlusive dressing in our patients. Whenever possible, we try to keep a dialysis-free period of 2–3 weeks after catheter insertion to prevent leakage. In infants with congenital nephrotic syndrome, we insert the catheter at least 2 weeks before bilateral nephrectomy [16]. In neonates, infants with poor nutritional status and in nephrotics, the tissue texture is loose and wound healing is delayed. These infants are at high risk for leaks if dialysis is started early after catheter insertion.

Prescriptions

Continuous Ambulatory Peritoneal Dialysis (CAPD)

If dialysis has to be started immediately after catheter insertion (hyperkalemia, overhydration), we use CAPD with low fill volume (200 mL/m^2 or 10 mL/kg) and a dwell time of 30–50 min for, at least, 5–7 days to prevent leakage [21]. When the wounds have healed, the fill volume can be gradually increased to 800–1000 mL/m^2 [24] and the exchanges to 8–12 per 24 h. We recommend to use as maximal fill volume of 800 mL/m^2 for infants under 1 year of age, and thereafter 800–1000 mL/m^2 [24]. The choice of the fill volume is not only guided by general adequacy recommendations, but also by blood chemistry and intraperitoneal pressure (method described by Fischbach [25]). We try to keep the intraperitoneal pressure below 10 cm H_2O during infancy [25]. If the blood purification is not optimal, we increase the fill volume if IPP is under 10 cm H_2O. If dialysis can be delayed for 10–14 days from insertion of the catheter, the fill volume can be increased to target within a week.

CAPD with very low fill volumes can also be performed with commercially available acute PD sets for children. With the two chambers of the set, inflow and outflow volumes can be measured to 1 mL. The inflow solution should be warmed on the heating plate before filling the inflow chamber and the peritoneal cavity. When the inflow volume of the PD solution exceeds 100 mL, we use twin bags. The inflow and outflow volumes can be estimated from the bags with a precision of 10 mL using a digital scale (e.g., a digital fish scale).

The estimated normovolemic weight is the target weight of the infant. If the child is oliguric or anuric, weight should be checked every 6 h and the glucose concentration of the dialysis fluids for the next 6 h period is defined by individual weight limits (e.g., if the target weight is 3 kg and the actual weight is < 3 kg: use low glucose concentration; actual weight 3.0–3.2 kg: use medium glucose concentration; actual weight > 3.2 kg: use high glucose concentration). To avoid major imbalances of hydration, these weight limits should be frequently reevaluated and adapted for growth, temporary weight loss, etc. (see paragraph "Estimation of Ideal Weight").

Automated Peritoneal Dialysis (APD)

With the new generation of cycler devices, APD can be successfully performed when the fill volume is greater than 100–150 mL. With lower fill volume, outflow is slow, resulting in frequent alarms. Pediatric tubing sets with minimized recirculation volumes are available and APD produces sufficient purification even for infants.

For APD, we use continuous cycling peritoneal dialysis (CCPD) with a cycler treatment time of 10–12 h, 10–14 exchanges and a fill volume of 800–1000 mL/m^2 during the night (800 mL/m^2 during the first year of life and 800–1000 mL/m^2 during the second year of life), and a last fill for the day of 400–500 mL/m^2 [16]. We use lower fill volumes in the daytime, because of the risk for hernias, leakage, and/or vomiting. The fill volume is determined according to the principles described in the paragraph CAPD.

In nephrectomized and anuric infants, two manual exchanges are performed in the late afternoon with 1 h interval, with a fill volume of 400–500 mL/m^2, usually with medium or high glucose solutions to achieve ultrafiltration during the afternoon in order to avoid hypervolemia and high blood pressure in the evening, and to optimize purification [6]. To get appropriate ultrafiltration from an anuric or oliguric child, we specify more precise weight limits for the night for additional use of different combinations of glucose solutions. In these children, it is also important to restrict water intake to avoid the use of high-glucose solutions. In cyclers, available nowadays, there are possibilities to mix solutions with different glucose concentrations (Home Choice®, Baxter and Serena®, Fresenius) or perform each cycle with solution of certain glucose concentration or even with different fill volume (Sleep Safe®, Fresenius). With different combinations of solutions, we can fine-tune the ultrafiltration volume achieved during treatment, depending on the properties of the peritoneum of the child. The child is weighed 2–3 times during the day and solutions and program are chosen according to weight limits. As the child grows, weight limits should be reevaluated every 1–2 weeks.

Tidal Peritoneal Dialysis (TPD)

Tidal peritoneal dialysis can also be successfully used in infants. However, as sufficient adequacy mostly can be achieved with CCPD also in infants and TPD is more expensive [26], we recommend it only for patients with high peritoneal membrane permeability and reduced outflow, and for those with mechanical outflow problems or outflow pain.

Choice of Dialysis Solution

Glucose is the standard osmotic agent for PD for infants. It is possible to choose dialysis fluid also according to calcium content: low calcium (1.25 mmol/L) and standard calcium (1.75 mmol/L). Low-calcium PD fluid is beneficial for infants because of the high need of calcium-based phosphate binders caused by milk/protein-rich diet. Amino acid containing dialysis fluid may be used in protein malnourished infants [27], although we prefer aggressive enteral nutrition. We have tried polyglucose solutions also in infants with variable results in respect of ultrafiltration. The use of them must be closely monitored because long-term experiences in children and infants are lacking [28, 29]. PH-neutral, bicarbonate-buffered PD fluid has been shown to provide more effective correction of metabolic acidosis and better preservation of peritoneal cell mass than conventional low-pH, lactate-based fluid in infants as well as in older children [30]. Infants should be treated with pure bicarbonate solutions whenever possible, as they do not metabolize lactate well [31].

Estimation of Ideal Weight

An estimate of the ideal, normovolemic weight in an oliguric or anuric infant is extremely difficult. Signs of overhydration are edema of the eyelids and legs, a full fontanel, high blood pressure, and high serum N-terminal atrial natriuretic peptide concentration (>3.0 nmol/L) [32]. In addition, any elevation of blood pressure in a nephrectomized child indicates overhydration [32, 33]. Signs of hypovolemia are reduced skin turgor, a low/sunken fontanel, dizziness, vomiting in the morning and a low serum N-terminal atrial natriuretic peptide concentration [32, 33]. If hypervolemia has been present for a longer time, cardiac ultrasound shows left ventricular hypertrophy [32, 33].

Bioelectrical impedance analysis (BIA) and inferior vena cava diameter assessments can be helpful in estimating volemia in experienced hands [34, 35]. However, in infants these measurements are technically difficult to perform, and the results may not always be reliable. In addition, the available equipment for BIA measurement is not validated for estimation of hydration status in infants. Thus, according to our experience, BIA has not been helpful for estimation of hydration status in infants [33].

Adequacy

Adequacy control assessment and a peritoneal equilibration test (PET) should be performed in infants every 3–6 months as part of the evaluation of the individual prescription for adequate purification [24, 36]. Infants have been shown to have similar peritoneal membrane transport as older children if the test volume is scaled to body surface area [37]. However, the reference PET studies have been conducted with test exchange volume of 1100 mL/m^2, which is high and might be risky to use in small infants. In addition, low-pH dialysis solution was used to collect the reference data. Small solute clearance has been shown to be slightly lower with pH-neutral, bicarbonate-based than with low-pH, lactate-based dialysis fluid [30]. Thus, the suitability of these reference values for small infants dialyzed with bicarbonate-based, pH-neutral, dialysis fluid is not clear.

A weekly Kt/V$_{urea}$ over 2.1, which is recommended for adult APD patients [38] is easily achieved also in children with CCPD [39, 40] and even in infants without residual renal function [6, 8, 33]. However, the recommendation of a weekly creatinine clearance (CCR) greater than 63 L/week/1.73 m^2 [38] is difficult to achieve in anephric infants or in infants with minimal residual renal function [33, 39]. Whether these target clearances for adults should be striven for in children is unclear since a correlation between small-solute clearance and growth and other outcomes has not been demonstrated.

According to our experience with 21 children under 2 years of age, we suggest that Kt/V$_{urea}$ > 2.1 (even > 2.5) is easily achieved in infants and a CCR of > 40 L/week/1.73 m^2 is sufficient to guarantee normal growth [33]. In the study of Hölttä et al. [6], catch-up growth was documented in 62% of the patients who met or exceeded DOQI target clearances. Thus, it is evident that if the dialysis exchange volume is maximized and the exchange frequency individualized and adjusted according to peritoneal membrane transport characteristics, it is possible to achieve the current DOQI clearance targets for Kt/V$_{urea}$ in most infants on PD and a lower creatinine clearance is acceptable. Also in our later study [33], 57% of 21 infants with a mean creatinine clearance of 49 ± 20 L/week showed catch-up growth during PD. Several single-center pediatric studies demonstrate a lack of association between small-solute clearance alone and patient growth. Schaefer et al. [41] showed a weak positive association between small-solute clearance and growth by multivariate analysis. Thus, good small-solute clearance, in addition to adequate nutrition and good metabolic balance, is an important goal for optimal growth [6, 8, 33].

Nutrition

Many infants with chronic renal failure have abnormal gastric motility, delayed gastric emptying, and gastroesophageal reflux. Much food can be lost with vomiting [42]. It is essential to compensate these losses. Regular assessments by a pediatric renal dietitian are crucial for the close and frequent supervision required (minimum interval 0.5–2 months) to monitor and maintain qualitative standards of care for each infant because of the changing needs for growth and development [43].

For optimal nutrition, most infants need either a nasogastric tube or gastrostomy feeding. Some centers have made Nissen fundoplication for infants with severe gastroesophageal reflux [5]. We have not performed Nissen fundoplication in our center for infants on PD. Nasogastric tube feeding has some disadvantages, including frequent reinstitution of the tube, risk for aspiration, inhibition of development of oro-motor skills, and an altered appearance of the child [44–46]. On the other hand, gastrostomy tube feeding may increase the rate of exit site infection and peritonitis (particularly fungal), and it may leak [47–49]. A percutaneous gastrostomy should be placed prior to starting dialysis and with careful open surgical placement if PD is already established [50].

To attain satisfactory protein and caloric intake, supplemental enteral feeds are often required, especially during infancy. The energy intake should be 100% for the chronological age

[51]. In children below the age of 1 year, oral nutrition should include energy 80–90 kcal/kg/d. Up to 10 kcal/kg may be obtained daily from glucose in the dialysate, and that intake should be considered when calculating energy requirements [51]. Recent guidelines suggest the dietary protein intake to be kept at 100% of DRI for ideal body weight, with an added compensation of dialytic protein and amino acid losses. The recommended protein intakes for infants on PD at age 0–6, 7–12 months and 1–3 years are 1.8, 1.5, and 1.3 g/kg/d, respectively (0.15–0.3 g/kg/d is added to DRI to compensate for peritoneal losses) [43]. We have traditionally given 2.0–3.0 g/kg/d protein to our infants during PD [16, 38]. Phosphate intake parallels protein intake. The more phosphate the infant receives, the more phosphate binders are required to maintain a normal plasma phosphate level and to avoid hyperparathyroidism. With high calcium-based phosphate binder intake, there is risk of high calcium–phosphate ratio, which can lead to tissue calcification [52]. However, the infants with congenital nephrotic syndrome are in protein malnutrition at the initiation of PD because of protein losses before nephrectomy. Whereas these patients need high protein substitution in the beginning of PD to correct their protein status, it might be beneficial to reduce the protein intake according to the new recommendations as soon as the nutritional status has normalized to avoid excess intake of phosphate.

Dietary and supplemental vitamin intake is also routinely used in infants [43]. In infants aged 0–6, 7–12 months and 1–3 years, the upper limit for calcium (dietary + phosphate binders) are 420, 540, and 1000 mg, and for phosphorus intakes 100, 270, and 460 mg, respectively [43]. Infants on PD require sodium supplementation to compensate for their losses into the ultrafiltrate [53]. The amount of sodium supplementation reflects the amount of UF (about 13 mmol for every 100 mL of UF). We use oral sodium supplementation. We start with half of the estimated need and increase the dose gradually until plasma sodium is in lower normal range (>135 mmol/L). High sodium intake should be avoided because of the risk of overhydration and hypertension.

Growth

It has been shown that adequate nutrition is a prerequisite for normal growth, and can be successfully achieved in infants on PD with nasogastric or gastrostomy feeding and frequent consultations with a dietitian [4, 8, 33]. As a matter of fact, there is great potential even for catch-up growth [4, 8, 33, 54].

Many growth studies are hampered by the fact that children of different ages and those with or without growth hormone therapy are mixed together [9]. Recent experience shows that normal or even catch-up growth can be achieved in infants without growth hormone, when an adequate small-solute clearance, adequate nutrition, and fluid and electrolyte balance is maintained [5, 6, 8, 33] (Fig. 13.1). In the long term, our group has demonstrated that children transplanted under the age of five, previously dialyzed for a mean time of 9 months, have a mean height standard deviation score of −0.8 7 years after transplantation (27% with recombinant growth hormone therapy) [55]. Thus, the long-term outcome for height is good in infants with ESRD. Noteworthy is the fact that head circumference usually develops in parallel to relative height [5, 56].

Complications

Young age is a risk factor for peritonitis, thus infants have more peritonitis compared to older children [6, 14]. According to the NAPRTCS report, there was an increased risk of peritonitis with single-cuff PD catheter, straight tunnel, and upward pointing exit site [14], i.e., the typical catheter configuration in infants. Moreover, the duration and intensity of PD training of the parents is a factor that apparently influences the rate of peritonitis [57].

After initiation of PD, leakage and hernias are common, especially in hypoproteinemic infants [8]. These events can be minimized by delaying the start of dialysis for 2–3 weeks after implantation of the catheter [58, 59] and through the use

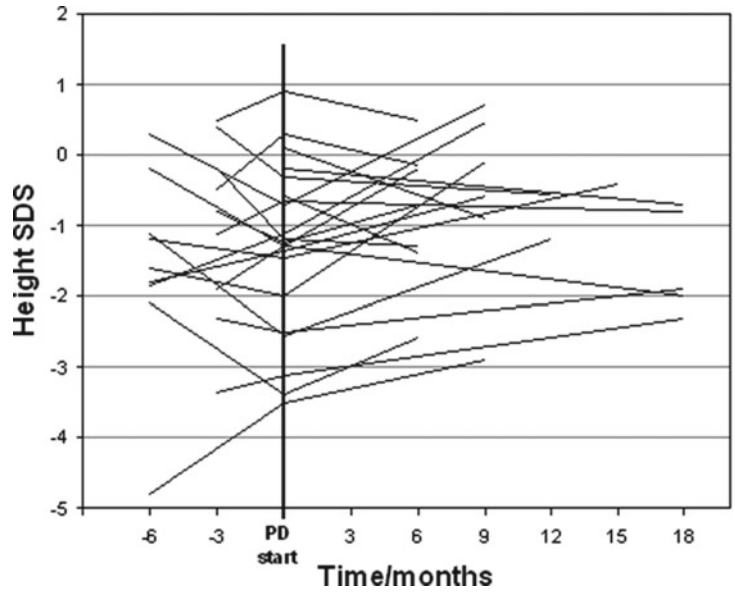

Fig. 13.1 Height SDS in 21 PD patients under 2 years of age before, at onset, and at end of PD (or at 18 months). (Reprinted with permission from Ref. [33])

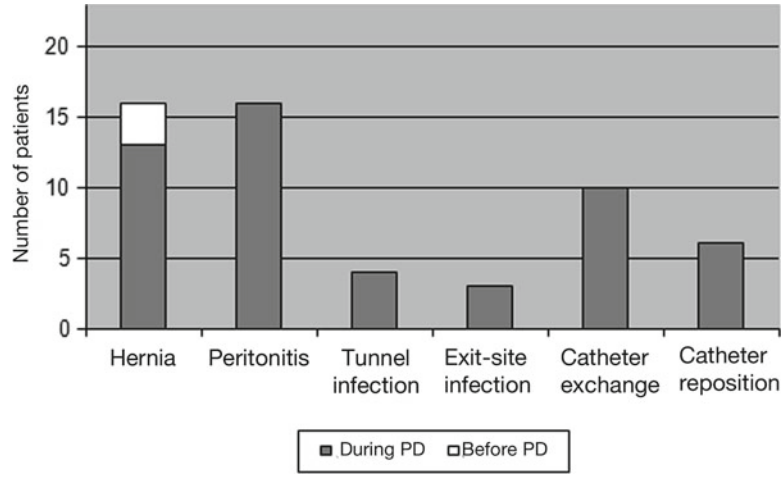

Fig. 13.2 Hernias, peritonitis, tunnel- and exit-site infections, catheter exchanges, and repositions in 23 patients under age of 2 years at PD initiation (Reprinted with permission from Ref. [8])

of low dwell volumes during the first weeks to avoid high intraperitoneal pressure [60]. Infants develop hernias frequently despite delayed dialysis start and repeated IPP measurements. Of 23 infants, treated with PD between the years 1995 and 2000 in our clinic, hernias were diagnosed in 13 (57%) [8] (Fig. 13.2). In our recent patient material of 21 infants, 47% underwent hernia operation during PD (40% were boys and 70% of the hernias were inguinal). However, already before the initiation of PD, 42% had undergone a hernia operation (89% were boys having CNF as renal diagnosis and 78% of hernias were inguinal) [33]. Although many male infants have an inguinal hernia already before PD catheter insertion, it would be beneficial to make a laparoscopy at the time of PD catheter insertion to be able to make a prophylactic surgical/laparoscopical closure of the open processus vaginalis to avoid inguinal hernia in some male infants during PD.

Infant Tenckhoff® PD catheters have an intraperitoneal part that is too long in relation to the size of a small infant, which may cause migration of the catheter. Vertical positioning of the subcutaneous tunnel may decrease the likelihood of migration. The migrated catheter can often be successfully replaced with stiff-wire manipulation [61]. We recommend the use of Flex-Neck® PD catheters for infants, since these smaller special silicone blend catheters seem to cause less migration and outflow problems.

High blood pressure is seen more frequently in infants and is mainly the result of volume overload [6, 8, 32, 33, 62]. To avoid cardiac and other complications associated with hypertension, it is important to maintain a normal blood volume [32].

We have observed less vomiting in our infants while using pH-neutral bicarbonate-based dialysis solution. Although vomiting is still a problem in some patients, we do not routinely perform Nissen fundoplication, because of the risk for intestinal complications. In addition, vomiting usually subsides after renal transplantation.

Outcome

There are only a few studies on the long-term outcome and quality of life in infants and young children with ESRD, treated with early dialysis and transplantation. According to NAPRTCS 2008 report, the 12 months patient survival for pediatric dialysis patients (including acute and chronic renal failure) was 81.9% for the age group <1 year, 92.2% for 2–5 years, and 97.6% for >12 years [14]. The main causes for death were infections (32%) and cardiopulmonary diseases (21.3%). Also renal comorbidity, i.e., anuria, and nonrenal comorbidity, including pulmonary hypoplasia and developmental delay are significant risk factors increasing mortality in infants and young children. The relative risk of death was almost three times higher in children ≤5 years of age when starting dialysis treatment compared to older children [54]. In the study of Wedekin et al., the mortality rate on PD was 18% in infants who started PD before the age of 1 year (mean 0.31 years) [10]. The main causes of death were severe cardiovascular and cerebral comorbidities. In a single center study of 50 infants on PD treated between 1983 and 2008 (mean age at initiation of dialysis was 4.4 ± 5.3 months, and average time on PD 15 ± 15 months), 38% mortality was seen during the first year of life [9]. Infants who had oliguria, ARPKD, or other comorbidities were at highest mortality risk. Eighteen percent were switched to HD. In a study of infants requiring chronic dialysis prior to the age of 28 days, the 1- and 5-year patient survival rates were 52% and 48%, respectively [11]. Eleven patients died prior to receiving a kidney transplant at a median age of 149 days (range 8–362 days). Causes of death included respiratory failure on day 8 of life in one patient with ARPKD, with the remaining ten patients succumbing to sepsis and multisystem organ failure. Five children (22%) required a change in dialysis modality to hemodialysis at a medium age of 396 days due to recurrent peritonitis (n = 3), ultrafiltration failure (n = 1), and persistent coagulopathy (n = 1).

Encouraging long-term results have been published on neurological development of infants and toddlers treated with dialysis and transplantation. Sixty to eighty percent of the children attend full time school in appropriate classes [5, 7, 9, 56, 63–65]. Neuropsychological impairment has been diagnosed in 20–40% of these patients. Qvist et al. has reported our experience with 33 school-aged children dialyzed and transplanted before 5 years of age between 1986 and 1999 [64]. All were attending full time school, 79% in a normal class. Psychosocial adjustment was normal in quality of life assessment [66]. Patients with neurodevelopmental handicaps, all had comorbidity, and included the first patients with congenital nephrotic syndrome of the Finnish type treated at our center without anticoagulation, some of whom developed cerebral thrombosis.

Thus, the presently available data allows to conclude that with early diagnosis and aggressive early treatment of uremia from the beginning, including PD with adequacy control and optimal nutrition prior to renal transplantation, normal

development can be achieved. Because dialysis treatment in infants is demanding and expose the child to comorbidity, the timing of kidney transplantation should be individualized without a predetermined minimum age or weight [11, 67, 68]. An important measure to improve the treatment quality and short- and long-term outcomes of infant dialysis would be to centralize the treatment of this small demanding patient group to centers with enough experience.

References

1. Bunchman TE. The ethics of infant dialysis. Perit Dial Int. 1996;16:S505–8.
2. Shooter M, Watson A. The ethics of withholding and withdrawing dialysis therapy in infants. Pediatr Nephrol. 2000;14:347–51.
3. Geary DF. Attitudes of paediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133:154–6.
4. Kari JA, Gonzales C, Lederman SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57:1681–7.
5. Lederman SE, Scanes ME, Frenando ON, Duffy PG, Madden SJ, Trompeter RS. Long-term outcome of peritoneal dialysis in infants. J Pediatr. 2000;136:24–9.
6. Hölttä T, Rönnholm K, Jalanko H, Holmberg C. Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control. Pediatr Nephrol. 2000;14:889–97.
7. 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.
8. Laakkonen H, Hölttä T, Lönnqvist T, Holmberg C, Rönnholm K. Peritoneal dialysis in children under 2 years of age. Nephrol Dial Transplant. 2008;23:1747–53.
9. 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;155:111–7.
10. Wedekin M, Ehrich JHH, Offner G, Pape L. Renal replacement therapy in infants with chronic renal failure in the first year of life. Clin J Am Soc Nephrol. 2010;5:18–23.
11. Rheault MN, Rajpal J, Chavers B, Nevins TE. Outcomes of infants <28 days old treated with peritoneal dialysis for end-stage renal disease. Pediatr Nephrol. 2009;24:2035–9.
12. Rees L. Long-term peritoneal dialysis in infants. Perit Dial Int. 2007;27:S180–4.
13. ERA-EDTA Registry: ERA-EDTA Registry Annual Report 2007. Academic Medical Center, Department of Medical Informatics, Amsterdam, The Netherlands, 2009. Available at: http://www-era-edta-reg.org.
14. North American Pediatric Renal and Collaborative Studies: NAPRTCS annual report 2008. Available at: http://web.emmes.com/study/ped/annlrept/Annual%20Reprint%20-2008.Pdf. Accessed 15 June 2009.
15. Orr NIT, 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;24:1719–26.
16. Rönnholm K, Holmberg C. Peritoneal dialysis in infants. Pediatr Nephrol. 2006;21:751–6.
17. Watson AR, Gartland C. Guidelines by hoc European committee for elective chronic peritoneal dialysis in pediatric patients. Perit Dial Int. 2001;21:240–4.
18. Daschner M, Gfrörer S, Zachariou Z, Mehls O, Schaefer F. Laparoscopic Tenckhoff catheter implantation in children. Perit Dial Int. 2002;22:22–6.
19. Rinaldi S, Sera F, Verrina E, Edelfonti A, Perfumo F, Sorino P, Zacchello G, Andreetta B, Ardissino G, Bassi S, Lapasso G, Caringella DA, Gianoglio B, Gusmano R, Rizzoni G. The Italian registry of pediatric chronic peritoneal dialysis: a 10-year experience with chronic peritoneal dialysis catheters. Perit Dial Int. 1998;18:71–4.
20. 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.
21. Golej J, Kitzmueller E, Hermon M, Boigner H, Burda G, Trittenwein G. Low-volume peritoneal dialysis in 116 neonatal and paediatric critical care patients. Eur J Pediatr. 2002;161:385–9.
22. Warady BA, Schaefer F, Holloway M, Alexander S, Kandert M, Piraino B, Salusky I, Tranaeus A, Divino J, Honda M, Mujais S, Verrina E. International Society for Peritoneal Dialysis (ISPD) Advisory Committee on Peritonitis Management in Pediatric Patients. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int. 2000;20:610–24.
23. Holmberg C, Antikainen M, Rönnholm K, Ala-Houhala M, Jalanko H. Management of congenital nephrotic syndrome of the Finnish type. Pediatr Nephrol. 1995;9:87–93.
24. Fischbach M, Stefanidis CJ, Watson AR. Guidelines by hoc European committee on adequacy of the paediatric peritoneal dialysis prescription. Nephrol Dial Transplant. 2002;17:380–5.
25. Fischbach M, Terzic J, Laugel V, Escande B, Dangelser CI, Helmstetter A. Measurement of hydrostatic intraperitoneal pressure: a useful tool for the improvement of dialysis prescription. Pediatr Nephrol. 2003;18:976–80.
26. 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.

27. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int. 2008; 73:S137–44.
28. Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24:1633–42.
29. Dart A, Janusz F, Wong H, Filler G. Icodextrin reabsorption varies with age in children on automated peritoneal dialysis. Pediatr Nephrol. 2005;20: 683–5.
30. Haas S, Schmitt CP, von Heyl D, Schaub T, Bonzel KE, Fischbach M, Querfeld U, Passlick-Deetjen J, Mehls O, Schaefer F, Mid European Pediatric Peritoneal Dialysis Study Group. Improved acidosis correction and recovery of mesothelial cell mass by pH neutral bicarbonate dialysis solution in children on automated peritoneal dialysis. J Am Soc Nephrol. 2004;14:2632–8.
31. Diaz-Buxo JA. Bicarbonate solutions: update. Adv Perit Dial. 2005;21:115–9.
32. Hölttä T, Happonen J-M, Rönnholm K, Fyhrquist F, Holmberg C. Hypertension, cardiac state and the role of volume overload during peritoneal dialysis in children. Pediatr Nephrol. 2001;16:324–31.
33. Laakkonen H, Happonen J-M, Marttinen E, Paganus A, Hölttä T, Holmberg C, Rönnholm K. Normal growth and intravascular status with good metabolic control can be achieved during peritoneal dialysis in infancy. Pediatr Nephrol. 2010;25:1529–38.
34. Dietel T, Filler G, Grenda R, Wolfish N. Bioimpedance and inferior vena cava diameter for assessment of dialysis dry weight. Pediatr Nephrol. 2000;14:903–7.
35. Fenech M, Maasrani M, Jaffrin MY. Fluid volumes determination by impedance spectroscopy and hematocrit monitoring: application to pediatric hemodialysis. Artif Organs. 2001;25:89–98.
36. Fischbach M. Effect of posture on intraperitoneal pressure and peritoneal permeability in children. Pediatr Nephrol. 1998;12:311–4.
37. 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: 2385–91.
38. II. NKF-K/DOQI. Clinical practice guidelines for peritoneal dialysis adequacy: update 2000. Am J Kidney Dis. 2001;37:S65–136.
39. van der Voort JH, Harvey EA, Braj B, Geary DF. Can the DOQI guidelines be met by peritoneal dialysis alone in pediatric patients? Pediatr Nephrol. 2000;14: 717–9.
40. Chandha V, Warady BA. What are the critical correlates of adequate peritoneal dialysis? Semin Nephrol. 2001;21:480–9.
41. Schaefer F, Klaus G, Mehls O, the 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.
42. Ledermann SE, Shaw V, Trompeter RS. Long-term enteral nutrition in infants and young children with CRF. Pediatr Nephrol. 1999;13:870–5.
43. KDOQI. Clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53:S1–126.
44. Heimlich HJ, O'Connor TW. Relearning the swallowing process. Ann Otol Rhinol Laryngol. 1979;88: 794–7.
45. Bernbaum JC, Pereira GR, Watkins JB, Peckham GJ. Non-nutritive sucking during gavage feeding enhances growth and maturation in premature infants. Pediatrics. 1983;71:41–5.
46. Dello-Strologo L, Principato F, Sinibaldi D, Appiani AC, Terzi F, Dartois AM, Rizzoni G. Feeding dysfunction in infants with severe CRF after long-term nasogastric feeding. Pediatr Nephrol. 1997;11:84–6.
47. Ramage IJ, Harvey E, Geary DF, Hébert D, Balfe JA, Balfe JW. Complications of gastrostomy feeding in children receiving peritoneal dialysis. Pediatr Nephrol. 1999;13:249–52.
48. Butani L, Beg G, Makker SP. Gastrostomy tube leak in a patient receiving peritoneal dialysis. Pediatr Nephrol. 2001;16:787–9.
49. Ledermann SE, Spitz L, Moloney J, Rees L, Trompeter RS. Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol. 2002;17: 246–50.
50. von Schnakenburg C, Feneberg R, Plank C, Zimmering M, Arbeiter K, Bald M, Fehrenbach H, Griebel M, Licht C, Konrad M, Timmerman K, Kemper MJ. Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int. 2006;26:69–77.
51. K/DOQI, National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2000;35:S1–140.
52. Tan O, Atik B, Kizilkaya A, Ozer E, Kavukcu S. Extensive skin calcifications in an infant with chronic renal failure: metastatic calcinosis cutis. Pediatr Dermatol. 2006;23:235–8.
53. Paulson WD, Bock GH, Nelson AP, Moxey-Mims MM, Crim LM. Hyponatremia in very young chronic peritoneal dialysis patient. Am J Kidney Dis. 1989;14:196–9.
54. Shroff R, Lederman S. Long-term outcome of chronic dialysis in children. Pediatr Nephrol. 2009;24: 463–74.
55. Qvist E, Marttinen E, Rönnholm K, Antikainen M, Jalanko H, Sipilä I, Holmberg C. Growth after renal transplantation in infancy or early childhood. Pediatr Nephrol. 2002;17:438–43.
56. Becker N, Brandt JR, Sutherland TA, Avner ED, Watkins SL. Improved outcome of young children on nightly automated peritoneal dialysis. Pediatr Nephrol. 1997;11:676–9.
57. Holloway M, Mujais S, Kandert M, Warady BA. Pediatric peritoneal dialysis training: characteristics and impact on peritonitis rates. Perit Dial Int. 2001;21:401–4.

58. Lebanc M, Ouimet D, Pichette V. Dialysate leaks in peritoneal dialysis. Semin Dial. 2001;14:50–4.
59. 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.
60. Aranda RA, Romao 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.
61. Moss SJ, Minda SA, Newman GE, Dunnick NR, Vernon WB, Schwab SJ. Malpositioned peritoneal dialysis catheters: a critical reappraisal of correction by stiff-wire manipulation. Am J Kidney Dis. 1990;15:305–8.
62. Hölttä TM, Rönnholm KAR, Jalanko H, Ala-Houhala M, Antikainen M, Holmberg C. Peritoneal dialysis in children under 5 years of age. Perit Dial Int. 1997;17:573–80.
63. Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol. 1999;13:759–65.
64. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, Sainio K, Rönnholm K, Jalanko H, Holmberg C. Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant. 2002;6:53–62.
65. Madden SJ, Lederman SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev. 2003;29:55–61.
66. Qvist E, Närhi V, Apajasalo M, Rönnholm K, Jalanko H, Almqvist F, Holmberg C. Psychosocial adjustment and quality of life after renal transplantation in early childhood. Pediatr Transplant. 2004;8:120–5.
67. Humar A, Arrazola L, Mauer M, Matas AJ, Najarian JS. Kidney transplantation in young children: should there be a minimum age? Pediatr Nephrol. 2001;16:941–5.
68. Becker T, Neipp M, Reichart B, Pape L, Ehrich J, Klempnauer J, Offner G. Pediatric kidney transplantation in small children – a single centre experience. Transpl Int. 2006;19:197–202.

Peritonitis and Exit-Site Infections

14

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Keywords
Peritoneal Dialysis • Peritonitis • Exit-Site Infection

Introduction

Worldwide, peritoneal dialysis (PD) remains the most common dialysis modality utilized for the management of children with end-stage renal disease (ESRD), and its usage is expanding in many developing countries [1–3]. Despite the decreasing incidence of PD-related infectious complications in both children and adults over the past two decades, peritonitis remains the most significant complication of PD in children receiving either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) [4, 5]. Records from the United States Renal Data System (USRDS) reveal that infectious complications, primarily peritonitis, remain the most frequent cause for hospitalization in children receiving PD [6]. The infection can also have a significant impact on the long-term availability of effective dialysis in children who may be dependent upon a functional peritoneum for a prolonged period of time. Peritonitis can lead to irreversible technique failure and according to data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), peritonitis is the primary reason for modality change in children receiving CPD [2]. These facts mandate an effective approach to the prevention and treatment of peritonitis in children who face a lifetime of ESRD care.

When initially published in 2004, most of the information in this chapter was derived from the largely opinion-based pediatric clinical practice guidelines for the prevention, diagnosis, and treatment of peritonitis developed by an international committee of the International Society for Peritoneal Dialysis (ISPD) in 2000 [7], and the much larger adult experience [8–10]. Subsequently, the International Pediatric Peritonitis Registry (IPPR) was established in order to assess the efficacy and validity of the pediatric guidelines and to enhance existing knowledge regarding the global bacteriology and antibiotic susceptibility associated with peritonitis in

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children [11]. The data that has been collected/published by a consortium of 47 pediatric dialysis centers in Europe, Turkey, Asia, and America has yielded a wealth of information on the topic of peritonitis that has been added to this chapter, including the impact of the findings on empiric antibiotic recommendations [12–16].

Finally, as prevention of peritonitis is of paramount importance in improving the outcome of patients receiving PD, the section of this chapter which addresses risk factors and preventative measures has been made more comprehensive.

Incidence of Peritonitis

Over the past several decades, there has been a steady decline in the rate of peritonitis in both children and adults that is largely due to improvements in connection technology and a decreased incidence of touch contamination [17–20]. While the rate of infection in adults has fallen to 0.5 episodes per patient year (one infection every 24 months) in many centers, and rates as low as 0.23–0.29 episodes per patient year have been reported [21, 22], the frequency of peritonitis in children regularly exceeds that of adults. In the most recent annual report of the NAPRTCS which includes data collected through January 2008, there were 3,999 episodes of peritonitis in 6,008 years of follow-up for an annualized rate of 0.67 (one episode every 18 months) [2]. This rate has significantly improved in comparison to the annualized rate of 0.91 that was reported in 1997 NAPRTCS data [23]. Similar to previous reports, the current NAPRTCS report reveals an inverse relationship between the age of the patient and peritonitis rate with the youngest patients (<1 year) having an annualized rate of 0.85 (one infection every 14.1 months), while the adolescents (>12 years) have an annualized rate of 0.6 (one infection every 20 months). These rates are derived from the American experience and although comparable to what has been documented in European centers, they are inferior to the exceptional rates (0.17 episodes per year at risk or one infection every 70.6 months) found in Japanese children [24–26].

The frequency of peritonitis is also affected by the type of PD modality with somewhat better rates experienced by patients who receive APD versus CAPD. According to the latest NAPRTCS annual data report, 50% of patients receiving CAPD had their first peritonitis episode by 16.6 months post-dialysis initiation compared to 19.2 months for APD patients [2].

Population-based peritonitis rates can, however, be misleading because peritonitis risk is not evenly spread across the PD population as some patients never develop peritonitis, while others experience frequent episodes [27]. Review of the recent NAPRTCS data revealed that the majority of infections occur in a minority of patients; of the 3,999 peritonitis episodes, the frequency varied from only one infection in 825 patients to more than eight infections in each of 49 patients [2]. This type of data emphasizes the potential value of the determination of subject-specific peritonitis incidence data [27] that can help focus efforts and resources on patients who need them the most.

Another important rate to be tracked by PD programs is the organism-specific peritonitis rate as it can provide a clue to the etiology of the infections that can be addressed in patient/caregiver training and retraining. Skin organisms such as coagulase-negative *Staphylococcus* are generally felt to lead to peritonitis through touch contamination, *Staphylococcus aureus* and *Pseudomonas aeruginosa* generally cause peritonitis through involvement of the exit-site and tunnel, and enteric organism–related peritonitis may arise from a bowel source. The rate with which these infections occur is invaluable in the evaluation and development of unit-specific prevention protocols [28].

Microbiology of Peritonitis

Similar to adults, the majority of peritonitis episodes in children on PD are caused by bacteria, and fungi are responsible for less than 5% of the episodes [29]. Historically, 50–60% of the peritonitis episodes have been caused by gram-positive bacteria and 20–30% by gram-negative organisms, with cultures remaining negative in a

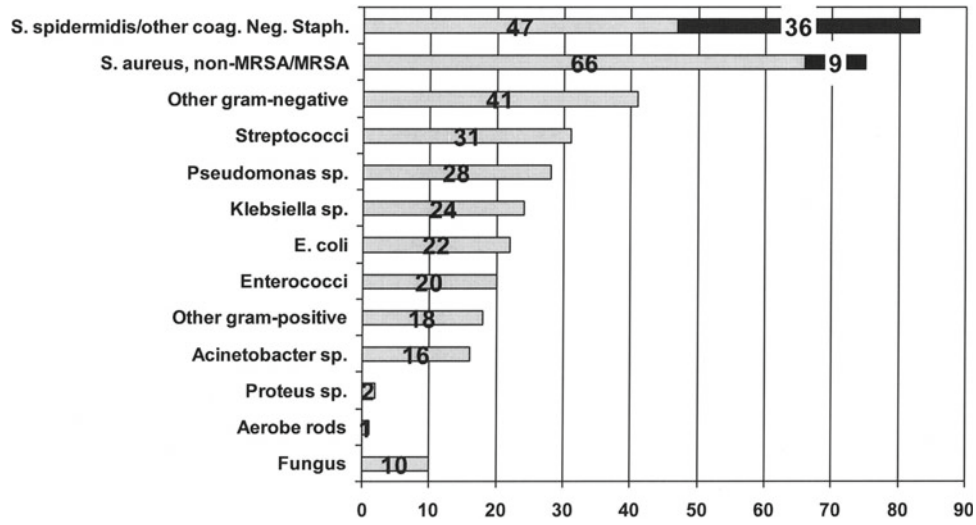

Fig. 14.1 Distribution of causative organisms among 350 episodes of peritonitis reported by the IPPR (With permission from Warady et al. [13])

substantial percentage (<20%) of peritonitis episodes. Due to a steady decline in the peritonitis rate over the last few decades, likely as a result of improvements in connection technology and exit-site care, and prophylaxis for *S. aureus* nasal carriage, the distributive pattern of microorganisms has changed and is reflected by a selective decrease in the incidence of gram-positive peritonitis, leaving gram-negative peritonitis as an increasingly important infectious complication [22, 30, 31]. This pattern, apart from minor disparities, had been believed to be fairly consistent across different dialysis centers caring for children and adults, until the recent analysis of IPPR data revealed a significant worldwide variation of dialysis-associated peritonitis characteristics in children [12].

Between October 2001 and December 2004, the IPPR gathered data on 501 episodes of peritonitis that occurred in 392 children. Ten (2%) of these episodes were caused by fungi. Of the remaining 491 episodes, 44% were caused by gram-positive organisms, 25% by gram-negative organisms, and the culture remained negative in a remarkable 31% of episodes. While the results confirmed the earlier impression of a decrease in the rate of gram-positive infections, the bacteriological profile of the gram-positive organisms was somewhat different from that recently reported in a survey of >4,000 episodes of peritonitis in adult patients from the United States and Canada [32]. In contrast to the results of the adult survey in which coagulase-negative Staphylococci were three times more common than *S. aureus* as a cause of peritonitis, staphylococcal organisms were nearly evenly divided among the above two groups in the data gathered by the IPPR (Fig. 14.1). Furthermore, there was significant variation in the distribution of organisms between different global regions (Fig. 14.2). Gram-positive infections were predominant in Europe with coagulase-negative Staphylococci most common in Eastern Europe, *S. aureus* predominating in Western Europe, and Enterococci in Turkey [12].

Worldwide variation was also seen among gram-negative organisms. Whereas gram-negative organisms accounted for 70% of culture-positive infections in Argentina, they accounted for 46% of infections in the United States and for only 25% of infections in the European countries. While *Pseudomonas* was the predominant gram-negative organism in the United States, other gram-negative organisms were more common in Argentina [12]. The reason for this marked geographical variation of the bacterial spectrum is most likely multifactorial and may include environmental influences (climate and humidity) and various aspects of PD practices, such as exit-site care and the routine use of topical antibiotic prophylaxis (vide infra) [3].

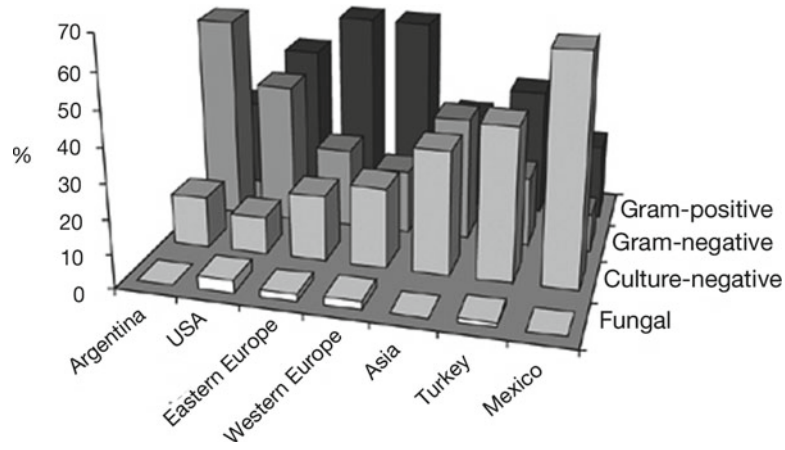

Fig. 14.2 Distribution of causative organisms according to regions among 501 episodes peritonitis reported by the IPPR (With permission from Schaefer et al. [12])

Not only did the bacteriological profile differ from region to region in the IPPR data, but there was also a striking regional variation with regard to the rate of culture-negative peritonitis episodes. In Turkey and Mexico, effluent cultures remained sterile in 42% and 67% of cases, respectively in contrast to a figure of 11–23% in the other regions [12]. Survey of the laboratory procedures practiced in the individual centers did not reveal any systematic differences in culture technique that would explain these marked differences. It is possible that other issues such as incubation of insufficient effluent volumes, long transport times in rural areas, and extreme ambient temperatures might have adversely affected the ability to obtain positive culture results.

At the turn of the century, a number of culture-negative peritonitis episodes were reported that were associated with the usage of icodextrin solution for PD [33–35]. Further investigations revealed that these cases of sterile peritonitis were caused by a peptidoglycan (released from *Alicyclobacillus acidocaldarius*, a gram-positive organism) contaminating the cornstarch used for icodextrin production [36]. The problem has since resolved after implementation of routine serial monitoring of icodextrin solutions for peptidoglycan during the manufacturing process. A recently concluded multicenter, longitudinal, prospective cohort study that included 722 PD patients did not find any difference in the rates of either infectious or culture-negative peritonitis associated with the usage of icodextrin [37].

As mentioned before, fungi account for a minority of peritonitis episodes and represent just 2% of episodes in the latest IPPR report [13] and 3% in the 2008 annual report of the NAPRTCS [2]. Yeasts belonging to the 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 *C. albicans* and more than 26% secondary to *C. parapsilopsis* [38–40].

Mycobacterium tuberculosis is a very rare cause of peritonitis and mandates a peritoneal biopsy for diagnosis [41]. Diphtheroid infections are most commonly the result of skin organisms contaminating the peritoneum by the intraluminal or periluminal route. Viruses have not been confirmed to be the primary cause of any episodes of peritonitis in pediatric CPD patients to date.

Pathogenesis

Peritonitis can result from bacteria reaching the peritoneum by one of several routes: transluminal (mainly touch contamination), periluminal (through an exit-site or tunnel infection), enteric, hematogenous, and rarely ascending (through vagina).

Coagulase-negative *Staphylococcus* characteristically infects the peritoneum by the transluminal route following touch contamination [29, 42]. The incubation period is typically 24–48 h, but

may be as short as 6–12 h. This organism is also commonly associated with recurrent peritonitis due to biofilm formation. The decrease in the overall incidence of peritonitis experienced during the past decade is largely accounted for by a selective decrease in the frequency of infection caused by this organism.

Staphylococcus aureus infections are commonly associated with a catheter exit-site/tunnel infection with/without *S. aureus* nasal carriage [29, 42]. In the IPPR data, 16% of *S. aureus* peritonitis episodes were associated with *S. aureus* nasal carriage [13]. It is also commonly associated with recurrent peritonitis secondary to a catheter tunnel infection. Symptoms of *S. aureus* peritonitis are often more severe at presentation than those associated with coagulase-negative *Staphylococcus*, as demonstrated by Disease Severity Score (DSS) (vide infra) data collected by the IPPR, and clinical improvement is typically slower with the *S. aureus*–related infection [13].

Streptococci and Enterococci generally account for less than 5% of peritonitis episodes each [29]. Streptococci usually belong to the alpha-hemolytic group of bacteria and 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, which often suggests a transmural route of infection. Reports of the emergence of vancomycin-resistant Enterococci associated with increased patient mortality have been a cause of concern [43, 44], and remains one of the most convincing arguments made against the widespread usage of glycopeptides (vide infra). Enterococcal peritonitis has usually been reported to be associated with severe symptoms; however, according to the recent and largest pediatric series of enterococcal peritonitis reported by the IPPR, the disease severity (score of 2.1) of these patients at presentation as assessed by the Disease Severity Score was no different than that found in other patients in the Registry [15].

Gram-negative infections are caused by a wide variety of organisms, and are usually acquired by touch contamination, intra-abdominal pathology (e.g., ischemic colitis, ruptured appendicitis), or a catheter-related infection. The detection of enteric bacteria is indicative of fecal contamination, and intra-abdominal sources of infection should be suspected when multiple gram-negative organisms are cultured. In this setting, anaerobic organisms should be looked for as well. *Pseudomonas/Stenotrophomonas* species are the most common gram-negative species causing catheter exit-site and/or tunnel infections resulting in peritonitis and can be extremely resistant to treatment [7, 14]. The organism may also form a biofilm on the catheter precluding successful antibiotic management without removal of the catheter. Gram-negative peritonitis is particularly troublesome as it commonly results in severe abdominal pain, is associated with dramatic alterations of peritoneal membrane transport capacity, and may result in technique failure [14, 45–47]. Finally, infections secondary to *Acinetobacter* may be an indication of contamination from a water source [48].

Risk Factors Associated with Peritonitis and Preventive Measures

If further episodes of peritonitis are to be prevented, each episode of peritonitis should be rigorously analyzed to elucidate its root cause. Unfortunately, the cause of peritonitis in most cases is not obvious. Of the 491 episodes of non-fungal peritonitis recently analyzed by the IPPR, there were no identifiable factors associated with 72% of the episodes. In the remainder, the most common causes were touch contamination (12% of all episodes), exit-site/tunnel infection (7% of episodes), and catheter perforation/leakage (2.1% of episodes). The presence of a nasogastric tube, gastrostomy, or ureterostomy was associated with 9.5, 7, and 5.5% of the 491 episodes, respectively [13]. It is noteworthy that patients on nocturnal intermittent PD (cycler at night with a dry day) may have a decreased risk of infection compared to those with a wet day because the empty abdomen can enhance local immune function [49]. Apart from these identified factors, several other risk factors can potentially heighten the incidence of peritonitis in children and an understanding of them is important if one hopes to optimize prevention and patient outcome.

Patient Age

While it is well known that the rate of peritonitis in children is inversely related to age [2], recent IPPR data has confirmed for the first time a statistical association between young patient age and gram-negative peritonitis [13, 14]. The reasons for the increased incidence of infection in infants are not known, but they may in part be related to the proximity of the catheter exit-site to the diaper region or to the gastrostomy/vesicostomy/nephrostomy sites [13, 50]. In some centers, this issue has been successfully addressed by placing the PD catheter exit-site in a chest wall location [51, 52]. The role of low serum IgG levels as a predisposing factor for peritonitis in the infant PD population remains unproven [53].

Catheter Design, Insertion, and Immediate Postoperative Care

Careful selection of PD catheter characteristics, exit-site location, implantation technique, and postoperative care of the exit-site are vital activities for the prevention of peritonitis. Studies in children and adults have repeatedly demonstrated that the time to first peritonitis episode is significantly shorter and the peritonitis rate is significantly higher when a catheter with one cuff is used as opposed to a two-cuffed catheter [4, 54, 55]. A one cuff catheter has most recently been determined to be a risk factor for relapsing peritonitis in children as well [16]. The role of the superficial cuff in preventing infection is primarily to anchor the catheter and prevent trauma at the catheter exit-site [56]. The preferred catheter in children, from the standpoint of peritonitis risk, appears to be the double-cuffed swan neck catheter with its inherent downward directed exit-site. In fact, the NAPRTCS has demonstrated that the time to first peritonitis episode is significantly longer with the latter PD access when compared to all other combinations of catheter characteristics [2]. Accordingly, both the European Pediatric Peritoneal Dialysis Working Group [57] and the Canadian Association of Pediatric Nephrologists (CAPN) Peritoneal Dialysis Working Group [58] recommend the Tenckhoff curled, two-cuff catheter with a swan neck and a downward oriented exit-site. These recommendations have likely influenced catheter preferences as more than 30% of new catheters have these characteristics in NAPRTCS data from 2005 to 2009, a substantial increase when compared to previous reports [2]. Nevertheless, data to the contrary do exist and a systematic review of adult patients [59], in addition to a retrospective pediatric study, found no relationship between catheter configuration and the prevention of peritonitis [26].

In young infants, the right side is preferred for catheter placement to allow for gastrostomy placement at a later date if needed. Ideally however, a gastrostomy should be placed before or at the time of PD catheter placement as gastrostomy placement following catheter placement is associated with an increased risk for the development of peritonitis [60–62]. In patients who already have an ostomy, the catheter exit-site should be placed as far away as possible from the ostomy site. Preoperative stenciling can be helpful in planning the best exit-site location [63] and the exit-site should be made with a puncture hole rather than a scalpel to produce a tight fit of the skin around the catheter and minimize the risk for local trauma and infection [64]. Whereas catheter anchoring at the exit-site is mandatory, sutures should never be used at the exit-site as suture material can act as a nidus for bacterial growth and increase the risk of catheter-related infections.

A sterile dressing should be applied postoperatively and should not be changed more often than once a week until the exit-site has completely healed, unless the dressing is soaked or contaminated. During this time, dressing changes should be conducted by trained dialysis personnel using aseptic technique [65–67] to decrease the risk of early peritonitis. The catheter should be anchored with no torque to promote healing of the exit-site without any pressure points. The exit-site should also be prevented from getting wet by avoiding showers until it is well healed. Preoperative or perioperative intranasal mupirocin application in *S. aureus* carriers may reduce the risk of infection by this organism during the healing process [68].

Finally, dialysis initiation should be delayed for at least a couple of weeks after catheter placement whenever possible to allow optimal surgical wound

healing as failure to do so predisposes to dialysate leakage with an increased risk of infection.

Prophylactic Antibiotics

A single dose of an intravenous antibiotic given at the time of catheter placement decreases the risk of a subsequent early peritonitis episode [69–71]. While a first-generation cephalosporin has been used most frequently in this context, a single randomized trial found that vancomycin was superior to a first-generation cephalosporin in preventing early peritonitis [69]. However, routine usage of vancomycin for prophylaxis (unless patient is known to be colonized with a methicillin-resistant organism) is not favored because of the risk for emergence of vancomycin-resistant Enterococci [64]. Prophylactic antibiotics are also indicated following intraluminal contamination (vide infra), and prior to dental procedures and procedures involving the gastrointestinal or urinary tract to decrease the risk of peritonitis [7, 69, 72, 73]. The combination of prophylactic antibiotics and antifungal therapy is also recommended during gastrostomy placement in patients already receiving PD [61, 74–76].

Chronic Exit-Site Care

Chronic exit-site care begins once the site has completely healed and is performed by the patient and/or the parents or caregivers. The purpose of routine exit-site care is to prevent and monitor an exit-site infection that can predispose to the development of peritonitis. The exit-site care procedure should include the use of surgical masks by the patient and caregiver, thorough hand washing with antibacterial soap and an alcohol-based cleaning agent, and complete drying of the hands prior to touching the exit-site. Artificial nails should be avoided as they increase the bacterial counts on the hand [77]. The exit-site itself should be cleansed daily or every other day with antibacterial soap and water or other mild and non-irritating cleansing agent such as chlorhexidine, sodium hypochlorite, or octenidine. Antiseptics in cytotoxic concentrations should be discouraged as they can impair local immune defense mechanisms. The exit-site should be carefully examined for erythema and drainage and its appearance can be characterized quantitatively with a standardized scoring system that can aid in the diagnosis of local infection (Table 14.1) [78].

Table 14.1 Exit-site scoring system [78]

	0 point	1 point	2 points
Swelling	No	Exit only; <0.5 cm	>0.5 cm and/or tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain	No	Slight	Severe
Drainage	No	Serous	Purulent

Infection should be assumed with exit-site score of 4 or greater. Purulent drainage, even if alone, is sufficient to indicate infection. A score of less than 4 may or may not represent infection

Over the years, recommendations have been made regarding the local application of antibiotics, designed to decrease the risk for *S. aureus* exit-site and peritonitis infections, especially in those patients who are *S. aureus* nasal carriers [79–81]. In children receiving PD, colonization of the catheter exit-site with *S. aureus* and the subsequent development of infection, however, may not only originate from *S. aureus* nasal carriage of the patient [13, 82–85], but it may also come from family members and caregivers since as many as 45% of families with children on PD have been found to have one or more members with evidence of *S. aureus* nasal carriage [86]. Early preventative protocols focused on eradication of the nasal carrier state of the patient and possibly the caregiver by application of intranasal mupirocin [87]. While this approach did reduce the incidence of *S. aureus* exit-site infection, it did not reduce the incidence of *S. aureus* peritonitis [87] and recolonization required periodic treatments [88]. Subsequently, daily application of mupirocin to the exit-site was found to be very effective in reducing rates of both exit-site infection and peritonitis due to *S. aureus* [89]. More recently, emerging resistance to mupirocin and preferential colonization of mupirocin-treated exit-sites with *Pseudomonas* has raised new concerns about this practice [12, 31, 90–92].

In fact, the IPPR data suggests that the global variation in gram-negative peritonitis may well be influenced by exit-site care and mupirocin usage. The incidence of peritonitis secondary to *Pseudomonas* was eightfold higher in the United States than in Western Europe and was associated with exit-site care practices characterized by daily washing, the use of non-sterile cleansing agents, and the application of mupirocin [12]. In turn, in a double-blinded randomized trial of adult PD patients, gentamicin cream applied daily to the exit-site was shown to be as effective as mupirocin in reducing *S. aureus* exit-site infections, and highly effective in reducing *P. aeruginosa* exit-site infections as well [93]. Exit-site infections secondary to Candida sp. are more frequent with the use of the broader spectrum gentamicin cream compared to mupirocin, but are easily managed with a short course of fluconazole and so far have not been associated with the development of fungal peritonitis. In a recently published study, Chua and colleagues demonstrated that a daily exit-site care regimen consisting of soap and water, followed by the application of sodium hypochlorite spray and mupirocin was associated with a significant reduction in peritonitis and exit-site infection rates and prolonged catheter survival in pediatric patients [94].

It should, however, be noted that there is global variation in the bacteriology of exit-site infections and exit-site care protocols. In the absence of a standard protocol and proven benefit of one protocol over other, it is suggested that each center should evaluate the type, frequency, and resistance patterns of organisms causing exit-site infections and institute a center-specific protocol. In some centers, a very low incidence rate of exit-site infections and peritonitis may actually preclude the need for any topical prophylaxis whatsoever.

Exit-Site and Tunnel Infections

Prompt diagnosis and aggressive therapy of exit-site/tunnel infections is crucial because of the associated substantial risk of developing peritonitis as a result of these infections [95, 96]. As mentioned previously, regular assessment of the tunnel and exit-site and characterization of the appearance of the exit-site with a standardized scoring system (vide supra) can aid in the diagnosis of local infection and ideally, in the prevention of peritonitis. If an accompanying tunnel infection is suspected, but clinical signs are ambiguous, ultrasound can be helpful in making the diagnosis [97, 98]. It is important to emphasize that isolation of a pathogen is not necessary to diagnose an exit-site infection, and antibiotic therapy should be instituted promptly when clinical signs and symptoms are suggestive of an infection.

In culture-positive cases, the antibiotic choice is determined by culture results; for gram-positive organisms, a penicillinase-resistant penicillin or a first-generation cephalosporin (with/without rifampin) is chosen most often, and for gram-negative organisms either oral ciprofloxacin or intraperitoneal ceftazidime is usually selected. In patients in whom the exit-site culture is negative, or prior to obtaining the results in a patient with a severe infection, empiric therapy with either a first-generation cephalosporin or oral ciprofloxacin should be initiated. Antibiotic therapy should be prescribed for 2–4 weeks, and for at least 7 days following complete resolution of the infection. When the same organism is cultured from the exit-site and the dialysate effluent, an occult tunnel infection should be suspected, as is often the case with *S. aureus* and *P. aeruginosa* infections [99, 100]. In the latest IPPR report on gram-negative peritonitis in children, 12% of children with gram-negative peritonitis had the same microorganism (most commonly *Pseudomonas* species) retrieved from the peritoneal fluid and exit-site; interestingly, less than half of these patients showed symptoms of a concurrent exit-site infection [14]. If an exit-site/tunnel infection does not resolve despite treatment and threatens to result in peritonitis, further interventions such as cuff resection, tunnel revision, exit-site relocation or most commonly, catheter replacement may become necessary.

Connection Methodology

Spiking of dialysis bags is a “high-risk” procedure because of the potential for contamination of the system. The introduction of double-bag,

disconnect systems in CAPD, which eliminate the need for spiking and permit the flushing of the connection site and tubing with spent dialysate prior to the inflow of fresh dialysate, has contributed to a marked reduction of the incidence of peritonitis due to touch contamination. The "flush before fill" procedure has also proven to be beneficial in children and adults receiving APD [101, 102]. For dialysis equipment that still requires spiking, assist devices such as a Compact Assist Device (Baxter Healthcare Corp., Deerfield, IL) should always be used [103]. In the IPPR analysis, spiking connection systems were associated with an increased risk of acquiring gram-negative peritonitis. Fortunately, the procedure is likely to soon become a thing of the past as Baxter Healthcare Corp., is replacing the need for spiking with Luer-lock technology, as has been instituted by other manufacturers for some time.

Contamination Care

Accidental contamination at the time of an exchange procedure can lead to peritonitis. Touch contamination before the infusion of dialysate (before the clamp on the transfer set has been opened) can be treated with a sterile transfer set change without the need for antibiotic therapy. However, touch contamination after the transfer set clamp has been opened, as well as a disconnection anywhere in the system or discovery of a hole after the system has been set up, must be treated with both a sterile transfer set change and prophylactic intraperitoneal antibiotic therapy (usually first-generation cephalosporin) for 1–3 days, to reduce the risk of peritonitis [68]. A glycopeptide should be used only in the setting of a patient previously known to be colonized with a methicillin-resistant organism. Antibiotics should also be prescribed in cases in which there is doubt about whether the patient/caregiver infused dialysate after the contaminating event took place.

A unique source of contamination can occur if pets, particularly cats, are allowed in the room where the dialysis is being performed. Pet dander and fur create a risk of air contamination during sterile connections. Cats are also enticed by the cycler tubing and are known to chew on it with several cases of *Pasteurella* peritonitis reported in the literature [104, 105]. Therefore, the practice of having pets in the bedroom at night when APD is being conducted should be discouraged.

Antifungal Prophylaxis

The serious nature of fungal peritonitis with respect to clinical manifestations and its potential negative impact on technique survival makes it imperative to prevent this infection if at all possible [106, 107]. Since a majority of fungal peritonitis episodes are preceded by a course(s) of antibiotics, a variety of studies have examined the use of antifungal prophylaxis with either nystatin or fluconazole given during and immediately after antibiotic therapy to prevent fungal peritonitis, with mixed results. In general, those programs with high baseline rates of fungal peritonitis found such an approach to be beneficial, while those with low baseline rates did not detect a benefit [39, 75, 108–113]. However, a recent large prospective randomized control trial from Colombia revealed significant efficacy of prophylactic fluconazole in preventing secondary fungal peritonitis [114]. For fungal prophylaxis in children, fluconazole 3–6 mg/kg (max dose 200 mg) can be given either orally, intravenously, or intraperitoneally every other day.

Presence of Gastrostomy

While an earlier series of peritonitis episodes did not reveal any significant relationship between the presence of a gastrostomy and the development of fungal peritonitis in children [40], the recent IPPR data did reveal a nearly ($p = 0.06$) significant association between gram-negative peritonitis and presence of a gastrostomy [13]. This finding emphasizes the need for close monitoring of the gastrostomy site for signs of infection and lends support to the suggestion that the catheter exit-site should be placed on the contralateral side of the abdomen in infants for whom subsequent placement of a gastrostomy is possible.

Gastrointestinal Sources of Peritonitis

Transmural migration of bacteria due to severe constipation appears to be a cause of peritonitis in some patients [115]. Therefore, every effort should be made to avoid constipation in patients receiving PD. Recently, data has also emerged that suggests hypokalemia may be a risk factor for Enterobacter peritonitis [116]. One hypothesis is that hypokalemia leads to decreased bowel motility, which in turn may increase transmural migration of bacteria and increase the risk for peritonitis [117]. Correction of hypokalemia may, in turn, prove to be an important prophylactic measure.

Training

Strategies designed to prevent peritonitis undoubtedly begin with effective patient/caregiver training techniques. Current ISPD recommendations suggest a 6–8 week orientation for the PD nurse and assignment to a mentor who will observe the nurse perform at least one patient training course prior to the time that he/she becomes an independent trainer. The learning skills of the patient/caregiver should also be assessed so that the education that is provided is most effective. The nurse to patient/caregiver ratio for training should be 1:1 and should highlight the basics of performing the dialysis procedure correctly so as to prevent infection, along with the ability to recognize and initiate prophylactic measures when contamination occurs.

The ideal length and content of training as it relates to peritonitis prevention remains unproven. Patients receiving PD in Japan routinely experience very low peritonitis rates which are likely related, at least in part, to the practice of prolonged (6–7 weeks) training sessions characterized by repetition and the understanding of PD principles. While some studies have not validated the correlation between length of training and peritonitis rates [118], an international survey of centers caring for children found that longer training time and the percentage of training time dedicated to the general principles of good PD practice were related to lower peritonitis rates ($p < 0.01$) [119]. Training issues may be particularly pertinent with respect to the more than 10% of patients who develop peritonitis during the initial month of home therapy [2]. Review of PD procedures by the patient and caregivers with a trainer should be strongly considered following an episode of peritonitis, especially for patients with a history of recurrent peritonitis [119].

In summary, recognition of risk factors for peritonitis and implementation of prophylactic measures is imperative if the frequency of peritonitis is to be decreased in children receiving PD [67]. The impact of this approach to treatment was recently highlighted by data published from the Children's Mercy Hospital, which revealed a marked decrease in the peritonitis rate from 0.56 episodes/year during 1997–2000 to 0.19 episodes/year during 2001–2004 [66].

Presentation and Diagnosis

Peritoneal dialysis patients presenting with abdominal pain and/or cloudy effluent should be presumed to have peritonitis and should be evaluated for the infection. While a small percentage of pediatric and adult patients with peritonitis may present with clear effluent and abdominal pain [13, 108], the presence of cloudy peritoneal effluent almost always represents infectious peritonitis. However, there are a number of non-infectious causes of cloudy peritoneal effluent that should be recognized and include chemical peritonitis, eosinophilic peritonitis, hemoperitoneum, chylous ascites, and rarely, malignancy. As noted previously, the severity of presentation in terms of abdominal pain and fever in patients with peritonitis also varies and is somewhat organism-specific; for example, pain is generally of mild–moderate severity with culture-negative peritonitis and peritonitis secondary to *coagulase-negative Staphylococcus*, whereas it is of greater severity with peritonitis resulting from *Streptococcus*, gram-negative organisms, *S. aureus* and fungi. Objective assessment of the severity of a patient's clinical status at presentation can be made by evaluating the Disease Severity Score (DSS, 0–5) which is defined by the sum of points

for pain (0, no pain; 1 moderate pain or nausea not requiring specific therapy; 2, severe pain, usually requiring analgesic therapy, or vomiting; 3, peritoneal pain with a tense abdomen and/or paralytic bowel) and fever (0, <37.5°C; 1, 37.5–38.9°C; 2, >38.9°C) [78]. Data from the IPPR has revealed that nearly half of the 121 gram-negative peritonitis episodes occurred in children aged less than 5 years and initial clinical manifestations were severe for the majority of patients [14].

The diagnosis of peritonitis is confirmed when the effluent white blood cell (WBC) count is greater than 100/mm^3, and at least 50% of the WBCs are polymorphonuclear leukocytes. The recent analysis by the IPPR did, however, reveal that the WBC count was <100 cells/μL in 2.8% of clinical peritonitis episodes, and the percentage of polymorphonuclear cells was <50% in 8.5% of cases [13]. These findings may be related to the fact that the number of cells in the effluent is dependent in part on the length of the exchange dwell which is typically shorter in patients receiving APD. In this case, the WBC differential in the effluent may be more informative than the total count [108]. The diagnosis of peritonitis can also be missed if the effluent from the cycler is not collected in a drain-bag and is being directly drained into toilet, precluding its availability for inspection.

It is imperative that the culture technique used as part of the diagnostic work-up of peritonitis be performed according to a standardized protocol [7, 108]. The correct technique is of the utmost importance to establish the responsible microorganism. Identification of the organism and subsequent antibiotic susceptibilities not only help guide antibiotic selection, but can also help identify the possible source of infection. Routine peripheral blood cultures are unnecessary since they are usually negative, but they should be obtained if the patient appears septic.

Patients who reside in distant areas away from medical facilities should be taught the technique to collect the peritoneal effluent, either in blood-culture bottles, or to refrigerate (not freeze) the effluent bag until the sample can be brought to the dialysis center for dispatch to the laboratory. The optimum culture technique is the combination of sediment culturing of 50 mL of centrifuged effluent, and inoculation of 5–10 mL effluent in two blood-culture bottles. The specimens should arrive to the laboratory within 6 h. Should there be any delay in either the transport or processing for culture, the peritoneal effluent samples must be refrigerated at 4°C until processing, whereas blood-culture bottles should be incubated at 37°C. Centrifugation of 50 mL of the peritoneal effluent at 3,000 g for 15 min, followed by re-suspension of the sediment in 3–5 mL of sterile saline, and inoculation of this material both on solid culture media and into a standard blood-culture medium is a sensitive method to identify the causative organisms. The solid culture media should be incubated in aerobic, anaerobic, and microaerophilic conditions. With this method, the culture-negative rate is expected to be <5% [120, 121]. If equipment for centrifuging large amounts of fluid is not available, blood-culture bottles can be directly injected with 5–10 mL of the effluent, as noted above. This method generally results in a culture-negative rate of 20% [108]. Rapid blood-culture techniques, such as BACTEC, Septi-Chek, BacT/Alert, are useful in reducing the time to isolation and identification of the microorganism. With these culture techniques, the majority of cultures will become positive after the first 24 h and in over 75% of cases, a diagnosis can be established in less than 3 days. If the cultures remain negative after 3–5 days in an automated culture system, but the clinical picture is highly suggestive of peritonitis, further subculturing of blood-culture bottles on media with aerobic, anaerobic, and microaerophilic incubation conditions for an additional 3–4 days may be necessary to identify slow-growing bacteria and yeasts. Centers with culture-negative rates >20% should review and ideally improve their culture methodology [108].

Management of Peritonitis

General Guidelines

To prevent a delay in treatment, antibiotic therapy should be initiated as soon as the diagnosis of peritonitis is suspected and after samples of the

Table 14.2 Antibiotic dosing recommendations: administration should be via intraperitoneal route unless specified otherwise and intermittent doses should be applied once daily unless specified otherwise

	Continuous therapy		
	Loading dose	Maintenance dose	Intermittent therapy
Aminoglycosides[a]			
Gentamicin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg, Non-anuric: 0.75 mg/kg
Netilmycin	8 mg/L	4 mg/L	
Tobramycin	8 mg/L	4 mg/L	
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[b]			
Vancomycin	1,000 mg/L	25 mg/L	30 mg/kg; repeat dosing 15 mg/kg every 3–5 days
Teicoplanin[c]	400 mg/L	20 mg/L	15 mg/kg q 5–7 days
Penicillins[a]			
Ampicillin	–	125 mg/L	–
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	–
Others			
Aztreonam	1,000 mg/L	250 mg/L	–
Clindamycin	300 mg/L	150 mg/L	–
Imipenem/cilastin	250 mg/L	50 mg/L	–
Oral			
Linezolid	<5 years: 30 mg/kg/day divided TID; 5–11 years: 20 mg/kg/day divided BID; ≥12 years 600 mg/dose BID		
Metronidazole	30 mg/kg/day divided TID		
Rifampin	10–20 mg/kg/day divided BID		
Antifungals			
Fluconazole	6–12 mg/kg IP, IV, or PO every 24–48 h (max dose 400 mg)[122]		
Caspofungin	IV only: Initial dose 70 mg/m^2 on Day 1 (max dose 70 mg); Subsequent dosing 50 mg/m^2 daily (max dose 50 mg)		

q every, *IV* intravenously, *IP* intraperitoneally, *PO* orally

[a]Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation

[b]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 3–5 days after the initial dose. Re-dosing 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

[c]Teicoplanin is not currently available in the United States

dialysis effluent are obtained for cell count and culture, often without waiting for confirmation of the cell count from the laboratory. This is especially true if signs of severe infection such as pain and fever are present. Several rapid flushes with dialysis solution may be performed before initiating antibiotic therapy to help reduce the severity of abdominal pain. As therapy is initiated prior to knowledge of the causative organism, initial empirically chosen antibiotics must cover both gram-positive and gram-negative organisms. Antibiotics selected for the treatment of peritonitis should be administered intraperitoneally to ensure immediate bioavailability and effective treatment. Recommendations for continuous (provided in each exchange) and intermittent (once daily) dosing are available (Table 14.2).

While both intermittent and continuous dosing of antibiotics such as aminoglycosides, glycopeptides, and the third-generation cephalosporin

ceftazidime have been reported to be equally efficacious in adult patients receiving CAPD, data in children, especially those receiving APD is limited [123–125]. When intermittent dosing is used, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 h to allow adequate absorption of the antibiotic into the systemic circulation. Most antibiotics have significantly enhanced absorption during peritonitis (e.g., IP vancomycin is about 50% absorbed in the absence of peritonitis but closer to 90% in the presence of peritonitis), which permits subsequent reentry into the peritoneal cavity during ensuing fresh dialysis solution exchanges. A randomized trial in children that included both CAPD and APD patients found that intermittent dosing of vancomycin/teicoplanin was as efficacious as continuous dosing in patients with gram-positive peritonitis [78]. However, a pediatric study that evaluated the disposition of intraperitoneal vancomycin in children suggested that an enhanced total body vancomycin elimination (relative to adults) coupled with a slow peritoneal transfer might be associated with inadequate time to achieve therapeutic intraperitoneal levels by the reentry mechanism in children [126]. This is particularly true in patients receiving short-dwell PD regimens and should prompt reevaluation of the recommendations for intermittent vancomycin therapy with consideration of longer dwell times or higher concentrations of vancomycin [126]. As subsequent intraperitoneal levels of vancomycin are always lower than serum levels of vancomycin, the serum levels need to be kept higher than would be otherwise indicated [127]. Re-dosing is recommended once serum vancomycin levels are less than 15 mcg/mL. Whereas a dosing interval of 4–5 days will generally keep serum levels above 15 mcg/mL, in view of the variability of drug losses due to residual renal function and peritoneal permeability, it is best to check levels.

In contrast to the experience with vancomycin/teicoplanin, intermittent dosing in children with gram-negative peritonitis with the third-generation cephalosporin ceftazidime has been found to be less successful than continuous treatment according to clinical judgment, although not by the objective disease severity score criteria [78]. Importantly, the recent IPPR analysis of 121 episodes of gram-negative peritonitis revealed a 14-fold increased risk of empiric treatment failure associated with intermittent versus continuous ceftazidime therapy [14], thus questioning the advisability of intermittent dosing of ceftazidime in children. A possible reason for failure of intermittent ceftazidime therapy could be the observed lack of post-antibiotic effect of beta-lactam antibiotics against gram-negative organisms [128].

On the other hand, intermittent dosing of aminoglycosides such as gentamicin is currently encouraged over continuous dosing in the adult guidelines, as a means of potentially decreasing the risk of nephro- and ototoxicity [108, 129–131]. In addition, intermittent (once daily) administration of aminoglycosides is considered efficacious due to the "post-antibiotic" bacteriostatic effect of this drug class [128, 131]. A similar effect has not been demonstrated for cephalosporins.

Even when continuous intraperitoneal antibiotic dosing is used for children on APD, the approach taken with most pediatric patients, the dwell times should likely be prolonged to 3–6 h for the initial 24–48 h of the therapy until there is clearing of the peritoneal effluent. The prolongation of the dwell time helps prevent depletion of the cellular components of the local host defense mechanism that may occur with frequent exchanges [132, 133]. However, prolongation of the dwell time may not be necessary/advisable for asymptomatic patients or for those with compromised ultrafiltration capacity and the need for more frequent exchanges to maintain euvolemia. Finally, a full dwell volume should be provided 24 h/day (other than possibly the first day when the volume is decreased secondary to pain) throughout the course of treatment to enhance the efficacy of antibiotic treatment.

Adjuvant Therapy

Patients with extremely cloudy effluent may benefit from the addition of low-dose heparin (500–1,000 U/L) into the dialysate as it can help prevent occlusion of the catheter due to fibrin that is often

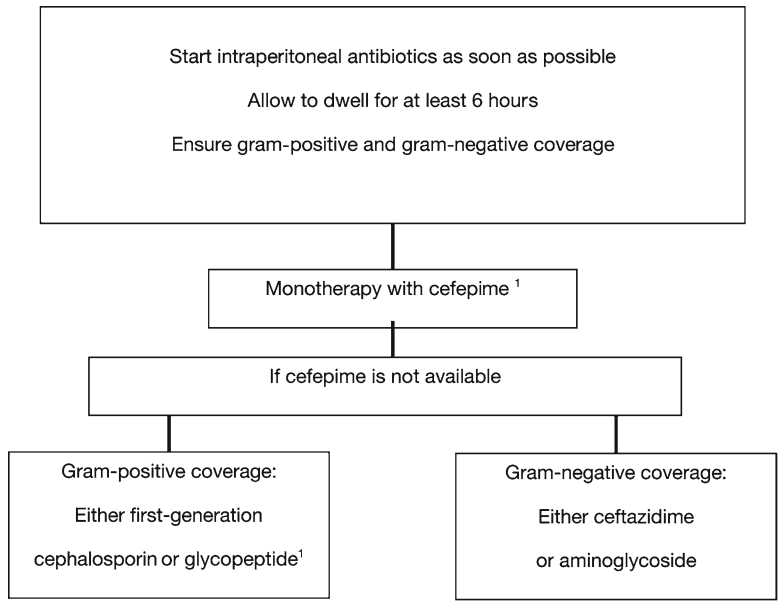

Fig. 14.3 Empiric therapy: 1. If the center's MRSA rate exceeds 10% or patient has history of MRSA colonization, glycopeptide (vancomycin/teicoplanin) should be added to cefepime or should replace the first-generation cephalosporin for gram-positive coverage. Glycopeptide usage can also be considered if patient has a history of severe allergy to penicillins and cephalosporins

present as a result of the inflammatory process [134]. As infants receiving CPD with peritonitis can lose substantial amounts of gamma globulin across an inflamed peritoneum, they may benefit from intravenous immunoglobulin therapy, especially if they have low measured serum IgG levels and/or they appear septic [53, 135].

Antibiotic Therapy

Initial (Empiric) Therapy

Empiric antibiotic therapy (Fig. 14.3) must cover both gram-positive and gram-negative organisms to ensure that treatment addresses all serious pathogens that have the potential to be present. The recent analysis of 491 episodes of non-fungal peritonitis by the IPPR was particularly noteworthy in that it revealed significant variation in the distribution of organisms and their susceptibility patterns between different global regions [12], emphasizing that the selection of empiric antibiotics must be made in light of both the patient's and the center's culture isolates and susceptibility patterns.

Of interest, the IPPR analysis did not support the earlier opinion-based recommendations of assigning young infants and children to glycopeptide treatment based on risk stratification, as no significant correlation was seen between the presence of the previously described risk factors such as young age, history of *S. aureus* infection, or a history of recent catheter-related infection, the empiric antibiotic therapy chosen, and either the early treatment response or the final functional outcome. The earlier recommendation of a glycopeptide and ceftazidime combination in "high-risk patients" or those thought to be at high risk for severe disease was based on the increasing prevalence of methicillin resistance and the expected severe clinical course in these patients. This decision was also influenced by the superiority of this combination in a meta-analysis of studies performed in adults, and its safety and efficacy profile in children [30, 78, 136–138]. The registry data, however, revealed that there was significant in vitro resistance to ceftazidime in patients with gram-negative peritonitis, and that this group of patients actually responded better clinically to a combination of a first-generation and a third-generation cephalosporin than to a combination of ceftazidime and a glycopeptide, likely a manifestation of synergy between the former pair of antibiotics. Overall, only 80% of gram-negative organisms showed in vitro susceptibility to ceftazidime, whereas the proportion of susceptible

organisms increased to 91% for the combination of a first-generation and a third-generation cephalosporin and to 94% for the combination of a third-generation cephalosporin and an aminoglycoside. The susceptibility of gram-negative organisms to aminoglycosides varied globally, ranging from 82% in Eastern Europe to 96% in Western Europe [12].

On the other hand, the susceptibility of gram-positive organisms to glycopeptide antibiotics was consistently high (96–100%), but their susceptibility to a first-generation cephalosporin varied by country, ranging from 50% in the United States to 94% in Eastern Europe. Overall, only 69% of gram-positive organisms were susceptible to either cefazolin or cephalothin and the combined susceptibility increased to 94% when an aminoglycoside was combined with the former antibiotic. Furthermore, in vitro evaluation revealed that 50% of the coagulase-negative *Staphylococcus* and 14% of the *S. aureus* strains were resistant to methicillin.

The heretofore unrecognized global variability in antibiotic susceptibilities is likely the result of antibiotic preferences in different regions, which are in turn influenced by local experience and treatment guidelines, cost considerations and, at least for some drugs, availability issues and marketing activities.

The limited success with ceftazidime treatment of gram-negative infections, the substantial morbidity associated with these infections, the variable and usually low susceptibility of gram-positive organisms to first-generation cephalosporins, and the greater susceptibility of gram-negative as well as gram-positive organisms to aminoglycosides emphasizes the importance of being cognizant of the patient and center-specific history of microorganisms and their susceptibility patterns, with subsequent modification of treatment protocols, as deemed necessary [108].

Characteristically, a combination of a first-generation cephalosporin or vancomycin/teicoplanin to cover gram-positive organisms and a third-generation cephalosporin or an aminoglycoside to cover gram-negative organisms is used by majority of centers as empiric therapy. As an interesting alternative, if available, the fourth-generation cephalosporin cefepime can be used as empiric monotherapy. Cefepime is not broken down by the extended spectrum beta-lactamases produced by many gram-negative bacilli and thus, theoretically, it has better gram-negative coverage than ceftazidime. In addition, it provides effective coverage against gram-positive bacteria, excluding MRSA, making it an ideal option for empiric monotherapy when there is not significant concern for the presence of MRSA. Cefepime usage is currently limited by its cost and availability, although in one study it was found to be cost-effective when compared to the combination of intraperitoneal vancomycin and netilmycin [139]. If the center's MRSA isolate rate exceeds 10%, or if the patient has a history of MRSA colonization/infection, a glycopeptide (vancomycin/teicoplanin) should be used in place of the first-generation cephalosporin or added to cefepime if the latter is being used for gram-negative coverage. Vancomycin/teicoplanin can also be considered for those patients who have history of severe allergy to penicillins and cephalosporins. Glycopeptide usage should, however, be restricted because of the fear of promoting the proliferation of vancomycin-resistant Enterococci and the potential emergence of glycopeptide-resistant Staphylococci [43, 44, 140–142].

When combined with cephalosporins, aminoglycosides increase coverage for both gram-positive as well as gram-negative bacteria (vide supra). As mentioned previously, intermittent aminoglycoside therapy has been shown to be as effective as continuous therapy in adult patients and may be associated with less toxicity than continuous therapy [128–130, 143]. The usage of aminoglycosides has been restricted in children because of concerns for accelerating the loss of residual renal function, as children with hypoplastic kidney disorders usually have significant residual renal function that can have a positive impact on their outcome [144–146]. While repeated or prolonged courses of aminoglycoside therapy are probably not advisable, their short-term use appears to be safe and without detrimental effect on residual renal function [147].

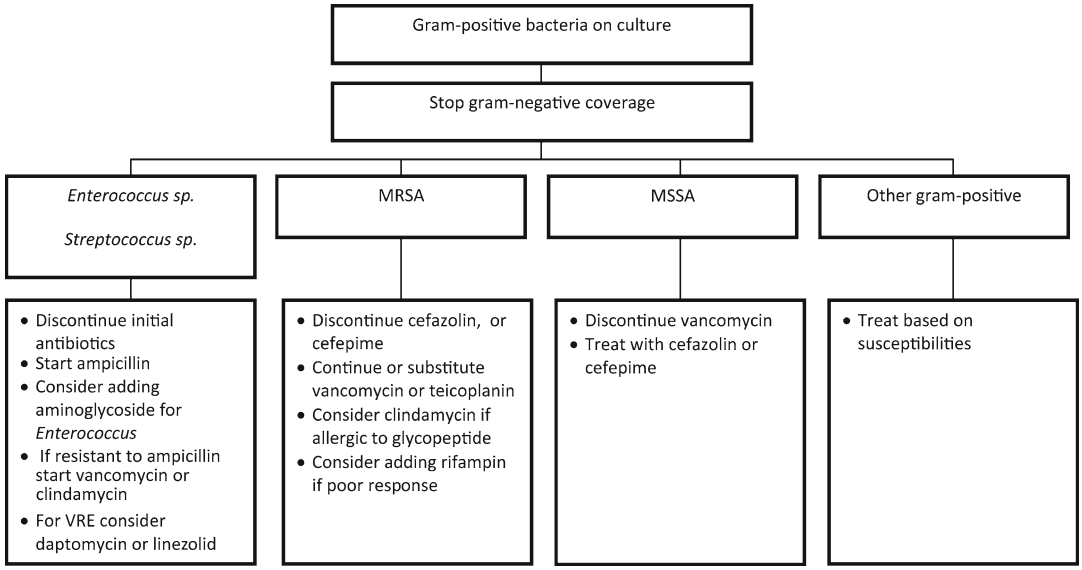

Fig. 14.4 Gram-positive organism on culture. *MRSA* methicillin resistant *S. aureus*; *MSSA* methicillin sensitive *S. aureus*; *VRE* vancomycin resistant Enterococci

Maintenance Therapy

Once culture results and susceptibilities are known, antibiotic therapy should be adjusted in accordance with this information. The current pediatric peritonitis treatment guidelines for therapy modification according to dialysate culture results are as follows:

Gram-positive peritonitis (Fig. 14.4): The empiric use of ceftazidime or an aminoglycoside should be discontinued. For methicillin-sensitive Staphylococci, the first-generation cephalosporin or cefepime should be continued or should replace the empiric glycopeptide. Note that the use of a first-generation cephalosporin as monotherapy has been shown to be associated with an increased risk of relapsing peritonitis (vide infra) [16]. For patients with methicillin-resistant Staphylococci, a glycopeptide (vancomycin or teicoplanin) should be continued or should replace the first-generation cephalosporin or cefepime. Clindamycin is a satisfactory alternative for those who do not tolerate glycopeptide antibiotics. The addition of oral rifampicin (provided as a single or split dose) as adjunctive therapy has been shown to significantly lower the risk of relapse or repeat *S. aureus* peritonitis [148]. The duration of rifampicin usage should be limited to 1 week, as resistance often develops with longer courses of therapy. Ampicillin is considered a suitable monotherapy for peritonitis caused by Enterococci and Streptococci and can be replaced with clindamycin or a glycopeptide if the organisms are resistant to ampicillin. Emerging resistance to glycopeptides is of concern as a recent IPPR report on enterococcal peritonitis revealed that 21% of isolates demonstrated glycopeptide resistance [15]. In contrast, 100% of Enterococci were susceptible to imipenem. Daptomycin or linezolid can also be considered for vancomycin-resistant Enterococci. Surprisingly, despite the high level of in vitro resistance to cephalosporins and the not insignificant resistance to glycopeptides among Enterococci observed in the IPPR report, the clinical response to empiric therapy was excellent regardless of the empiric antibiotic combination employed. Treatment duration should be 2 weeks for all organisms except *S. aureus*, for which therapy should be 3 weeks.

Gram-negative peritonitis (Fig. 14.5): Upon culture of a single gram-negative organism (*Escherichia coli*, *Proteus*, *or Klebsiella species*),

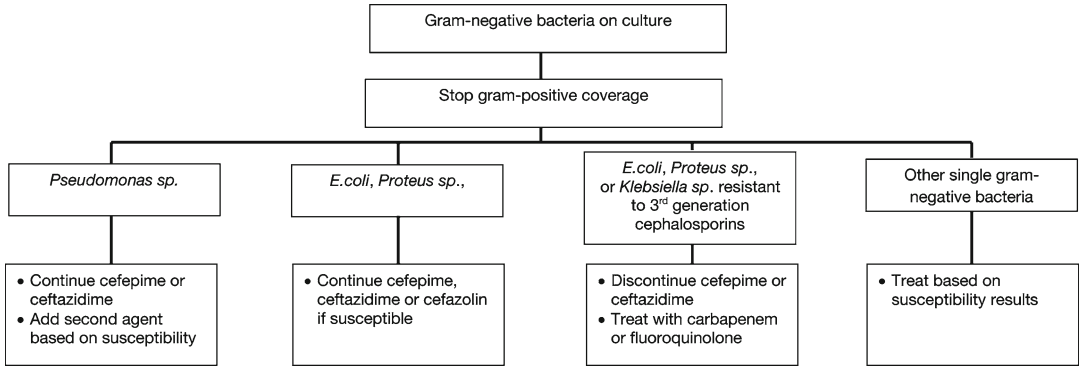

Fig. 14.5 Gram-negative organism on culture

the glycopeptide (if it was part of empiric therapy) should be discontinued and cefazolin, ceftazidime, or cefepime continued if the organism is susceptible to the antibiotic and the patient is responding well clinically. If an aminoglycoside was part of the empiric therapy, but another less toxic antibiotic displays evidence of equivalent in vitro efficacy, the aminoglycoside should be replaced with the less toxic alternative. In the case of *E. coli* or *Klebsiella* species which are resistant to third-generation cephalosporins, carbapenem or fluoroquinolones can be used instead. However, if the organism belongs to the *Pseudomonas/Stenotrophomonas* family, a second antibiotic with synergistic activity (e.g., an aminoglycoside) should be added to cefepime or ceftazidime. If multiple gram-negative organisms or anaerobic bacteria are grown, metronidazole should be added and the patient should be investigated for intra-abdominal pathology. The recommended duration of treatment is 3 weeks for *Pseudomonas/Stenotrophomonas* species, multiple organisms, and/or anaerobic organisms, and 2 weeks for other single gram-negative organisms.

Culture-negative peritonitis: In cases where the peritoneal fluid culture remains sterile at 72 h and the patient's clinical condition is improving, combined empiric therapy should be continued for 2 weeks. As culture-negative peritonitis is unlikely to be due to gram-negative organisms, the aminoglycoside (if part of empiric therapy) should be replaced with a third or fourth-generation cephalosporin. Aztreonam can be used for the individual allergic to cephalosporins.

The use of other antibacterial agents such as aztreonam, carbapenems, and quinolones can be considered under special circumstances. As per the IPPR data, 90% of the gram-positive organisms tested and 96% of the gram-negative organisms tested were susceptible to ciprofloxacin [13]. Although this data suggests that ciprofloxacin may be an ideal single agent providing broad spectrum coverage against both gram-positive and gram-negative organisms, the potential for rapid development of bacterial resistance and the possible risk of interference with cartilage development in young children make this a less desirable choice for therapy [149, 150].

Carbapenems such as meropenem belong to the family of beta-lactam antibiotics with a broad spectrum of antibacterial activity. This class of drugs should be reserved for the treatment of selected cases which are resistant to other drugs because of an increasing prevalence of carbapenem resistance in gram-negative bacteria belonging to the Enterobacteriaceae, Acinetobacter, and *Pseudomonas* species, a development which poses a serious clinical and therapeutic concern [151].

Assessment of Initial Response

The patient's clinical condition should be assessed daily subsequent to the initiation of therapy. An assessment of the dialysis effluent after 3 days of therapy will typically reveal the dialysate leukocyte count to have decreased by more than 50%, with a shift from a predominance of

polymorphonuclear to mononuclear cells. It is noteworthy that on occasion, microorganisms may still grow in the peritoneal cavity after 72 h of treatment, particularly in patients receiving intermittent antibiotic administration. These positive cultures, however, do not predict a poor outcome [78].

Failure to respond within 72 h of therapy initiation should prompt further investigation, including a repeat assessment of the dialysate cell count, Gram stain and culture, an assessment of the catheter tunnel and exit-site by clinical and possibly ultrasound evaluation, and an exit-site culture [98, 152].

Management of Refractory and Fungal Peritonitis

By definition, peritonitis is deemed refractory to treatment if there is failure of the effluent to clear after 5 days of appropriate antibiotic therapy. In turn, the most common cause of refractory peritonitis is a catheter tunnel–related infection, usually due to a *S. aureus* or *P. aeruginosa* infection of the subcutaneous tissue around the catheter cuffs [7, 153]. The confirmation of a tunnel infection in therapy-resistant peritonitis mandates immediate removal of the catheter, followed by 2–3 weeks of temporary hemodialysis and intravenous antibiotic therapy before a new catheter can be inserted, preferably on the contralateral side [7].

In patients whose peritoneal fluid culture is positive for anaerobic bacteria or multiple gram-negative organisms, the possibility of intra-abdominal pathology (e.g., ruptured appendix) should be considered.

Another possible explanation of refractory peritonitis is fungal infection, which usually develops following antibiotic treatment of bacterial peritonitis, but can occur without any risk factors in a substantial number of patients [38–40]. If fungi are identified by Gram stain or culture, all antibiotics should be discontinued, susceptibility data should be obtained, and empiric antimycotic treatment should be initiated with a combination of an imidazole/triazole (e.g., intravenous or oral fluconazole) and flucytosine (if available). Whereas amphotericin B has historically been recommended as primary treatment for fungal peritonitis in patients receiving PD, data collected in children and adults provide evidence that the peritoneal penetration of amphotericin B following systemic administration is poor and the intraperitoneal use of the drug is extremely painful [154]. On the other hand, fluconazole is characterized by excellent bioavailability and peritoneal penetration and is almost always active against the Candida species [155]. Lately, however, there have been reports of resistance to fluconazole, emphasizing the importance of susceptibility data. Successful management of these cases may require caspofungin or micafungin [114, 156]. Unfortunately, fungi usually colonize the surface of the silastic material of the PD catheter making medical therapy alone rather futile. Accordingly, in virtually all circumstances, the prognosis for successful management of the infection and for the ongoing use of PD will be improved by early catheter removal. Antimycotic treatment should be continued during temporary hemodialysis for at least 2–3 weeks after the complete resolution of clinical symptoms and before considering placement of a new PD catheter [7].

Relapsing Peritonitis

Relapsing peritonitis is defined as the recurrence of peritonitis with the same organism as in the immediately preceding episode according to culture results and antibiotic susceptibilities, within 4 weeks of completion of antibiotic treatment. Relapsing peritonitis has been reported to occur in 8–21% of initially antibiotic responsive episodes of peritonitis. Slime-forming coagulase-negative Staphylococci, which can survive antibiotic treatment in fibrinous adhesions and in the biofilm matrix on the catheter surface, have been reported as the most common responsible microorganism [157]. *S. aureus* and *P. aeruginosa*, which may cause subclinical microabscesses in the tunnel region or in intra-abdominal adhesions, may also

be the source of this complication. The IPPR recently published the results of the largest series of relapsing peritonitis in children [16]. Of 491 episodes of non-fungal peritonitis, 52 (11%) were followed by a relapse; of note, there was no significant difference in the spectrum of causative organisms between the initial and the relapsing episodes. In fact, relapsing peritonitis with *S. aureus* occurred more frequently (21%) than episodes with coagulase-negative *Staphylococcus* (11.5%). As mentioned before, the presence of a single-cuff Tenckhoff catheter was associated with an increased risk of relapse but surprisingly, there was no correlation with concomitant colonization of the exit-site with the organism that caused the peritonitis, nor with the appearance of the exit-site as assessed by the exit-site score (vide supra). The choice of initial empiric therapy did not affect the likelihood of a relapse; however, and as noted previously, a significantly higher relapse rate (23%) occurred when patients were switched to monotherapy with a first-generation cephalosporin on the basis of the culture and in vitro sensitivity results when compared with other maintenance monotherapy or combination therapies [16].

Since the causative organism of relapsing peritonitis is not known when clinical symptoms occur, empiric treatment should be reinitiated initially. After confirmation of relapse by culture and antibiotic susceptibilities, organism-specific treatment should be continued for 3 weeks. Early catheter removal is recommended in cases where the origin of the re-infection can be localized to the catheter tunnel and in any case of a relapsing infection with *Pseudomonas* or *Stentrophomonas* species. Catheter removal is also indicated when there are repeated relapses of peritonitis.

Catheter Removal and Reinsertion

Peritoneal dialysis catheter removal should be seen as part of the recommended peritonitis management in situations in which failure to do so is unlikely to result in successful outcome. The primary goal in managing peritonitis should always be the optimal treatment of the patient and protection of the peritoneum, and not saving the catheter. Whereas there are no data to permit an evidence-based recommendation with respect to the length of antibiotic treatment following catheter removal and the appropriate time for catheter replacement, an interval of 2–3 weeks between catheter removal and catheter replacement with at least 2 weeks of systemic antibiotic therapy during the intervening period is considered acceptable [7].

Simultaneous catheter removal and reinsertion can on occasion obviate the need for interval hemodialysis and has been successfully reported in cases with recurrent peritonitis, relapsing peritonitis (unless caused by *Pseudomonas/Stentrophomonas* species) and refractory exit-site or tunnel infections, including those caused by Pseudomonas [158–161]. In patients with refractory exit-site infection, timely replacement of the catheter can prevent the occurrence of peritonitis. Catheter exchange should be performed once the infection has responded to antibiotics and the effluent cell count is <100 leukocytes/μL [162] and should be followed by 3 weeks of appropriate antibiotic therapy. Simultaneous catheter removal and reinsertion is not advocated for refractory and fungal peritonitis.

Final Outcome

Peritonitis is the primary reason for technique failure in children receiving chronic peritoneal dialysis. According to the 2011 NAPRTCS annual report, 748 patients entered in the dialysis registry discontinued PD for reasons other than transplantation, and excessive infection was the primary reason in 43.8% of these cases [163].

In the IPPR experience, 89% of peritonitis episodes were followed by full functional recovery (Fig. 14.6). PD was permanently discontinued (technique failure) in 8.1% of cases because of persistent ultrafiltration problems, abdominal adhesions, persistent infection, secondary development of fungal peritonitis, or general therapy failure. The outcome of infections caused by pseudomonas species tended to be the least

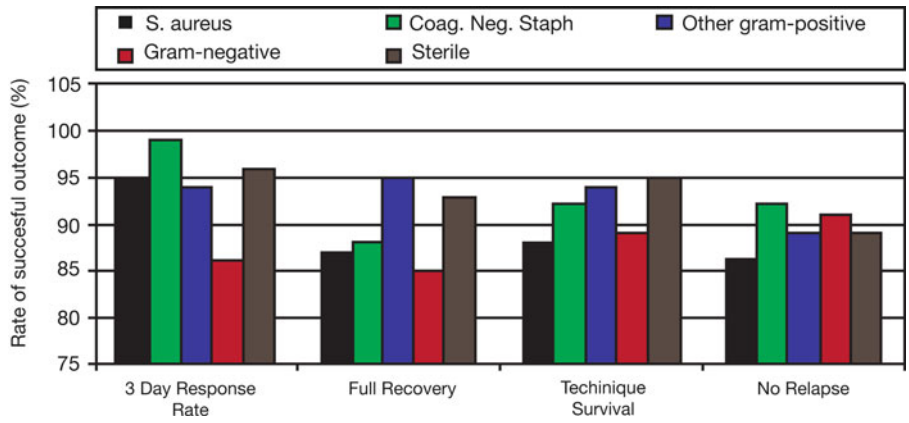

Fig. 14.6 Peritonitis outcome by organisms as reported by the IPPR (With permission from Warady et al. [13])

favorable with only 74% of the cases achieving full recovery. When outcome was compared by geographic region, the final outcome was least favorable in Eastern Europe where PD was permanently discontinued in 20% of patients; this poor outcome was associated with the preferential usage of straight rather than coiled Tenckhoff catheters in this part of the world, which may be contributory [12]. The occurrence of relapsing peritonitis also had an impact on outcome as full recovery was less common in this group of patients (75%), than it was following those episodes of peritonitis without a subsequent relapse (91%) [13, 16].

The mortality rate in children who develop acute peritonitis is approximately 1% [164]. Six deaths were reported by the IPPR, representing 1.2% of the peritonitis episodes. Three of the deaths were associated with the development of gram-negative peritonitis. Repeated episodes of peritonitis have been associated with patient mortality following the development of sclerosing encapsulating peritonitis [165, 166].

In summary, peritonitis remains the most significant complication of peritoneal dialysis in children. New technologies, a better understanding of the epidemiology of the infection and individualized as well as geographically influenced antibiotic therapy should result in greater success in terms of prevention and treatment, with resultant preservation of PD as a viable long-term dialysis modality for the pediatric patient.

References

1. Alexander SR, Warady BA. The demographics of dialysis in children. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht: Kluwer Academic Publishers; 2004. p. 35–46.
2. North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS). 2008 Annual Report. Rockville: EMMES Corporation, 2008.
3. Szeto CC, Chow KM, Wong TY, Leung CB, Li PK. Influence of climate on the incidence of peritoneal dialysis-related peritonitis. Perit Dial Int. 2003;23(6): 580–6.
4. Warady BA, Sullivan EK, Alexander SR. Lessons from the peritoneal dialysis patient database: a report of the North American pediatric renal transplantation cooperative study. Kidney Int. 1996;53:S68–71.
5. Tranaeus A. Peritonitis in pediatric continuous peritoneal dialysis. In: Fine RN, Alexander S, Warady BA, editors. CAPD/CCPD in children. Norwell: Kluwer Academic Publishers; 1998. p. 301–47.
6. U.S. renal data system. USRDS 2008 annual data report: atlas of end-stage renal disease in the United States. Bethesda: National Institute of Health/ National Institute of Diabetes and Digestive and Kidney Diseases; 2009;S239–256.
7. Warady BA, Schaefer F, Holloway M, Alexander S, Kandert M, Piraino B, Salusky I, Tranaeus A, Divino J, Honda M, Mujais S, Verrina E, International Society for Peritoneal Dialysis (ISPD) Advisory Committee on Peritonitis Management in Pediatric Patients. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int. 2000;20:610–24.
8. Keane WF, Everett ED, Golper TA, Gokal R, Halstenson C, Kawaguchi Y, Riella M, Vas S, Verbrugh HA. Peritoneal dialysis-related peritonitis treatment recommendations. 1993 Update. The Ad

Hoc Advisory Committee on Peritonitis Management. International Society for Peritoneal Dialysis. Perit Dial Int. 1993;13:14–28.
9. Keane WF, Alexander SR, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, Huang CC, Kawaguchi Y, Piraino B, Riella M, Schaefer F, Vas S. Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. Perit Dial Int. 1996;16:557–73.
10. Keane WF, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, Kawaguchi Y, Piraino B, Riella M, Vas S. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. Perit Dial Int. 2000;20:828–9.
11. Feneberg R, Warady BA, Alexander SR, Schaefer F, Members of the International Pediatric Peritoneal Registry. The international pediatric peritoneal registry: a global internet-based initiative in pediatric dialysis. Perit Dial Int. 2004;24(3):S130–4.
12. Schaefer F, Feneberg R, Aksu N, Donmez O, Sadikoglu B, Alexander SR, Mir S, Ha IS, Fischbach M, Simkova E, Watson AR, Moller K, von Baum H, Warady BA. Worldwide variation of dialysis-associated peritonitis in children. Kidney Int. 2007;72:1374–9.
13. Warady BA, Feneberg R, Verrina E, Flynn JT, Muller-Wiefel DE, Besbas N, Zurowska A, Aksu N, Fischbach M, Sojo E, Donmez O, Sever L, Sirin A, Alexander SR, Schaefer F. Peritonitis in children who receive long-term dialysis: a prospective evaluation of therapeutic guidelines. J Am Soc Nephrol. 2007;18:2172–9.
14. Zurowska A, Feneberg R, Warady BA, Zimmering M, Monteverde M, Testa S, Calyskan S, Drozdz D, Salusky I, Kemper MJ, Ekim M, Verrina E, Misselwitz J, Schaefer F. Gram-negative peritonitis in children undergoing long-term peritoneal dialysis. Am J Kidney Dis. 2008;51(3):455–62.
15. Sutherland SM, Alexander SR, Feneberg R, Schaefer F, Warady BA. Enterococcal peritonitis in children receiving chronic peritoneal dialysis. Nephrol Dial Transplant. 2010 Epub ahead of print.
16. Lane JC, Warady BA, Feneberg R, Majkowski NL, Watson AR, Fischbach M, Kang HG, Bonzel KE, Simkova E, Stefanidis CJ, Klaus G, Alexander AR, Ekim M, Bilge I, Schaefer F. Relapsing peritonitis in children who undergo chronic peritoneal dialysis: a prospective study of the International Pediatric Peritonitis Registry. Clin J Am Soc Nephrol. 2010;5:1041–6.
17. Burkart J, Hylnader B, Durnell-Figel T, Roberts D. Comparison of peritonitis rates during long-term use of standard spike versus ultraset in continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int. 1990;10:41–3.
18. Burkart J, Jordan JR, Durnell TA, Case LD. Comparison of exit-site infections in disconnect versus nondisonnect systems for peritoneal dialysis. Perit Dial Int. 1992;12:317–20.
19. Valeri A, Radhakrishnan J, Vernocci L, Carmichael LD, Stern L. The epidemiology of peritonitis in acute peritoneal dialysis: a comparison between open- and closed-drainage systems. Am J Kidney Dis. 1993;21:300–9.
20. Monteon F, Correa-Rotter R, Paniagua R, Amato D, Hurtado ME, Medina JL, Salcedo RM, Garcia E, Matos M, Kaji J, Vazquez R, Ramos A, Schettino MA, Moran J. Prevention of peritonitis with disconnect systems in CAPD: a randomized controlled trial. Kidney Int. 1998;54:2123–8.
21. Li PK, Law MC, Chow KM, Chan WK, Szeto CC, Cheng YL, Wong TY, Leung CB, Wang AY, Lui FS, Yu AW. Comparison of clinical outcome and ease of handling in two double-bag systems in continuous ambulatory peritoneal dialysis: a prospective, randomized controlled, multicenter study. Am J Kidney Dis. 2002;40(2):373–80.
22. Kim DK, Yoo TH, Ryu DR, Xu ZG, Kim HJ, Choi KH, Lee HY, Han DS, Kang SW. 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.
23. Benfield MR, McDonald R, Sullivan EK, Stablein DM, Tejani A. The 1997 annual renal transplantation in children: report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Transplant. 1999;2:152–67.
24. Verrina E, Bassi S, Perfumo F, Edefonti A, Zacchello G, Andreetta B, Pela I, Penza R, Piaggio G, Picca M. Analysis of complications in a chronic peritoneal dialysis pediatric patient population. The Italian Registry of Pediatric Patient Population. Perit Dial Int. 1993;13:S257–9.
25. Schaefer F, Klaus G, Muller-Wiefel DE, Mehls O. Current practice of peritoneal dialysis in children: results of a longitudinal survey. Perit Dial Int. 1999;2:S445–9.
26. Hoshii S, Wada N, Honda M. Japanese study group of pediatric peritoneal dialysis: a survey of peritonitis and/or tunnel infections in Japanese children on PD. Pediatr Nephrol. 2006;21:828–34.
27. Schaefer F, Kandert M, Feneberg R. Methodological issues in assessing peritonitis incidence in children. Perit Dial Int. 2002;22:234–8.
28. Piraino B, Bernardini J, Bender FH. An analysis of methods to prevent peritoneal dialysis catheter infections. Perit Dial Int. 2008;28:437–434.
29. Vas S, Oreopoulos DG. Infections in patients undergoing peritoneal dialysis. Infect Dis Clin N Am. 2001;15:743–74.
30. Zelenitsky S, Barns L, Findlay I, Alfa M, Ariano R, Fine A, Harding G. Analysis of microbiological trends in peritoneal dialysis-related peritonitis from 1991 to 1998. Am J Kidney Dis. 2000;36(5):1009–13.
31. Piraino B, Bernardin J, Florio T, Fried L. *Staphylococcus aureus* prophylaxis and trends in gram-negative infections in peritoneal dialysis patients. Perit Dial Int. 2003;23(5):456–9.

32. Mujais S. Microbiolgy and outcomes of peritonitis in North America. Kidney Int Suppl. 2006;103:S55–62.
33. MacGinley R, Cooney K, Alexander G, Cohen S, Goldsmith JA. Relapsing culture-negative peritonitis in peritoneal dialysis patients exposed to icodextrin solution. Am J Kidney Dis. 2002;40:1030–5.
34. Boer WH, Vos PF, Fieren MW. Culture-negative peritonitis associated with the use of icodextrin containing dialysate in twelve patients treated with peritoneal dialysis. Perit Dial Int. 2003;23:33–8.
35. Toure F, Lavaud S, Mohajer M, Lavaud F, Canivet E, Nguyen P, Chanard J, Rieu P. Icodextrin-induced peritonitis: study of five cases and comparison with bacterial peritonitis. Kidney Int. 2004;65(2):654–60.
36. Martis L, Patel M, Giertych J, Mongoven J, Taminne M, Perrier MA, Mendoza O, Goud N, Costigan A, Denjoy N, Verger C, Owen Jr WF. Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. Lancet. 2005;365: 588–94.
37. Vychytil A, Remon C, Michel C, Wiliams P, Rodriguez-Carmona A, Marron B, Vonesh E, van der Heyden S, Filho JC (On behalf of the Extraneal Peritonitis Study Group). Icodextrin does not impact infectious and culture-negative peritonitis rates in peritoneal dialysis patients: a 2-year multicenter, comparative, prospective cohort study. Nephrol Dial Transplant. 2008 On line.
38. Goldie SJ, Kiernan-Troidle L, Torres C, Gorban-Brennan N, Dunne D, Kliger AS, Finkelstein FO. Fungal peritonitis in a large chronic peritoneal dialysis population: a report of 55 episodes. Am J Kidney Dis. 1996;28:86–91.
39. Wang AYM, Yu AWY, Li PKT, Lam PKW, Leung CB, Lai KN, Lui SF. Factors predicating 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;36:1183–92.
40. Warady BA, Bashir M, Donaldson LA. Fungal peritonitis in children receiving peritoneal dialysis: a report of the NAPRTCS. Kidney Int. 2000;58: 384–9.
41. Lui SL, Lo CY, Choy BY, Chan TM, Lo WK, Cheng IK. Optimal treatment and long-term outcome of tuberculous peritonitis complicating continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1996;28:747–51.
42. Piraino B. Peritoneal infections. Adv Ren Replace Ther. 2000;7:280–8.
43. Troidle L, Kilger AS, Gorban-Brennan N, Fikrig M, Golden M, Finkelstein FO. Nine episodes of CPD-associated peritonitis with vancomycin-resistant enterococci. Kidney Int. 1996;50:1368–72.
44. Von Baum H, Schehl J, Geiss HK, Schaefer F. Prevalence of vancomycin-resistant enterococci among children with end-stage renal failure. Clin Infect Dis. 1999;29:912–6.
45. 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.
46. Andreoli SP, Leiser J, Warady BA, Schlichting L, Brewer ED, Watkins SL. Adverse effect of peritonitis on peritoneal membrane function in children on dialysis. Pediatr Nephrol. 1999;13:1–6.
47. 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.
48. Aflaiw A, Vas S, Oreopoulos DG. Peritonitis in patients on automated peritoneal dialysis. Contrib Nephrol. 1999;129:213–28.
49. Ramalakshmi S, Bernardini J, Piraino B. Nightly intermittent peritoneal dialysis to initiate peritoneal dialysis. Adv Perit Dial. 2003;19:111–4.
50. Schaefer F. Management of peritonitis in children receiving chronic peritoneal dialysis. Paediatr Drugs. 2003;5:315–25.
51. Warchol S, Roszkowska-Blaim M, Sieniawska M. Swan neck presternal peritoneal dialysis catheter: five-year experience in children. Perit Dial Int. 1998;18:183–7.
52. 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.
53. Neu AM, Furth SL, Lederman HM, Warady BA, Fivush B. Hypogammaglobulinemia in infants on peritoneal dialysis. Perit Dial Int. 1998;18:440–3.
54. Warady BA, Hebert D, Sullivan EK, Alexander SR, Tejani A. Renal transplantation, chronic dialysis, and chronic renal insufficiency in children and adolescents. The 1995 annual report of the North American pediatric renal transplant cooperative study. Pediatr Nephrol. 1997;11:49–64.
55. Furth SL, Donaldson LA, Sullivan EK, Watkins SL, North American Pediatric Renal Transplant Cooperative Study. Peritoneal dialysis catheter infections and peritonitis in children: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 2000;15: 179–82.
56. Twardowski ZJ, Dobbie JW, Moore HL, Nichols WK, DeSpain JD, Anderson PC, Khanna R, Nolph KD, Loy TS. Morphology of peritoneal dialysis catheter tunnel: macroscopy and light microscopy. Perit Dial Int. 1991;11(3):237–51.
57. Watson AR, Gartland C, European Pediatric Peritoneal Dialysis Working Group. Guidelines by an Ad Hoc European Committee for Elective Chronic Peritoneal Dialysis in Pediatric Patients. Perit Dial Int. 2001;21:240–4.
58. White CT, Gowrishankar M, Feber J, Yiu V, Canadian Association of Pediatric Nephrologists (CAPN) and the Peritoneal Dialysis Working Group. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol. 2006;21:1059–66.
59. 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;15:2735–46.
60. Ledermann SE, Spitz L, Moloney J, Rees L, Trompeter RS. Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol. 2002;17:246–50.
61. von Schnakenburg C, Feneberg R, Plank C, Zimmering M, Arbeiter K, Bald M, et al. Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int. 2006;26:69–77.
62. Watson AR. Gastrostomy feeding in children on chronic peritoneal dialysis. Perit Dial Int. 2006;26:41–2.
63. Crabtree JH, Burchette RJ, Siddiqi NA. Optimal peritoneal dialysis catheter type and exit-site location: an anthropometric analysis. ASAIO J. 2005;51:743–7.
64. Flannagan M, Gokal R. Peritoneal catheters and exit site practices toward optimum peritoneal access: a review of current developments. Perit Dial Int. 2005;25:132–9.
65. Twardowski ZJ, Prowant BF. Current approach to exit-site infections in patients on peritoneal dialysis. Nephrol Dial Transplant. 1997;12:1284–95.
66. Auron A, Simon S, Andrews W, Jones L, Johnson S, Musharaf G, Warady BA. Prevention of peritonitis in children receiving peritoneal dialysis. Pediatr Nephrol. 2007;22:578–85.
67. Bakkaloglu SA. Prevention of peritonitis in children: emerging concepts. Perit Dial Int. 2009;29:S186–9.
68. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. Kidney Int. 2006;70:S44–54.
69. 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;36:1014–9.
70. Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC. Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev. 2004;18. CD004679.
71. 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.
72. Sardegna KM, Beck AM, Strife CF. Evaluation of perioperative antibiotics at the time of dialysis catheter placement. Pediatr Nephrol. 1998;12:149–52.
73. Katyal A, Mahale A, Khanna R. Antibiotic prophylaxis before peritoneal dialysis catheter insertion. Adv Perit Dial. 2002;18:112–5.
74. Akkersdijk WL. Endoscopy 1995;27(4);313–6.
75. Robitaille P, Merouani A, Clermont MJ, Hebert E. Successful antifungal prophylaxis in chronic peritoneal dialysis: a pediatric experience. Perit Dial Int. 1995;15:77–9.
76. Gossner L, Keymling J, Hahn EG, Ell C. Antibiotic prophylaxis in percutaneous endoscopic (PEG): a prospective randomized clinical trial. Endoscopy. 1999;31:119–24.
77. Guideline for hand hygiene in health-care settings recommendations of the healthcare infection control practices advisory committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force MMWR (2002):51. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf.
78. Schaefer F, Klaus G, Mueller-Wiefel DE, Mehls O, Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. J Am Soc Nephrol. 1999;10:136–45.
79. Piraino B. Management of catheter-related infections. Am J Kidney Dis. 1996;27:754–8.
80. Piraino B. Infectious complications of peritoneal dialysis. Perit Dial Int. 1997;17:S15–8.
81. Piraino B. Peritonitis as a complication of peritoneal dialysis. J Am Soc Nephrol. 1998;9:1956–64.
82. Luzar MA, Coles GA, Faller B, Slingeneyer A, Dah GD, Briat C, Wone C, Knefati Y, Kessier M, Peluso F. *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. N Engl J Med. 1990;322(8):505–59.
83. Piraino B, Perlmutter JA, Holley JL, Bernardini J. *Staphylococcus aureus* peritonitis is associated with *Staphylococcus aureus* nasal carriage in peritoneal dialysis patients. Perit Dial Int. 1993;13(2):S332–4.
84. 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.
85. Kingwatanakul P, Warady BA. *Staphylococcus aureus* nasal carriage in children receiving long-term peritoneal dialysis. Adv Perit Dial. 1997;13:281–4.
86. Oh J, von Baum H, Klaus G, Schaefer F, European Pediatric Peritoneal Dialysis Study Group (EPPS). Nasal carriage of *Staphylococcus aureus* in families if children on peritoneal dialysis. Adv Perit Dial. 2000;16:324–7.
87. The Mupirocin Study Group. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infection during peritoneal dialysis. J Am Soc Nephrol. 1996;11:2403–8.
88. Perez-Fontan M, Rosales M, Rodriguez Carmona A, et al. Mupirocin resistance after long-term use for *Staphylococcus aureus* colonization in patients undergoing chronic peritoneal dialysis. Am J Kidney Dis. 2002;39:337–41.
89. Bernardini J, Piraino B, Holley J, Johnston JR, Lutes R. 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;27:695–700.

90. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* after widespread use of nasal mupirocin ointment. Concise Commun. 1996;17:811.
91. Thomas DG, Wilson JM, Day MJ, Russell AD. Mupirocin resistance in staphylococci: development and transfer of isoleucyl-tRNA systhetase-mediated resistance in vitro. J Appl Microbiol. 1999;86:715–22.
92. Annigeri R, Conly J, Vas S, Dedier H, Praskashan KP, Bargman JM, Jassal V, Oreopoulos D. Emergence of mupirocin-resistant *Staphylococcus aureus* in chronic peritoneal dialysis patients using mupirocin prophylaxis to prevent exit-sire infection. Perit Dial Int. 2001;21(6):554–9.
93. Bernardini J, Bender F, Florio T, Sloand J, Palmmontalbano L, Fried L, Piraino B. 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.
94. 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;4:1939–43.
95. Piraino B, Bernardini J, Sorkin M. The influence of peritoneal catheter exit-site infections on peritonitis, tunnel infections, and catheter loss in patients on CAPD. Am J Kidney Dis. 1986;8:436–40.
96. Abraham G, Savin E, Ayiomamitis A, et al. Natural history of exit-site infection (ESI) in patients on continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Bull. 1988;8:211–6.
97. Plum J, Sudkamp S, Grabensee B. Results of ultrasound associated diagnosis of tunnel infections in continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1994;23:99–104.
98. Vychytil A, Lorenz M, Schneider B, et al. New criteria for management of catheter infections in peritoneal dialysis patients using ultrasonography. J Am Soc Nephrol. 1998;9:290–6.
99. Bernardini J, Piraino B, Sorkin M. Analysis of continuous ambulatory peritoneal dialysis-related *Pseudomonas aeruginosa* infections. Am J Med. 1987;83:829–32.
100. Gupta B, Bernardini J, Piraino B. Peritonitis associated with exit site and tunnel infections. Am J Kidney Dis. 1996;28:415–9.
101. Smith CA. Reduced incidence of peritonitis by utilizing "flush before fill" in APD. Adv Perit Dial. 1997;13:224–6.
102. Warady BA, Ellis EN, Fivush BA, Kum GM, Alexander SR, Brewer ED, Ogrinc F, Watkins S. Flush before fill in children receiving automated peritoneal dialysis. Perit Dial Int. 2003;23:493–8.
103. Verrina E, Honda M, Warady BA, Piraino B. Prevention of peritonitis in children on peritoneal dialysis. Perit Dial Int. 2000;20:625–30.
104. Antony SJ, Oglesby KA. Peritonitis associated with *Pasteurella multocida* in peritoneal dialysis patients–case report and review of the literature. Clin Nephrol. 2007;68(1):52–6.
105. Rondon-Berrios H, Trevejo-Nunez GJ. Pets or pest: peritoneal dialysis-related peritonitis due to *Pasteurella multocida*. J Microbiol Immunol Infect. 2010;43(2):155–8.
106. Bren A. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Eur J Clin Microbiol Infect Dis. 1998;17:839–43.
107. Lo WK, Chan TM, Lui SL, Li FK, Cheng IKP. Fungal peritonitis – current status 1998. Perit Dial Int. 1999;19:S286–90.
108. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye WC, Salzer W, Schaefer F, Struijk DG. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int. 2010;30(4):393–423.
109. Lye WC, Sewell DL, 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 [Published erratum appears in Am J Kidney Dis 1991; 17(6):726].
110. Lo WK, Chan CY, Cheng SW, Poon JF, Chan DT, Cheng IK. A prospective randomized control study of oral nystatin prophylaxis for candida peritonitis complicating continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1996;28:549–52.
111. Thodis E, Vas SI, Bargman JM, Singhal M, Chu M, Oreopoulos DG. Nystatin prophylaxis: its inability to prevent fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Perit Dial Int. 1998;18:583–9.
112. Williams PF, Moncrieff N, Marriott J. No benefit in using nystatin prophylaxis against fungal peritonitis in peritoneal dialysis patients. Perit Dial Int. 2000;20(3):352–3.
113. Prasad KN, Prasad N, Gupta A, Sharma RK, Verma AK, Ayyagari A. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single centre Indian experience. J Infect. 2004;48(1):96–101.
114. 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 epub ahead of print.
115. Singharetnam W, Holley JL. Acute treatment of constipation may lead to transmural migration of bacteria resulting in gram-negative, polymicrobial, or fungal peritonitis. Perit Dial Int. 1996;16:423–5.
116. Chuang YW, Shu KH, Cheng CH, Chen CH. Hypokalaemia: an independent risk factor of Enterobacteriaceae peritonitis in CAPD patients. Nephrol Dial Transplant. 2009;24(5):1603–8.
117. Shu KH, Chang CS, Chuang CH, Cheng CH, Wu MJ, Yu TM. Intestinal bacterial overgrowth in CAPD patients with hypokalaemia. Nephrol Dial Transplant. 2009;24(4):1289–92.
118. Bernardini J, Price V, Figueriredo A, Riemann A, Leung D. International survey of peritoneal dialysis training programs. Perit Dial Int. 2006;26:658–63.
119. Holloway M, Mujais S, Kandert M, Warady BA. Pediatric peritoneal dialysis training: characteristics

and impact on peritonitis rates. Perit Dial Int. 2001;21(4):401–4.
120. Sewell DL, Golper TA, Hulman PB, Thomas CM, West LM, Kubey WY, et al. Comparison of large volume culture to other methods for isolation of microorganisms from dialysate. Perit Dial Int. 1990;10:49–52.
121. Lye WC, Wong PL, Leong SO, Lee EJ. Isolation of organisms in CAPD peritonitis: a comparison of two techniques. Adv Perit Dial. 1994;10:166–8.
122. Brammer KW, Coates PE. Pharmacokinetics of fl uconazole in pediatric patients. Eur J Clin Microbiol Infect Dis. 1994;13:325–9.
123. Boyce NW, Wood C, Thomson NM, Kerr P, Atkins RC. Intraperitoneal (IP) vancomycin therapy for CAPD peritonitis a prospective, randomized comparison of intermittent v continuous therapy. Am J Kidney Dis. 1988;12(4):304–6.
124. Low CL, Bailie GR, Evans A, Eisle G, Venezia RA. Pharmacokinetics of once-daily IP gentamicin in CAPD patients. Perit Dial Int. 1996;16(4):379–84.
125. Low CL, Gopalakrishna K, Lye WC. Pharmacokinetics of once daily intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. J Am Soc Nephrol. 2000;11(6):1117–21.
126. 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;27:79–85.
127. Mulhern JG, Mulhern JG, Braden GL, O'Shea MH, Madden RL, Lipkowitz GS, Germain MJ. Trough serum vancomycin levels predict the relapse of gram-positive peritonitis in peritoneal dialysis patients. Am J Kidney Dis. 1995;25:611–5.
128. De Broe ME, Giuliano RA, Verpooten GA. Choice of drug and dosage regimen. Two important risk factors for aminoglycoside nephrotoxicity. Am J Med. 1986;80:115–8.
129. Spivey JM. The postantibiotic effect. Clin Pharm. 1992;11:865–75.
130. Chong TK, Piraino B, Bernardini J. Vestibular toxicity due to gentamicin in peritoneal dialysis patients. Perit Dial Int. 1991;11:152–5.
131. Craig WA. Once-daily versus multiple-daily dosing of aminoglycosides. J Chemother. 1995;7:47–52.
132. Jorres A, Topley N, Witowski J. Impact of peritoneal dialysis solutions on peritoneal immune defense. Perit Dial Int. 1993;13(2):S291–4.
133. Cameron JS. Host defences in continuous ambulatory peritoneal dialysis and the genesis of peritonitis. Pediatr Nephrol. 1995;9:647–62.
134. de Boer AW, Levi M, Reddingius RE, Willems JL, van den Bosch S, Schroder CH, Monnens LA. Intraperitoneal hypercoagulation and hypofibrinolysis is present in childhood peritonitis. Pediatr Nephrol. 1999;13:284–7.
135. Bouts AHM, Davin J-C, Krediet RT, van der Weel MB, Schroder CH, Monnens L, Nauta J, Out TA. Immunoglobulins in chronic renal failure of childhood: effects of dialysis modalities. Kidney Int. 2000;58:629–37.
136. Flanigan MJ, Lim VS. Initial treatment of dialysis associated peritonitis: a controlled trial of vancomycin versus cefazolin. Perit Dial Int. 1991;11:31–7.
137. Milliken SP, Matzke GR, Keane WF. Antimicrobial treatment of peritonitis associated with continuous ambulatory peritoneal dialysis. Perit Dial Int. 1991;11:252–60.
138. Mueller-Wiefel DE. Treatment of peritonitis in pediatric continuous peritoneal dialysis. Perit Dial Int. 1999;19(2):S450–7.
139. Wong KM, Chan YH, Cheung CY, Chak WL, Choi KS, Leung J, Chau KF, Tsang DN, Li CS. Cefepime versus vancomycin plus netilmicin therapy for continuous ambulatory peritoneal dialysis associated peritonitis. Am J Kidney Dis. 2001;38:127–31.
140. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. Infect Control Hosp Epidemiol. 1995;16:105–13.
141. Sieradzki K, Roberts RB, Haber SW, Tomasz A. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. N Engl J Med. 1999;340(7):517–23.
142. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E, Jarvis WR. Emergence of vancomycin resistance in *Staphylococcus aureus*. N Engl J Med. 1999;316:927–31.
143. Lye WC, van der Straaten JC, Leong SO, Sivaraman P, Tan SH, Tan CC, Lee EJ. Once-daily intraperitoneal gentamicin is effective therapy for gram-negative CAPD peritonitis. Perit Dial Int. 1999;19: 357–60.
144. 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;31:14–20.
145. 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; 20:429–38.
146. Chadha V, Blowey DL, Warady BA. Is growth a valid outcome measure of dialysis in children on peritoneal dialysis? Perit Dial Int. 2001;21: S179–84.
147. Baker RJ, Senior H, Clemenger M, Brown EA. Empirical aminoglycosides for peritonitis do not affect residual renal function. Am J Kidney Dis. 2003;41:670–5.
148. Szeto CC, Chow KM, Kwan BC, Law MC, Chung KY, Yu S, et al. *Staphylococcus aureus* peritonitis complicates peritoneal dialysis: review of 245 consecutive cases. Clin J Am Soc Nephrol. 2007;2: 245–51.
149. Grady R. Safely profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis. 2003; J22:1128–32.
150. Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, Bagchi P, Balis DA, Blumer JL. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific

musculoskeletal disorders. Pediatr Infect Dis J. 2007;26(10):879–91.
151. Livermore DM. Has the era of untreatable infections arrived? J Antimicrob Chemother. 2009;64: 29–36.
152. Gokal R, Alexander SR, Chen TW, Danielson A, Holmes C, Joffe P, Moncrief J, Nichols K, Piraino B, Prowant B, Slingeneyer A, Stegmayr B, Twardowski Z, Vas S. Peritoneal catheters and exit site practices. Toward optimum peritoneal access: update. Pediatr Dial Int. 1998;18:11–3.
153. Fried L, Piraino B. Peritonitis. In: Gokal R, Khanna R, Krediet R, Nolph K, editors. Textbook of peritoneal dialysis. Norwell: Kluwer Academic Publishers; 2000. p. 545–64.
154. Blowey DL, Garg UC, Kearns GL, Warady BA. Peritoneal penetration of amphotericin B lipid complex and fluconazole in a pediatric patient with fungal peritonitis. Adv Perit Dial. 1998;14: 247–50.
155. Dahl NV, Foote EF, Searson KM, Fein JL, Kapoian T, Steward CA, Sherman RA. Pharmacokinetics of intraperitoneal fluconazole during continuous cycling peritoneal dialysis. Ann Pharmacother. 2000;32:1284–9.
156. Cornely OA, Lasso M, Betts R, Klimko N, Vasquez J, Dobb G, et al. Caspofungin for the treatment of less common forms of invasive candidiasis. J Antimicrob Chemother. 2007;60:363–9.
157. Klaus G, Schaer F, Querfeld U, Soergel M, Wolf S, Mehls O. Treatment of relapsing peritonitis in pediatric patients on peritoneal dialysis. Adv Perit Dial. 1992;8:302–5.
158. Majkowski NL, Mendley SR. Simultaneous removal and replacement of infected peritoneal dialysis catheters. Am J Kidney Dis. 1997;29(5):706–11.
159. Posthuma N, Borgstein PJ, Eijsbouts Q, ter Wee PM. Simultaneous peritoneal dialysis catheter insertion and removal in catheter-related infections without interruption of peritoneal dialysis. Nephrol Dial Transplant. 1998;13(3):700–3.
160. Lui SL, Li FK, Lo CY, Lo WK. Simultaneous removal and reinsertion of Tenckhoff catheters for treatment of refractory exit-site infection. Adv Perit Dial. 2000;16:195–7.
161. Lui SL, Yip T, Tse KC, Lam MF, Lai KN, Lo WK. Treatment of refractory pseudomonas aeruginosa exit-site infection by simultaneous removal and reinsertion of peritoneal dialysis catheter. Perit Dial Int. 2005;25(6):560–3.
162. Swartz RD, Messana JM. Simultaneous catheter removal and replacement in peritoneal dialysis infections: update and current recommendations. Adv Perit Dial. 1999;15:205–8.
163. North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS). Annual Report. Rockville: EMMES Corporation;2011;36.
164. Warady BA, Schaefer FS. Peritonitis. In: Warady BA, Schaefer FS, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht: Kluwer Academic Publishers; 2004. p. 393–414.
165. Honda M, Warady B. Long-term peritoneal dialysis and encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2010; 25(1):75–81.
166. Maruyama Y, Nakayama M. Encapsulating peritoneal sclerosis in Japan. Perit Dial Int. 2008;28(3): S201–4.
167. Brammer KW, Coates PE. Pharmacokinetics of fluconazole in pediatric patients. Eur J Clin Microbiol Infect Dis. 1994;13:325–9.

Non-infectious Complications of Peritoneal Dialysis in Children

15

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Keywords
Peritoneal dialysis • Noninfectious complications • Hernia • Hydrothorax • Hydropericardium • Leakage • Catheter malposition • Hemoperitoneum • Hypokalemia • Membrane failure • Ultrafiltration failure • Encapsulated peritoneal sclerosis • Intraperitoneal pressure

Non-infectious complications of PD (NICPD) are increasing in relative importance due to the success in decreasing the rate of PD-related peritonitis over the last decade. These complications can be categorized into mechanical (catheter related and related to the increase in intra-abdominal pressure due to dialysate), technique-related (ultrafiltration problems and metabolic effects of the absorption of glucose and its degradation products), and other complications, which are listed in Table 15.1 [1, 2]. There is increasing appreciation that mechanical complications, mainly peritoneal catheter problems, are major causes of PD technique failure and patient morbidity. Membrane failure characterized by ultrafiltration failure and inadequate solute removal was responsible for 13.6–27.3% of CPD termination in different pediatric series [3, 4]. The adverse metabolic effects of the PD fluids may augment cardiovascular risk in adults and probably in children. Therefore, prevention, early recognition, and appropriate management of these complications are of particular importance.

Mechanical Complications of PD

The most common complications associated with PD catheters in children are inflow/outflow problems, catheter malposition, pericatheter leak, and hernia. Pain is another important complication, particularly for children, on PD. Commonly, children complain about pain on infusion possibly related to the jet of fluid or at the end of draining. This discomfort is frequently transient, resolving shortly after PD is initiated. The coiled catheter design is suggested to decrease infusion pain due to dispersal of fluid jet. Acidic pH and cold temperature of the fluid may cause infusion pain. Usage of warm, biocompatible fluids, slowing the rate of infusion, and tidal dialysis may alleviate infusion pain.

Obstruction of PD Fluid Flow

Inflow obstruction suggests intraluminal blockage with fibrin or blood and may be due to kinking of

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Table 15.1 Non-infectious complications of peritoneal dialysis [1, 2]

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
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
Hypercatabolism
Decreased peritoneal permeability
Inadequate ultrafiltration
Fast transport status
Encapsulated peritoneal sclerosis
Metabolic complications
Hyperglycemia
Hyperinsulinemia
Hypertriglyceridemia
Hyperleptinemia
Hypokalemia
Magnesium alterations
Other complications
Hemoperitoneum
Pneumoperitoneum
Pancreatitis
Ischemic colitis and necrotizing enterocolitis
Subcapsular steatosis

the catheter. 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].

Kinking of the catheter, which may cause inflow and outflow problems, usually becomes obvious soon after catheter placement. The degree of dysfunction may vary with patient position. Migration of the catheter out of the pelvic cavity usually causes poor drainage of the dialysate solution, and pain during infusion and poor inflow may also occur, which is usually obvious within days of placement. Omental occlusion is commonly observed within several weeks of catheter implantation. Episodes of outflow obstruction secondary to plugging of the catheter by the fimbriae of the fallopian tube are also reported. Large pediatric series from different countries showed the rate of malfunction or obstruction between 5% and 21% [5–7]. The Italian Pediatric PD Registry, analyzing a large cohort of children over a period of 15 years, demonstrated that malfunction and malposition of the catheters accounted for 11.3% of the cases [5]. Catheter-related mechanical problems were observed in 22% (26 catheters in total, 12 dislocations, 7 drainage problems, and 7 kinks) of the percutaneously implanted 108 PD catheters by pediatric nephrologists in a recent Turkish single-center retrospective study [6].

Prevention Strategies

Strategies to prevent early catheter malfunction include appropriate catheter selection, optimal surgical technique, and good postoperative care. Expertise in insertion of PD catheters is an acquired skill, and insertion of catheters by experienced and dedicated physicians is advised. The Italian registry showed a trend toward better catheter survival even in young patients, which was suggested to be related to increasing experience by dialysis centers (standardized surgical technique, cumulative experience by staff, better postimplantation care, education of patients and caregivers) [1]. In addition, the more widespread use of double-cuffed catheters, paramedian exit-site location, and prophylactic omentectomy could have positively influenced catheter survival [5].

A number of modifications of PD catheter design have been proposed, but overall the "swan neck" catheter has the lowest rate of drainage failure via migration, whereas the intraperitoneal configuration, straight vs. coiled, does not seem to

modify this risk [1, 2]. However, 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]. 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. Omentectomy can be readily and more completely done with laparoscopy to prevent blockage of the catheter [9]. 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). This group reported a reduction in the rate of catheter flow complications to <1% compared with 12% with standard laparoscopic technique [10]. Particularly for patients at higher risk for catheter malfunction as a result of previous complicated abdominal surgery, advanced laparoscopic technique provides the best results in experienced hands. Although laparoscopy allows extensive lysis of adhesions from previous operations and its primary use is recommended whenever available, the reported frequencies of flow problems in children are similar with the three implantation techniques, varying between 8.7% and 12% [5, 6, 9].

Another 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 bowel [1].

Treatment Options

Guide-wire 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 hypocondriac 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 [11]. If fluoroscopically guided manipulations fail, open or laparoscopic surgery is necessary to reposition the catheter.

Intraluminal instillation of thrombolytics is helpful if intraluminal obstruction persists after vigorous flushing and results in a high rate of restoration of flow [12]. Five to ten milligrams of tissue plasminogen activator (1 mg/mL) in 10–20 mL saline was shown to be effective. 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. A recent Turkish single-center retrospective study indicated that 12% (n = 13) out of 108 percutaneously implanted PD catheters were removed due to catheter-related causes: drainage problems (six patients), catheter dislocation (three patients), omental capture (two patients), and kink (two patients) (Table 15.2). There were no significant differences between early and delayed catheter use groups in terms of mechanical catheter problems [6]. Similarly, obstruction, which was reported as the second most common cause of catheter removal following catheter-related infections in Italian Registry data, showed a significant decrease, probably related to a higher frequency of omentectomy [5]. Indeed, omentectomy, partial omentectomy, or omentopexy are suggested as reasonable interventions for preventing omental capture and subsequent drainage problems.

Dialysate Leakage

An exit-site leak refers to the appearance of any moisture around the PD catheter identified as

Table 15.2 Non-infectious complications of Peritoneal dialysis: summary of pediatric studies from different countries

	Hooman [14]	Stringel [9]	Laakkonen [15]	Aksu [6]	Jander [16]	Macchini [17]	Donmez [18]	Rahim [7]	Rinaldi [5]	Lessin [19]	Holtta [20]
Publication year	2009, Iran	2008, USA	2008, Finland	2007, Turkey	2006, Poland	2006, Italy	2005, Turkey	2004, USA	2004, Italy	1999, USA	1997, Finland
Study period	1993–2006		1995–2000	1995–2005	1993–2004	1986–2002	1997–2004	1990–2000	1986–2000	18-month	1986–1994
Number of patients	122	21	23	93 (108 catheters)	29	78 (89 catheters)	53 (72 catheters)	90 (127 catheters)	363 (503 catheters)	12	34
Age	<14 years	3 months–16 years	<2 years	3 months–16 years	2 days–11 months		3 days–19 years	0–21 years	<15 years	3–26 years	<5 years
Insertion technique	Surgical	Laparascopic (+ omentectomy)	Open surgical	Percutaneous		Open surgical+ omentectomy in 70%	Percutaneous surgical laparascopic		Surgical, omentectomy in 82.4%	Laparoscopic	
PD modality	CAPD	–	CCPD	CAPD/CCPD		CAPD/CCPD	CAPD	CCPD			CAPD/CCPD
Catheter type	Double cuff straight or swan neck curled	Single cuff curled	Single cuff curled	Double cuff swan neck curled		Mainly double cuff straight	Mainly double cuff swan neck curled and straight		Mainly double cuff straight		Single cuff curled
Timing of catheter use	Early vs. late	After 1 week	After 2 weeks, if possible	Early vs. late			Early vs. late	Early vs. late		Early	
Hernia	20%		57%	No	31%	1.5%	15.1%			8%	29%
Leak	15%	Several minor leaks	Yes	No		2.5%	41.5%	14.2%	5.8%	16%	
Kink				7%							
Dislocation			Yes	12%		3.5%			5.8%	16%	
Malfunction (obstruction, drainage problems)			8	7%		5%	20.8%	21.3%	5.3%		
Cuff extrusion							5.7%		4.8%		
Catheter exchange	Catheter obstruction in 8.7% of the patients	7 catheters from 5 patients	5 catheters (leakage in 3, malposition in 1and obstruction in 1)	13 catheters from 11 patients (malfunction in 6, dislocation in 3, omental capture in 2, kink in 2)	9 catheter exchange including infectious causes	7 catheters (6 dislocation, 1 obstruction)	21 catheters from 20 patients, malfunction in 11 patients and leak in 9 patients	Catheter malfunction in 11.8% of the patients, leak with infection in 1.6%	38 catheters (17 obstruction, 14 dislocation, 4 cuff extrusion, 3 leakage)	3 catheters required laparoscopic revision for entrapment and 2 for leakage	9 catheters, leak in 5, obstruction in 3, migration in 1

dialysate; however, the spectrum of dialysate leaks also includes any dialysate loss from the peritoneal cavity other than via the lumen of the catheter. Most authors agree that dialysate leaks should also be classified according to how long after catheter placement they occur. 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. Late leaks 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.

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). Dialysate leakage can be considered as a mechanical, intra-abdominal pressure-related complication of PD, since intra-abdominal pressure increases linearly with the volume of dialysate infused [13]. 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 [13]. The reported incidence of pericatheter leak is widely variable (2.5–41.5%) in different pediatric series ([5–7, 14–20], Table 15.2). Initiating PD with low dialysate volume (300 mL/m² body surface area) has been recommended as a good practice measure [13]. 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 be an important factor in pediatric series [5, 6, 9]. However, leakage was less common in catheters with paramedian entry site compared with catheters implanted on the midline [17]. Additionally, 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 [21].

Factors suggested as potentially related to dialysate leak include the immediate initiation of PD, median PD catheter insertion, and weakness of the abdominal wall [13]. Rahim et al. recently evaluated risk factors for catheter related non-infectious problems. Young age, failure to thrive, and previous dialysis were not risk factors for dialysate leak or malfunction [7]. Indeed, young age was confirmed not to be a negative risk factor for catheter-related complications or catheter survival in large pediatric series from Italy and Turkey [5, 6]. In a retrospective, nonrandomized, single-center, pediatric study, delayed use of peritoneal catheter after its implantation (>14 days) was associated with a lower incidence of dialysate leak [7]. However, this was not confirmed by subsequent studies [6, 18]. A decreasing overall incidence of leakage was reported by the Italian registry, possibly related to improved surgical experience. Also, catheters with paramedian entry site were less likely to leak than catheters implanted in the midline [5, 17]. Abdominal weakness appears to predispose mostly to late leaks [7].

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 (Fig. 15.1). 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 [13].

Groin or genital swelling caused by leaks are usually related to underlying hernias (which are often palpable), with a patent processus vaginalis,

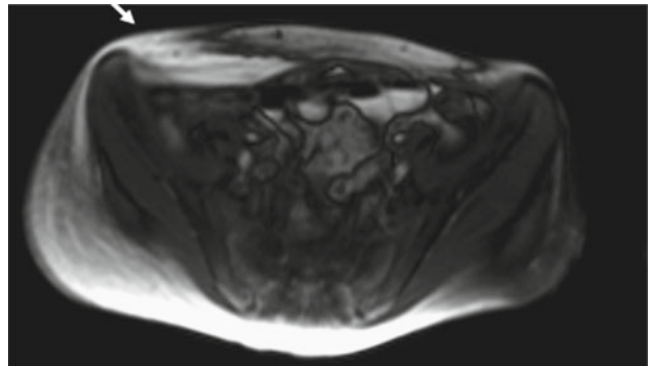

Fig. 15.1 Eleven-year-old boy with lack of ultrafiltration, rapid weight gain, and scrotal edema following start of PD. T2-weighted MRI shows massive generalized fluid accumulation in intermuscular and subcutaneous tissues extending to scrotum. Leakage was located to insertion site of instrumentation trocar used for laparoscopic Tenckhoff catheter placement. Surgical revision revealed 3 × 3 mm peritoneal defect (Courtesy of Franz Schaefer, MD)

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 [13].

Hernia

Hernia is a common complication in children on PD, with a reported incidence between 8% and 57% in different pediatric series (Table 15.2). Several different types of hernias have been described in PD patients. Some studies found that incisional hernia is the most common form, while other studies report inguinal or umbilical hernias as the most frequent. 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. 15.2).

Risk Factors

The risk of PD-associated hernia in children is affected by the intraperitoneal pressure (IPP), patient age [15, 22, 23], and the presence of anatomically weak sites in the abdominal wall [22].

The risk of hernia seems to be confined to neonates and infants, due to their high incidence of patent processus vaginalis and, possibly, higher intra-abdominal pressure. A patent processus vaginalis has been found in 90% of infants at birth and, at autopsy, in up to 37% of adults without hernias. Leakage of peritoneal fluid into a patent processus vaginalis, in conjunction with high IPP, can result in the formation of an indirect inguinal hernia. In a Finnish study, 57% of 23 children starting CPD during the first 2 years of life required hernia surgery [15]. In a study from Poland, 31% of infants on PD had hernia repair during follow-up [16]. Holtta et al. documented hernias in 29% of 34 children receiving PD under the age of 5 [20]. In contrast to the high incidence in neonates and young infants, the risk of hernia appears to be negligible in older children and adolescents [6, 17]. These findings support the concept of prophylactic closure of the processus vaginalis at the time of catheter insertion in neonates and young infants. Abdominal wall hernias

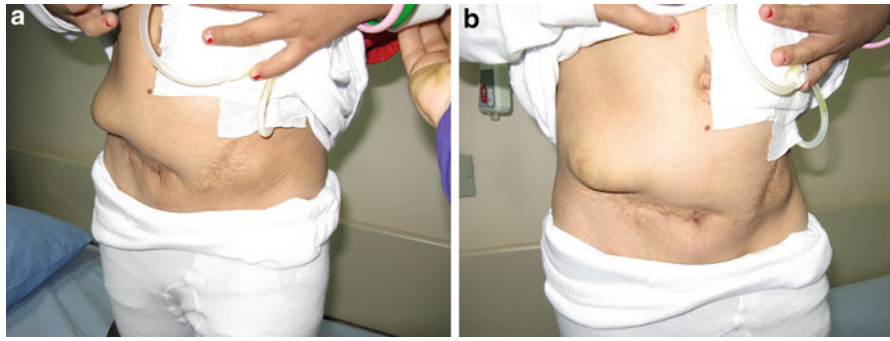

Fig. 15.2 Multiple abdominal incision scars and incisional hernias in a child on nightly intermittent peritoneal dialysis: **(a)** lateral view, **(b)** anterior view (With permission of Sevcan A. Bakkaloglu, MD)

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 [24]. 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. Obturator hernias may present with paresthesia and hyperesthesia of the anteromedial aspect of the thigh. Hernias through the foramen of Morgagni may present with right-sided chest pain or right hypochondrial pain [2].

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 [5]. 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 [9]. 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 patients during laparoscopic PD catheter placement. In addition, some authors have reported a lower incidence of postoperative leakage with laparoscopy.

IPP can be easily measured using a central venous pressure scale attached to the PD tubing system as the mean of in- and expiratory pressure in the mid axillary line in the supine position. IPP in the empty abdominal cavity is 0.5–2.2 cm H_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].

Additional determinants of IPP include obesity, sex, age, and abdominal girth. IPP monitoring may be used as an objective measure to guide fill volume prescription [22, 23]. IPP can help in determining how much intraperitoneal volume is tolerated and potentially lower the risk of mechanical complications such as hernia and leakage, although the concept has not been verified in controlled clinical studies. The maximal IPP tolerated without pain is around 18 cmH_2O. Since the normal IPP range in children on chronic PD is 7–14 cmH_2O [23], the volume prescribed for routing dwells should not cause IPP greater than 12–14 cmH_2O.

Treatment

Most hernias need surgical repair. Postoperatively, 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 ([25], Fig. 15.3a) or it can be massive, causing major respiratory symptoms. Hydrothorax can follow the first few dialysate exchanges or occur after years of uneventful PD [13]. 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, 13]. 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 [26].

Pathogenesis

The physiopathology of hydrothorax is not entirely clear. It is most commonly secondary to a pleuro-peritoneal communication. Possible mechanisms include a disorder of lymphatic drainage, pleuro-peritoneal 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, 13].

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. 15.3a). Thoracocentesis with biochemical analysis of pleural fluid is the first-line investigation. 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 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, 27].

Treatment

Once hydrothorax secondary to pleuro-peritoneal communication is confirmed, temporary cessation of PD remains the first-line treatment.

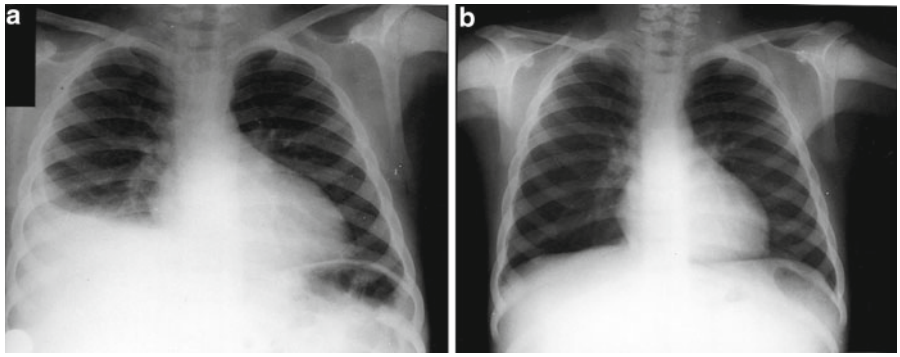

Fig. 15.3 (**a**) Right-sided massive pleural effusion. (**b**) Complete resolution of pleural effusion after pleurodesis with tetracycline (With permission of Sevcan A. Bakkaloglu, MD)

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 [27]. Chemical pleurodesis has been performed with talc, autologous blood, and tetracycline ([25], Fig. 15.3b), with uneventful recovery both in children and adults [2, 25, 27]. 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, 27].

Technique-Related Complications

Peritoneal Membrane Failure

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, have lactate buffer and contain high concentrations of glucose and glucose degradation products (GDPs) (see Chap. 12).

Pathogenesis: Continuous exposure to bio-incompatible PD solutions and bacterial infection causes inflammation of the peritoneal membrane, resulting in progressive fibrosis, neoangiogenesis 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 submesothelial zone and the extent of vasculopathy were positively correlated with duration of PD, and inversely with UF capacity [28].

There is emerging evidence that epithelial–mesenchymal transition (EMT) of peritoneal mesothelial cells is 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 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 [28].

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 peritoneal surface area in comparison with 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 [23]

The causes of membrane failure can be distinguished in part by the Peritoneal Equilibration Test (PET, see Chap. 11). 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 [29, 30]. Children with high transporter status are at risk for poor longitudinal growth [31].

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 is of particular importance [29, 32]. 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 [32, 33] and by minimizing peritoneal glucose exposure (see Chap. 12 for details).

Prognosis

Membrane failure is responsible for up to 27% of CPD termination in different pediatric series [3, 4, 34]. 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 drop out 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 [34]. 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 "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 [30].

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 [29].

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a serious complication of long-term PD characterized by encasement of 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. 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, nonacute clinical syndrome [34].

The cause of EPS is believed to be multifactorial. The development of EPS was associated with 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, the administration of drugs such as beta-blockers, and extended exposure to bioincompatible dialysis solutions [34]. There is also the possibility that some patients are genetically predisposed to develop EPS when exposed to one or more of the aforementioned etiologic agents, but this has not yet been confirmed.

A Pediatric EPS Registry was initiated in Japan in 1996. Of the 843 patients under 16 years of age who received PD between 1981 and the end of 1999, 17 were diagnosed with EPS. 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 [35]. EPS is the most serious complication of long-term PD with a mortality rate that exceeds 30%. 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 8 years are signals that should prompt the clinician to consider terminating PD as a possible means of preventing the development of EPS [34].

Diagnosis

The diagnosis 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 characteristic ultrasonographic, CT, or even plain X-ray imaging findings of the peritoneal cavity. The presence of localized ascites, adherent bowel loops, bowel luminal narrowing, calcification, and peritoneal membrane thickening (Fig. 15.4) can be visualized with either technique [36, 37].

Treatment

Although frequently unsuccessful, the treatment of sclerosing peritonitis most commonly entails cessation of PD with transfer to hemodialysis, bowel rest with total parenteral nutrition (TPN), and (possibly) immunosuppressive therapy including steroids, azathioprin, etc., and/or surgery [34, 36].

Metabolic Complications

Dyslipidemia and Insulin Resistance

Disturbances of glucose and lipid metabolism are 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, hyper-

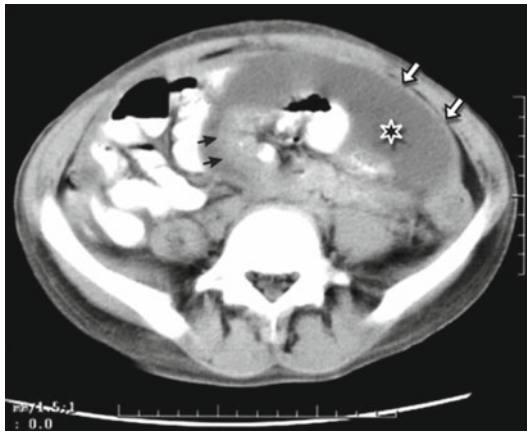

Fig. 15.4 Axial computed tomography of the abdomen showing localized fluid collection (*), and intestinal loops encapsulated by a thick visceral (*black arrows*) and parietal peritoneum (*white arrows*) (Reprinted with permission from Ref. [37])

leptinemia, hyperlipidemia, and an atherogenic lipid profile [38–40]. 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. Although chronic PD has been accused of conferring a higher technique-related risk of atherogenesis compared to hemodialysis, long-term studies have shown that, following a temporary deterioration, lipid profiles tend to stabilize or even improve during extended treatment. Hence, long-term PD appears equally safe as hemodialysis with respect to lipid status in children [39].

Hypokalemia

Ten to thirty-five percent of patients on continuous PD require potassium supplements. 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 [41]. 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 [42].

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 (usually 20 meq/day, 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 end-stage renal disease 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) [43]. Since there is an inverse relationship between concentrations of magnesium and intact parathyroid hormone (PTH), raising possibility that hypermagnesemia may contribute to adynamic bone disease [44], 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 [43].

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, 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, 45].

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. 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.

4. Honda M. The 1997 report of the Japanese national registry data on pediatric peritoneal dialysis patients. Perit Dial Int. 1999;19:S473–8.
5. 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;24:481–6.
6. Aksu N, Yavascan O, Anil M, et al. 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.
7. Rahim KA, Seidel K, McDonald RA. Risk factors for catheter-related complications in pediatric peritoneal dialysis. Pediatr Nephrol. 2004;19:1021–8.
8. Schaefer F, Feneberg R, Aksu N, et al. Worldwide variation of dialysis-associated peritonitis in children. Kidney Int. 2007;72:1374–9.
9. Stringel G, McBride W, Weiss R. Laparoscopic placement of peritoneal dialysis catheters in children. J Pediatr Surg. 2008;43:857–60.
10. Crabtree JH, Fishman A. A laparoscopic method for optimal peritoneal dialysis access. Am Surg. 2005;71: 135–43.
11. Ozyer U, Harman A, Aytekin C, et al. Correction of displaced peritoneal dialysis catheters with an angular stiff rod. Acta Radiol. 2009;50:139–43.
12. 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.
13. Leblanc M, Ouimet D, Pichette V. Dialysate leaks in peritoneal dialysis. Semin Dial. 2001;14(1):50–4.
14. Hooman N, Esfahani ST, Mohkam M, et al. The outcome of Iranian children on continuous ambulatory peritoneal dialysis: the first report of Iranian National Registry. Arch Iran Med. 2009;12:24–8.
15. Laakkonen H, Hölttä T, Lönnqvist T, et al. Peritoneal dialysis in children under two years of age. Nephrol Dial Transplant. 2008;23:1747–53.
16. Jander A, Nowicki M, Tkaczyk M, et al. Chronic peritoneal dialysis in infants – preliminary results of the multicenter survey. Przegl Lek. 2006;63(Suppl 3): S72–4.
17. Macchini F, Valadè A, Ardissino G, et al. Chronic peritoneal dialysis in children: catheter related complications. A single centre experience. Pediatr Surg Int. 2006;22:524–8.
18. Dönmez O, Durmaz O, Ediz B, et al. Catheter-related complications in children on chronic peritoneal dialysis. Adv Perit Dial. 2005;21:200–3.
19. Lessin MS, Luks FI, Brem AS, et al. Primary laparoscopic placement of peritoneal dialysis catheters in children and young adults. Surg Endosc. 1999;13: 1165–7.
20. Holtta TM, Ronnholm KA, Jalanko H, et al. Peritoneal dialysis in children under 5 years of age. Perit Dial Int. 1997;17:573–80.
21. Sojo ET, Grosman MD, Monteverde ML, et al. Fibrin glue is useful in preventing early dialysate leakage in children on chronic peritoneal dialysis. Perit Dial Int. 2004;24:186–90.
22. Aranda RA, Romão Jr JE, Kakehashi E, et al. Intraperitoneal pressure and hernias in children on peritoneal dialysis. Pediatr Nephrol. 2000;14:22–4.
23. Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. Pediatr Nephrol. 2009;24:1633–42.
24. Bargman JM. Complications of peritoneal dialysis related to increased intraabdominal pressure. Kidney Int Suppl. 1993;40:S75–80. Feb.
25. Bakkaloglu SA, Ekim M, Tümer N, et al. Pleurodesis treatment with tetracycline in peritoneal dialysis-complicated hydrothorax. Pediatr Nephrol. 1999;13: 637–8.
26. Borzych D, Ley S, Schaefer F, et al. Dialysate leakage into pericardium in an infant on long-term peritoneal dialysis. Pediatr Nephrol. 2008;23:335–8.
27. Szeto CC, Chow KM. Pathogenesis and management of hydrothorax complicating peritoneal dialysis. Curr Opin Pulm Med. 2004;10:315–9.
28. Kim YL. Update on mechanisms of ultrafiltration failure. Perit Dial Int. 2009;29(Suppl 2):S123–7.
29. Saxena R. Pathogenesis and treatment of peritoneal membrane failure. Pediatr Nephrol. 2008;23:695–703.
30. Chung SH, Heimbürger O, Lindholm B. Poor outcomes for fast transporters on PD: the rise and fall of a clinical concern. Semin Dial. 2008;21:7–10.
31. 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.
32. Canepa A, Verrina E, Perfumo F. Use of new peritoneal dialysis solutions in children. Kidney Int Suppl. 2008;108:S137–44.
33. 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.
34. Honda M, Warady BA. Long-term peritoneal dialysis and encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2010;25:75–81.
35. 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.
36. Kawaguchi Y, Saito A, Kawanishi H, et al. 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.
37. Ekim M, Fitöz S, Yagmurlu A, Ensari A, et al. Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients. Nephrology (Carlton). 2005; 10:341–3.
38. Bakkaloglu SA, Saygili A, Sever L, et al. Assessment of cardiovascular risk in paediatric peritoneal dialysis patients: a Turkish pediatric peritoneal dialysis study

group (TUPEPD) report. Nephrol Dial Transplant. 2009;24:3525–32.
39. Bakkaloglu SA, Ekim M, Tümer N, et al. The effect of CAPD on the lipid profile of pediatric patients. Perit Dial Int. 2000;20:568–71.
40. Buyan N, Bideci A, Ozkaya O, et al. 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.
41. 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.
42. Khan AN, Bernardini J, Johnston JR, et al. Hypokalemia in peritoneal dialysis patients. Perit Dial Int. 1996;16:652.
43. Hutchinson AJ. Serum magnesium and end-stage renal disease. Perit Dial Int. 1997;17:327–9.
44. 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.
45. Greenberg A, Bernardini J, Piraino BM, et al. Hemoperitoneum complicating chronic peritoneal dialysis: single-center experience and literature review. Am J Kidney Dis. 1992;19:252–6.

Part IV

Hemodialysis

Hemodialysis Vascular Access in Children

16

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Keywords
Hemodialysis • Children • Vascular access • Chronic kidney disease • Arteriovenous Fistula • Arteriovenous Graft

Introduction

Vascular access has been heralded as the backbone to the provision of dialysis, and in children poses unique challenges to the pediatric dialysis care provider due to smaller vessel diameters and vascular hyperreactivity. Whether in the face of acute kidney injury (AKI) requiring renal replacement therapy (RRT) or as a result of chronic kidney disease (CKD), children should not be considered "little adults." Further, a critical issue for these patients is to provide adequate vascular access for current RRT requirements without compromising future potential access sites. Because this requires a different surgical philosophy, it is important to develop a team composed of surgeons, pediatric nephrologists, and dialysis nurses interested in these unique challenges. This chapter will provide a basic overview of pediatric vascular access creation and maintenance including surgical and medical nuances.

Renal dysfunction necessitating RRT can be either chronic or acute. With AKI, establishment of adequate vascular access to accommodate a high-flow circuit is essential. Long-term consequences must also be considered in case renal function does not recover. Typically, a central venous catheter (CVC) is used emergently, and for a relatively short duration. Acute catheters for short-term dialysis are best placed in the femoral veins to protect future access sites in the arms and neck. With CKD, the patient has a few treatment options once ESRD is reached: renal transplantation, peritoneal dialysis, or hemodialysis. Given that many children triangulate between these modalities over the course of a lifetime, vein preservation is critical and should be initiated at the time of diagnosis.

Chronic Kidney Disease

The prevalence of chronic kidney disease in children continues to increase worldwide due at least in part to increased survival and better treatment for chronic conditions, including those of renal etiology as well as other, nonrenal conditions.

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For example, the use of calcineurin inhibitors in renal and nonrenal organ transplantation has caused permanent, chronic impairment in many cases, leading to renal replacement therapy. Although preemptive renal transplantation is the preferred renal replacement modality, it is not always possible due to a variety of factors including lack of suitable donors, high panel-reactive antibodies, or poor access to transplantation. For example, in developing countries, the patient may not have easy access to transplantation. Among the RRT modalities available, HD is the most commonly used initial therapy and is the most commonly used dialytic modality long term [1]. Hence, vascular access must be a consideration early to allow for the best possible treatment in these children.

Preparation for Vascular Access

In a child with known CKD, vein preservation should occur as soon as the diagnosis is made, even at CKD stage 1. In many instances, referral to a nephrologist is not made until CKD has progressed to stages 3 or 4. For that reason, education regarding vein preservation is important for primary care physicians, emergency room personnel, surgeons, anesthesiologists, and other providers. Early referral and physician education can improve access options and avoid morbidity associated with CVC use and venous access in the patient's arms, both of which can limit options for dialysis access [2] (Fig. 16.1). A single venipuncture or placement of an intravenous catheter into the cephalic vein at age 2 can render the vein useless at age 10, making permanent access creation impossible. Ideally, a venous catheter, 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 can be significant and can permanently affect outflow for future access. Subclavian stenosis in adults has been shown to occur in 5/15 patients at 1 week, 6/13 patients after 2–6 weeks, and in almost 50% of patients studied following catheter removal [3–6] (Fig. 16.2).

At stage 4 CKD, the patient should be referred to an experienced vascular access surgeon, locally or regionally, to be evaluated for permanent access. Based on the center, pediatric vascular access may be placed by a vascular surgeon, pediatric surgeon, or transplant surgeon. The key, regardless of the surgeon's background, is to identify a surgeon trained in, and willing to accept, the challenge 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…" [2]. This mantra is particularly important when approaching vascular access in the pediatric HD patient. Lack of surgical expertise is often identified as a barrier to access placement; therefore, the nephrology practitioner must identify an experienced vascular access surgeon willing to care appropriately for this unique patient population. Keeping in mind that arteriovenous fistulae (AVF) often take longer to mature in children than adults, sometimes up to several months after creation, early placement should be planned. Patient and family education regarding protection of the nondominant arm should be initiated early in the course of CKD (potentially at stages 1–2): avoiding venipuncture and even blood pressure measurements whenever possible. Education regarding AVF cannulation, with the use of a child life specialist, recreational therapist, or peer-to-peer observation/interaction, can be valuable in cannulation preparedness once the access is in place. The false perception that a child does not want to be "stuck" needs to be overcome. Prior studies have demonstrated cannulation of an AVF is not a deterrent to its use and that quality of life for children is equivalent, if not better, for children with AVF/AVG as compared to children with catheter-based hemodialysis [7, 8]. In essence, a catheter-avoidance approach should be undertaken whenever possible.

The preoperative evaluation of children is important in preventing primary failure of the access. The leading cause of primary failure is venous outflow obstruction, usually caused by stenosis or thrombosis. It is important to recognize possible outflow obstruction before creation of a

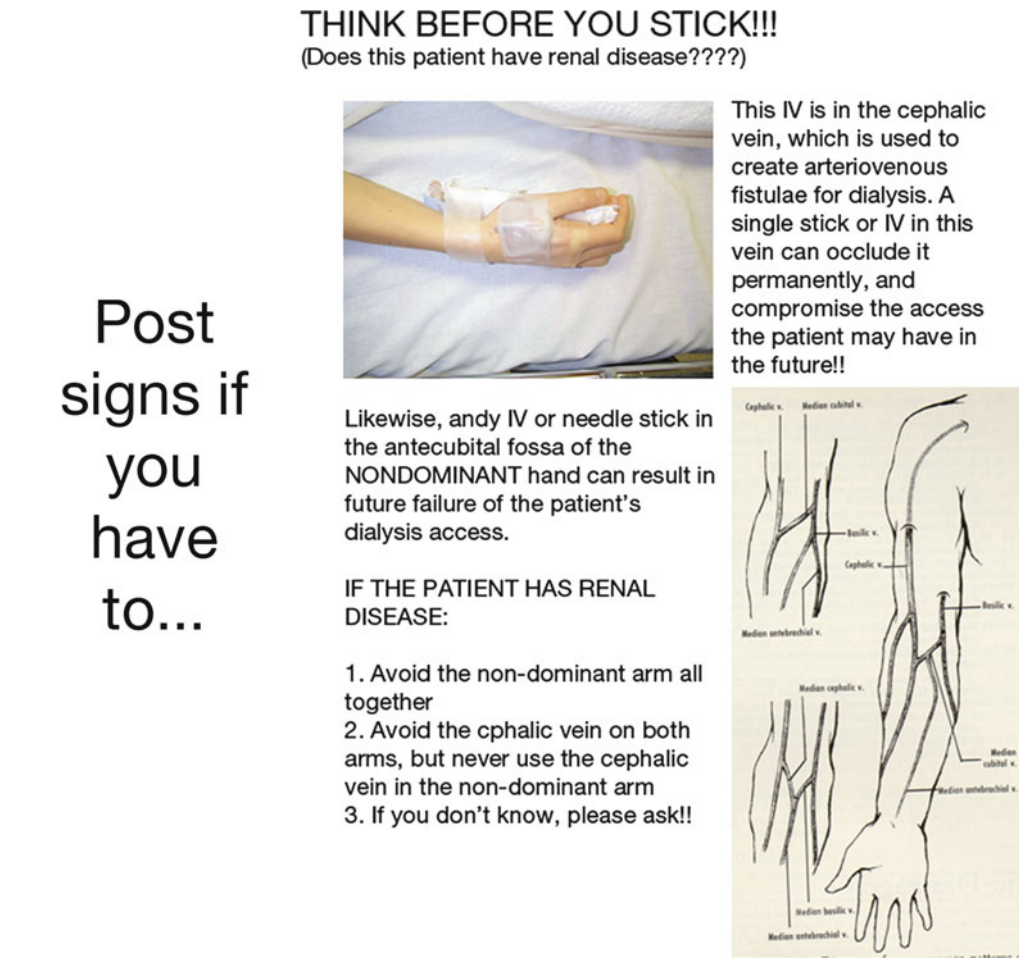

Fig. 16.1 Post signs if you have to…

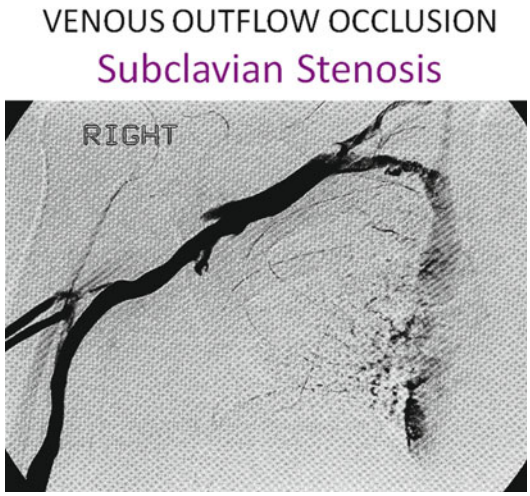

Fig. 16.2 Subclavian vein stenosis following central venous catheter placement in the subclavian vein precludes forever the use of that extremity for HD access

primary fistula. Specific attention should be paid to prior central line history and prior hospitalizations, including intensive care unit stays. Examination should include observation for extremity deformation and/or venous distention indicative of obstruction and evidence of prior central line placement. Once the decision has been made to evaluate the patient for fistula formation, Doppler vein mapping is obtained to establish vein diameter and patency (Fig. 16.3). Vein mapping is now considered standard of care in planning vascular access although, in rare situations, contrast venography may be necessary (Fig. 16.4). Examples of Doppler vein mapping are shown in Fig. 16.3. In general, minimal vessel diameter is 1.5 mm for the artery and 2.5 mm for the vein to allow for successful anastomosis and subsequent use [9]. A contrast venogram is

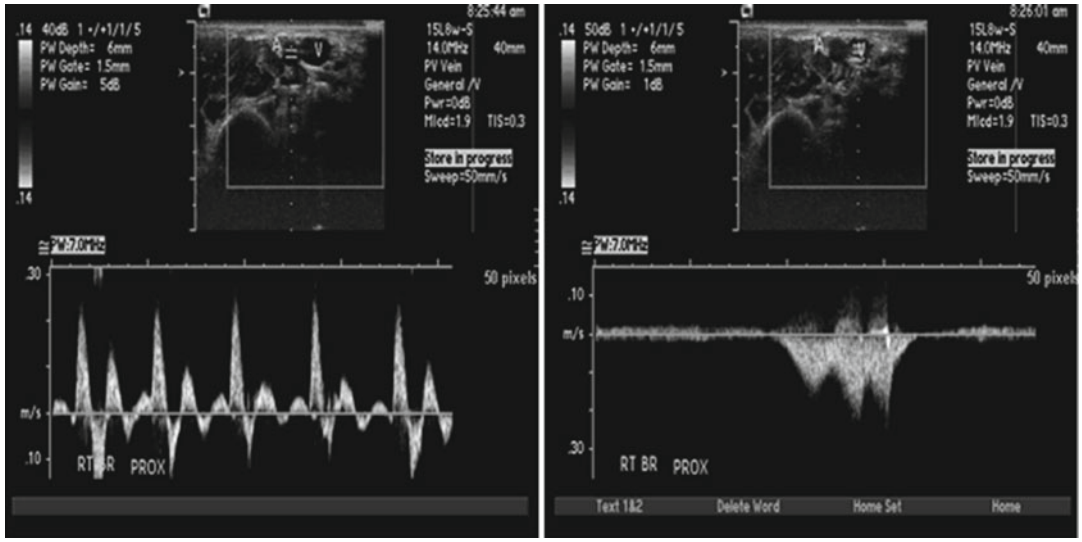

Fig. 16.3 Preoperative Doppler vein mapping. Courtesy of Maria Alonso, MD, Cincinnati Children's Hospital Medical Center

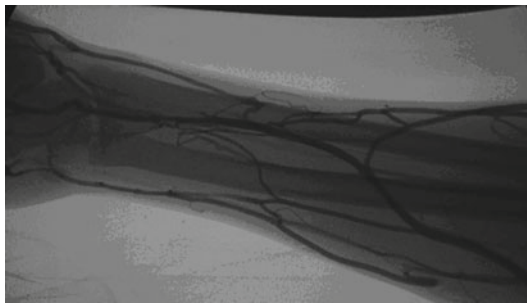

Fig. 16.4 Preoperative venography. Courtesy of Maria Alonso, MD, Cincinnati Children's Hospital Medical Center

recommended in any child who has collaterals present on physical exam or a history of prior central venous catheters, since Doppler ultrasound cannot identify subclavian stenosis.

Vascular Access Options

The first form of hemodialysis access was the Scribner shunt, first described in 1960. The Scribner shunt consisted of two external cannulae – one inserted into the radial artery and one inserted into the cephalic vein. Reports of the first shunts described an average shunt life of 113 days, but up to 50% required revision with one-third requiring multiple revisions [10–12]. Approximately 40% necessitated removal due to complications. Since then, multiple options for HD access have emerged. Chronic hemodialysis access can be obtained in children by creation of a primary arteriovenous fistula, placement of an arteriovenous synthetic graft (AV graft), or use of a cuffed central venous catheter. Deciding which access is best for an individual patient is based on the patient's diagnosis, size, likelihood of transplant, procedural risk, and probability of long-term patency [13]. Current data supports the concept of "fistula first"; whenever feasible, a primary fistula should be the access of choice [14].

Arteriovenous Fistula

Arteriovenous fistulae provide the best vascular access option in long-term hemodialysis because of increased longevity and low complication rates [14]. The 2006 National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-K/DOQI) guidelines recommend the creation of a permanent access in children weighing more than 20 kg in whom transplant is not eminent [15]. The advantages of a primary fistula are the low rate of

secondary failure, low rate of infection, and decreased incidence of pseudoaneurysm [16, 17]. Additionally, dialysis adequacy has been shown to be superior in children who have an AVF as primary vascular access for HD [18]. However, primary fistulae have the disadvantages of increased rate of primary failure, either by thrombosis or failure to mature, when compared to AV grafts [19–21]. The Brescia-Cimino (radiocephalic) AVF has been the preferred vascular access for decades in adults due to its low complications and longevity. The pediatric population poses a challenge due to small vessel caliber, causing a high incidence of primary failure. Further, because of small vessel size and lower systemic pressures, maturation of these fistulae may take several months. For that reason, primary brachial fistulae may be a better choice in some children.

The key to successful AVF placement is proper planning. Despite data supporting the use of primary AVF in children, a majority of pediatric patients initiating HD are doing so with a CVC according to The United States Renal Data Systems (USRDS) 2008 annual report [1]. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2007 Annual report also reports 77.3% of pediatric patients receiving hemodialysis use CVC as primary access compared to AVF (12.5%) and AVG (7.6%) [22]. Based on a recent study of 37 incident pediatric hemodialysis patients conducted in the Midwest, although a majority of patients were followed by a nephrologist for at least 6 months, CVC was the predominant vascular access (83.7%) at dialysis initiation [23]. Although CVCs are more expeditious, and may often be the only choice for acute dialysis, they should never be the default access for long-term dialysis in patients of sufficient size in whom fistulae are possible.

In older children and adults, a primary arteriovenous fistula is the established access of choice for long-term hemodialysis. The surgical principle in placing all fistulae, whether primary fistulae or AV grafts, is to use the most distal vessels possible in the nondominant extremity, preserving the more proximal vessels for future access [24]. Whenever technically possible, a primary fistula should be the access of choice. Although the primary patency rate for an AVG is typically higher than that for an AVF, secondary patency rates have been shown to be significantly longer with lower complication rates than polytetrafluoroethylene (PTFE) bridge grafts or external catheters [9, 15, 18, 25–27]. Review of 5 year access survival rates also demonstrated longer survival for AVF (59%) versus AVG (40%) [20].

Table 16.1 Arteriovenous sites

Artery	Vein	Fistula
Radial	Cephalic	Wrist
Brachial	Cephalic	Antecubital
Brachial	Basilic	Forearm
Brachial	Basilic	Upper arm/transposed
Femoral	Saphenous	Thigh

Primary fistulae are most commonly created between the radial artery and cephalic vein at the wrist (Brescia-Cimino), but can also be created 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 [28, 29]. Table 16.1 depicts AVF options. Although AVF creation in children >20 kg in size can be achieved without too much technical difficulty, AVF creation in smaller children may be difficult. Surgical adjuncts such as magnification loupes and the operating microscope have allowed for the successful creation of AVF in children as small as 5 kg [8, 9, 30]. Although primary patency rates in AVF created using the operating microscope have been as low as 33%, long-term assisted patency rates approximate more than 90%. Worldwide experience regarding AVF in children, including use of the operating microscope, has been promising, showing fewer complication rates and better long-term patency rates (5 year patency rates upward of 70%) [24, 31]. Again, it should be stressed that expertise using the operating microscope is required for successful AVF creation in these very small children. A summary of the surgical approach to AVF creation is depicted in Fig. 16.5.

It should be noted that primary fistulae in children take significantly longer to mature than in adults, up to 4 months in some patients compared to the usual 6 weeks recommended for maturation

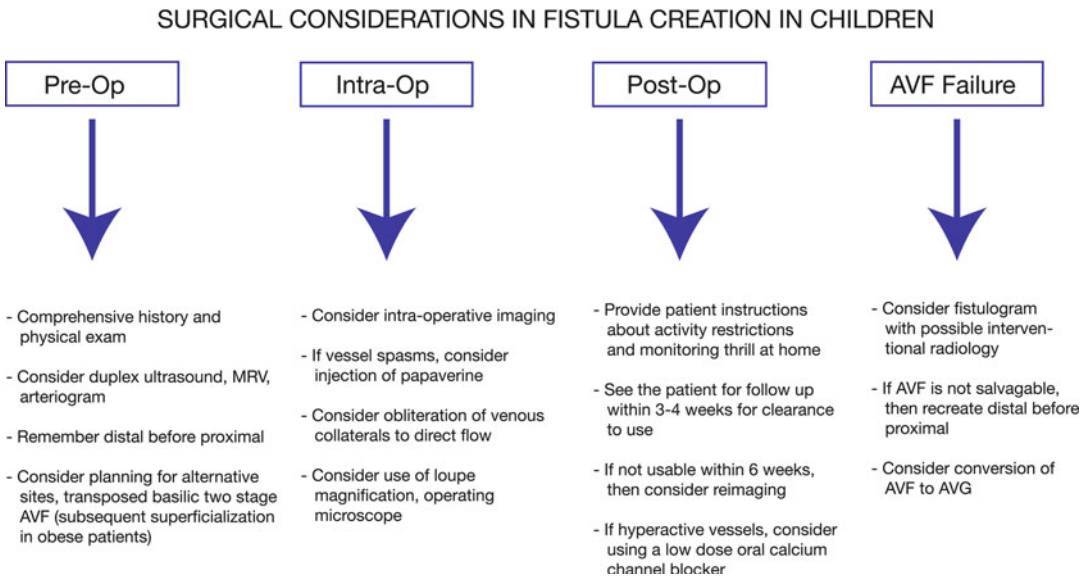

Fig. 16.5 Surgical approach to AVF

of AVF in adolescents and adults [30]. Although published guidelines regarding optimization of maturation do not exist, a few general principles hold true. Venipunctures and blood pressure measurements should be avoided in the ipsilateral extremity of a patient with a primary fistula or AV graft to avoid compression. Although there are no data, exercising the extremity with the AVF is anecdotally believed to improve maturation. If a child is noted to have hyperreactive vessels at the time of surgical creation, the use of a low-dose peripherally vasodilating calcium channel blocker such as amlodipine or nifedipine may allow for decreased risk of premature thrombosis [9].

Arteriovenous Graft

An arteriovenous graft (AVG) utilizes a vascular adjunct to create an arteriovenous anastomosis. When primary fistulae have failed, or are not technically possible, the alternative is an AVG. Polytetrafluoroethylene (PTFE) is the conduit of choice for AV access grafts in children, as in adults, due to better biocompatibility as compared to previously used bovine grafts. When compared to AVF, AVG can be used sooner, typically within 2–4 weeks of placement, and have higher primary patency rates. Sheth et al. described primary access failure rates of 3.7% in AVG in children as compared to 33% in AVF [20]. However, after excluding primary access failures; 1, 3, and 5 year patency rates were not statistically different. In contrast, in a study conducted in the United Kingdom, Ramage et al. described a primary access failure rate of 60% for AVG as compared to 23% for AVF. Long-term complications of AV grafts are significant and substantially greater than those of AVFs [32]. The rate of infectious complications is much higher, and graft infection often requires removal of the synthetic material. Access stenosis and infection occur more frequently in AVG than AVF. One study found the overall complication rate for AVF was 1.3 per 12 access-months as compared to 2.9 per 12 access-months for AVG [20]. Others have reported infection rates to be over tenfold higher with an AVG as compared to AVF [32]. Stenosis, usually near the venous anastomosis, is common and, with enough time, is essentially universal. Children with high-flow AV accesses, particularly PTFE femoral grafts, are at risk for unequal limb growth and "steal" phenomena [33, 34]. Overall, although PTFE grafts have a higher primary success rate, the higher rates of secondary failure and other complications make them a less desirable access.

The surgical technique for creating AVG in children has been well described [35, 36].

The most common site for placement of an AV graft is the forearm, with straight grafts (radial artery to brachial vein) more common in smaller children, and loop grafts (brachial artery to brachial vein) used in larger children. Alternate sites for AV grafts include the upper arm (brachial artery to distal brachial or axillary vein), and groin (femoral artery to femoral vein). In general, smaller, tapered grafts are used (4–6 mm taper) in children.

After failure of AVG, the child's vascular anatomy should be reassessed to determine if an AVF can be created. In many circumstances, a more proximal AVF can be created due to vascular enlargement from the prior AVG, which has created high-flow dynamics.

Permanent Access Surveillance

In order to optimize access longevity, careful surveillance and early intervention is required. Although the best monitoring technique remains controversial, in our view and that of others, ultrasound dilution flow provides a superior method compared to venous pressure monitoring, which is not accurate or reliable in children [37]. Although interval angiography can identify an area stenosis prior to graft thrombosis, this technique is more invasive and is better utilized once a problem has been identified using surveillance [38, 39]. If venous stenosis or thrombosis is present, angiography allows the interventionalist to perform balloon angioplasty which can successfully extend the life of the graft, and avoid surgical revisions. In the setting of acute thrombosis due to stenosis, a thrombectomy is performed. If flow can be restored, the patient undergoes angiography with balloon dilatation. If flow cannot be restored, surgical revision of the graft should be undertaken.

Central Venous Catheters

An external hemodialysis catheter is often the first access placed in a child with ESRD and for many patients, may be the only access used. It must be stressed that catheters should be avoided whenever possible by advance planning for AVF in children with ESRD. There is a trend toward decreased used of CVCs in children with ESRD, but they remain the most common form of vascular access. In the most recent NAPRTCS report, 77% of children receiving chronic hemodialysis used a percutaneous catheter for access, with only 11.4% using a primary AV fistula, and 12.3% using a graft [22]. The most important factor when using a CVC for HD is location. Specifically, the subclavian vein should be avoided; subclavian stenosis is common after placement of central venous catheters, which can profoundly affect subsequent permanent access placement. Schillinger et al. described a subclavian stenosis rate of approximately 42% as compared to 10% stenosis in the internal jugular vein with an average catheter life of 31 days [40]. Chronic hemodialysis catheters in children are silastic, cuffed, dual-lumen catheters. Catheter sizes available range in size from seven French upward. As in acute catheter placement, the smallest effective catheter should be used and the subclavian vein avoided. Three types of CVC are most commonly used in children: Ash split™ (Medcomp®, Harlesville, PA, USA) which is a bioflux polyurethane D-shaped catheter with a single cuff; Bio-Flex™Tesio® (Medcomp®, Harlesville, PA, USA), made of bioflux polyurethane with two single lumens; and the Opti-flow® (C.R. Bard, Inc., Murray Hill, New Jersey, USA) made of body soft polyurethrane with two cuffs containing antimicrobial silver ions [41]. Prior studies have shown conflicting data: some have demonstrated comparable blood flow and survival rates, while others have reported the Tesio™ CVC to be superior in children [41, 42]. Placing hemodialysis catheters in children can be a surgical challenge, as patient size may vary and an ideal catheter may not exist. A guide for placement of an appropriately sized catheter for a patient of a particular size is given in Table 16.2.

Table 16.2 Estimate of catheter size based on patient weight

Dual lumen catheters
8 French up to 20 kg
10 French from 20 to 30 kg
11.5 French above 30 kg
Tesio catheters
7 French from 20 to 40 kg
10 French from 40 to 60 kg
12 French above 60 kg

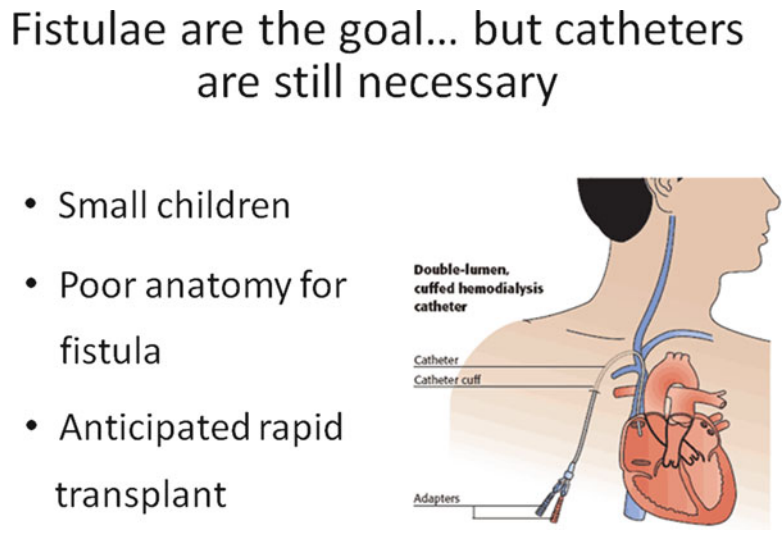

Fig. 16.6 AVF are the goal, but central venous catheters are still needed in small children, children in whom anatomy for fistulae is poor and in children for whom transplantation is eminent

However, this is just a guide; because of anatomic differences, a smaller or larger catheter may be required. Regardless of the catheter used, the final position of the most distal portion of the catheter should be the proximal right atrium (Fig. 16.6) Many catheters will function well with the tip in the SVC as well, although this can be problematic in small children. At the skin end of the catheter, the cuff should be positioned 1.5–2 cm from the exit site to allow for optimal epithelial ingrowth. Consequently, the choice of the exit site is critical to the final catheter position. In other words, the exit site should be 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.

Complications of CVC can occur at the time of placement as well as after usage. Risks associated with catheter insertion include vessel perforation and hemorrhage, pneumothorax, hemothorax, emboli formation, and arrhythmias associated with catheter tip location [43]. Long-term complications of hemodialysis catheters are common and include kinking or displacement, infection, and thrombosis [44]. In a multicenter pediatric study, Valentini et al. demonstrated a CVC dysfunction rate of 46% over a 1 month period [45]. Although urokinase, tissue plasminogen activator, or another thrombolytic agent can be used for treatment, the thrombosis often recurs, requiring CVC line removal/exchange. In most cases, a small cut down can be performed and the catheter divided near the point of venipuncture. The divided catheter can then be used to thread a wire to guide placement of the new catheter, avoiding a new venipuncture. Mechanical problems with the catheter (breakage, displacement, and inadequacy due to growth of the child) require replacement of the catheter. Although data are not available, many physicians feel acute venous thrombosis should be treated even in the absence of symptoms in order to avoid future chronic venous insufficiency and to protect future sites for hemodialysis.

Infectious complications of CVC are quite common and are a leading cause of increased morbidity and mortality in pediatric HD patients [1, 22]. Infections can occur within the catheter itself, or at the exit site, or both. If the dialysis patient presents with fever and/or exit-site erythema or drainage, a blood culture should be obtained. Initially, broad spectrum antibiotics such as vancomycin, and a third-generation cephalosporin or aminoglycoside should be given for empiric coverage. Ultimately, the choice of antibiotics used for treatment should be based upon culture results and sensitivities. Exit-site infections should be confirmed by culture of the exudates, and antibiotics given empirically pending culture results [43]. Indications for immediate removal of the catheter include serious systemic

symptoms such as septic shock or thrombocytopenia, persistently positive blood cultures, or the presence of specific organisms that do not respond to this conservative approach (such as Candida or other fungi). When possible, the central venous system should be kept free of any catheter for at least 2–3 days before a new hemodialysis catheter is placed (see also Chap. 21).

Acute Vascular Access

Acute hemodialysis access is obtained by placing a non-cuffed, dual-lumen catheter into the superior or inferior vena cava, using the Seldinger technique. In small infants, two single-lumen catheters may occasionally be used. The size of catheter used must be individualized to each patient, but the goal should be to place the smallest catheter allowing for optimal blood flows possible. The larger the catheter, the more effective the dialysis, but the higher the risk of thrombosis and other complications. The femoral route is preferred in settings where dialysis will be needed for less than a few weeks, in order to preserve all future routes of access to the superior vena cava. Under no circumstances should the subclavian vein be the initial vein used for dialysis access. The smaller the child, the more likely 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 also be avoided. This is important because future forearm fistulae in the ipsilateral extremity can fail from the outflow obstruction associated with a "minor" stenosis in the subclavian vein. When use of the femoral vein is not possible, a puncture of the internal jugular is the next preferred option (Seldinger technique), followed by a cut down on the external, then internal jugular vein.

Summary

Access for hemodialysis in children is a surgical challenge because of the size of the vessels, and the special physiology of the patients. Primary AV fistulae, with a lower rate of secondary failure and complications, are preferable for long-term hemodialysis access in children. The decision of which patients are "too small" for this surgical approach varies from institution to institution, based on the experience of the surgeon and availability of microsurgical techniques. 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 effective future access. Placement of an AV graft should be considered only when all options for an adequate primary arteriovenous fistula have been exhausted. The use of a central venous catheter should be reserved as a "bridge" to a more permanent access, or reserved for children so small that the risk of primary failure of an arteriovenous fistula is unacceptably high. In all cases, access must be planned *before* the procedure, with the long-term need for dialysis in mind. Whether the surgeon creating the access is a vascular surgeon, pediatric surgeon, or transplant surgeon, it imperative that the surgeon who is providing the access be an active participant in the decision-making process, be educated about the special needs of children in renal failure, and be aware of the issues surrounding the choice of access for each patient.

References

1. United States Renal Data System Annual Report. 2008. http://www.usrds.org. Accessed 1 Dec 2009.
2. Davidson I, Gallieni M, Saxena R, Dolmatch B. A patient centered decision making dialysis access algorithm. J Vasc Access. 2007;8(2):59–68. Apr-Jun.
3. 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.
4. Stalter K, Stevens G, Sterling W. Late stenosis of the subclavian vein after hemodialysis catheter injury. Surgery. 1986;100:924–7.
5. Fant G, Dennis V, Quarles L. Late vascular complications of the subclavian dialysis catheter. Am J Kidney Dis. 1986;7:225–8.
6. Konner K. Subclavian haemodialysis access: is it still justified in 1995? Nephrol Dial Transplant. 1995; 10(11):1988–91.
7. Brittinger WD, Walker G, Twittenhoff WD, Konrad N. Vascular access for hemodialysis in children. Pediatr Nephrol. 1997;11:87–95.

8. 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.
9. 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.
10. Franzone AJ, Tucker BL, Brennan LP, Fine RN, Stiles QR. Hemodialysis in children. Experience with arteriovenous shunts. Arch Surg. 1971;102(6):592–3.
11. Idriss FS, Nikaidoh H, King LR, Swenson O. Arteriovenous shunts for hemodialysis in infants and children. J Pediatr Surg. 1971;6(5):639–44.
12. 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.
13. Warady BA, Bunchman TE. An update on peritoneal dialysis and hemodialysis in the pediatric population. Curr Opin Pediatr. 1996;8(2):135–40.
14. Fistula First Breakthrough Initiative. 2009. http://www.fistulafirst.org. Accessed 15 Nov 2009.
15. Clinical practice recommendation 8: vascular access in pediatric patients. Am J Kidney Dis. 2006;48(Suppl 1):S274–276.
16. Kherlakian G, Roedersheimer LR, Arbaugh JJ, Newmark KJ, King LR. Comparison of autogenous fistula versus expanded polytetrafluoroethylene graft fistula for angioaccess in hemodialysis. Am J Surg. 1986;152:238–43.
17. Porile J, Richter M. Preservation of vascular access. J Am Soc Nephrol. 1993;4:997–1003.
18. Chand DH, Brier M, Strife CF. Comparison of vascular access type in pediatric hemodialysis patients with respect to urea clearance, anemia management, and serum albumin concentration. Am J Kidney Dis. 2005;45(2):303–8.
19. Hirth R, Turenne MN, Woods JD, Young EW, Port FK, Pauly MV, Held PJ. Predictors of type of vascular access in hemodialysis patients. JAMA. 1996;276:1303–8.
20. 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.
21. Palder SB, Kirkman RL, Whittemore AD, et al. Vascular access for hemodialysis. Patency rates and results of revision. Ann Surg. 1985;202(2):235–9.
22. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). Annual Report. Dialysis Access Data. 2008. http://web.emmes.com/study/ped/. Accessed 20 Dec 2009.
23. Valentini RP, Chand DH. Effects of demographic characteristics and medical care before starting hemodialysis on vascular access in incident pediatric hemodialysis patients. Presented at the international pediatric nephrology association annual meeting, 2007, Budapest, Hungary.
24. 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.
25. Feldman J, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. J Am Soc Nephrol. 1996;7(4):523–35.
26. Chazan J, London M, Pono L. Long-term survival of vascular accesses in a large chronic hemodialysis population. Nephron. 1995;69:228–33.
27. Swedberg SH, Brown BG, Sigley R, Wight TN, Gordon D, Nicholls SC. Intimal fibromuscular hyperplasia at the venous anastomosis of PTFE grafts in hemodialysis patients: clinical, immunocytochemical, light and electron microscopic assessment. Circulation. 1989;80:1726–36.
28. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. N Engl J Med. 1966;275(20):1089–92.
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. 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.
31. Sanabia J, Polo JR, Morales MD, et al. Microsurgery in gaining paediatric vascular access for haemodialysis. Microsurgery. 1993;14:276–9.
32. 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(4):708–14.
33. 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.
34. O'Regan S, Danais S, Yazbeck S. Postransplantation complications of lower limb polytetrafluoroethylene grafts in children. Nephron. 1989;52:90–2.
35. Conlon P, Nicholson M, Schwab SJ. Hemodialysis vascular access: practice and problems. New York: Oxford University Press; 2000.
36. Wilson S. Vascular access: principles and practice. 3rd ed. St. Louis: Mosby; 1996.
37. Chand DH, Poe SA, Strife CF. Venous pressure monitoring does not accurately predict access failure in children. Pediatr Nephrol. 2002;17(9):765–9.
38. May RE, Himmelfarb J, Yenicesu M, et al. Predictive measures of vascular access thrombosis: a prospective study. Kidney Int. 1997;52:1656–62.
39. Goldstein SL, Smith CM, Currier H. Noninvasive interventions to decrease hospitalization and associated costs for pediatric patients receiving hemodialysis. J Am Soc Nephrol. 2003;14:2127–31.
40. 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.
41. 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.
42. Richard 3rd HM, 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.
43. Ouwendyk M, Helferty M. Central venous catheter management: how to prevent complications. ANNA J. 1996;23(6):578–9.
44. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. Pediatr Nephrol. 1997;11:74–7.
45. Valentini RP, Geary DF, Chand DH. Central venous lines for chronic hemodialysis: survey of the Midwest pediatric nephrology consortium. Pediatr Nephrol. 2008;23(2):291–5.

Technical Aspects of Hemodialysis in Children

17

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Keywords
Hemodialysis • Children • Technical aspects • Bleeding • Thrombosis and anticoagulation

A hemodialysis system consists of a *blood circuit*, a *dialysate circuit*, and a *dialyzer* separating both circuits by a semipermeable filter membrane. The *blood circuit* includes a vascular access device, blood tubes (arterial and venous lines), one or two blood pumps, pressure and air-leak monitors, and security clamps. A separate pump delivers anticoagulants to prevent clotting in the arterial site of the extracorporeal blood circuit. The *dialysate circuit* requires at least one or two dialysis fluid pumps, and systems for ultrafiltration control and heating of the dialysis fluid. The composition of the dialysis fluid, the flow rates and pressures, and the presence of blood in the dialysate are continuously monitored. Most devices designed for routine maintenance hemodialysis provide water purification, degassing, and preparation of the dialysate from purified water and electrolyte/buffer concentrates. The dialyzer as the central component of the hemodialysis system consists of a semipermeable filter membrane to remove metabolic waste products, electrolytes, and excess of water.

The Extracorporeal Blood Circuit

Blood is pumped from the vascular access to the dialyzer (often called "arterial segment"). The dialyzed blood is recirculated to the patient, passing an air trap. The segment between dialyzer and patient is usually called "venous segment." Pressures in the blood line are usually monitored between the arterial blood pump and the dialyzer and at the venous air trap. Security clamps are located at the beginning of the arterial segment and at the outlet of the venous air trap (Fig. 17.1). Whenever any alarm is activated, the blood pump is stopped immediately and both blood lines are clamped to protect the patient.

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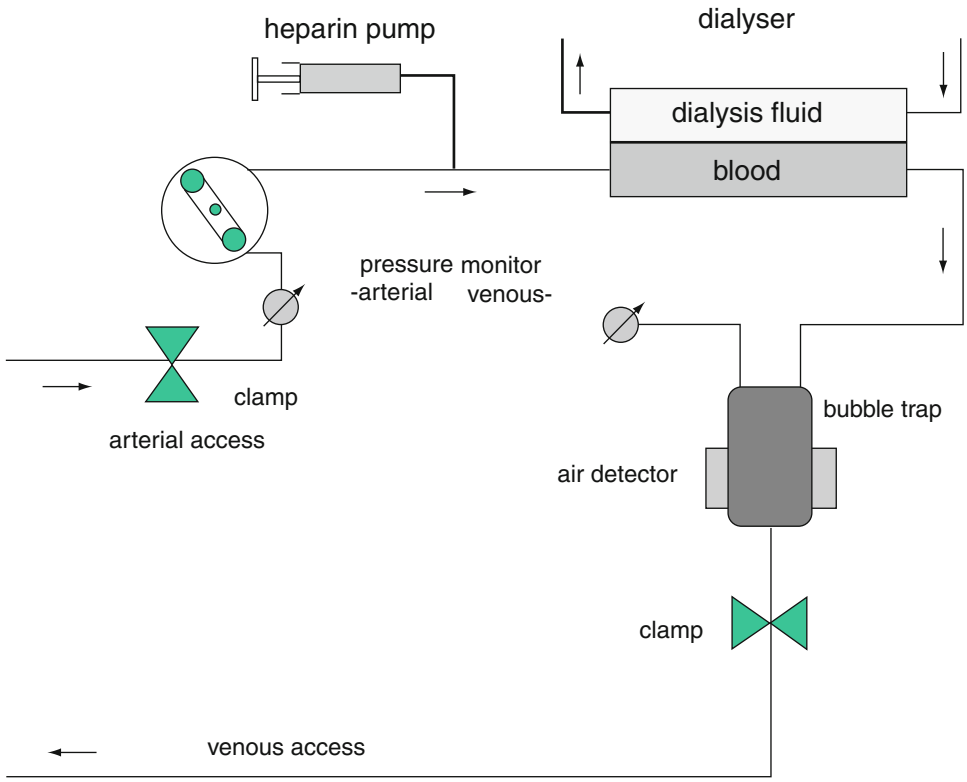


Fig. 17.1 Blood circuit

Blood Tubing

Blood tubing systems adapted to the dimensions of the dialysis machine are usually supplied by the manufacturer. The tubing is mainly made of polyvinylchloride and polycarbonate. Steam sterilization is favored over ethylene oxide, which may induce antibody formation and anaphylactoid reactions. To permit hemodialysis in small children and infants, tubing systems with reduced diameters and fill volumes (approx. 50–80 mL versus 150 mL in adult size systems) are provided by several manufacturers. As a rule of thumb, the total extracorporeal blood volume (needles, tubes, and dialyzer) should not exceed 10% of total patient blood volume.

Blood Pump

A compressible segment of the arterial line is inserted into a peristaltic roller blood pump. 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 is stopped. Thus, when blood flow is stopped, the rotor in the arterial line segment acts as an arterial clamp. The occlusion between rollers and roller track must be adjusted carefully: Inadequate occlusion results in back flow, foaming, and hemolysis, while overocclusion may lead to damage of the tubing resulting in spallation of silicone particles, tube rupture, or

increased hemolysis. In case of high outflow pressures, the rollers will be lifted and backflow may occur, because the rollers no longer completely occlude the pump segment. A characteristic smacking noise arises when the pump is operating against a low inflow and a high outflow pressure.

Blood Flow

The blood flow rate (Q_b) and the duration of dialysis are important factors in determining treatment efficiency. Blood flow rates are calculated 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.

Pressure

Line pressures are primarily measured for safety reasons. Sudden changes exceeding the allowable limits will trigger an alarm, stop the blood pump, and close the venous clamp. Pressure monitoring in the blood circuit allows detection of disconnections and obstructions caused by tube kinking or blood clotting. Pressures in the extracorporeal circulation 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 the blood pump is always positive. The arterial, venous, and dialysis fluid pressures are used to calculate the transmembranous 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 intraaccess 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 [1, 2], 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 [3].

Air Traps

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. Many different physical principles have been employed; probably the most reliable are ultrasonic devices measuring changes of ultrasound transmittance caused by air bubbles or foam. If foam or air is detected, the blood pump will be stopped and the tubes will be clamped immediately downstream of the air trap. The change in pressures and the action of the blood pump may lead to the formation of microbubbles. These may cause platelet activation and formation of microemboli.

Single-Needle Dialysis

In case of a single vascular access due to technical circumstances (for example, single lumen catheter or difficulties during puncture of an arteriovenous fistula), single-needle dialysis can be performed. The principle is based on alternating 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. The alternation of blood flow can be achieved in different ways. One system uses two clamps at both arterial and venous lines. When the arterial clamp is open, blood is pumped 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 is closed, the blood pump stopped and the venous clamp opened, allowing the blood to flow back to the patient. When the pressure reaches a lower limit, the venous clamp is closed, the arterial clamp opened and the blood pump started again. The efficacy of single-needle circuits can be optimized by using two separate pumps for arterial blood withdrawal and venous return. During single-needle dialysis, the compliance of the blood circuit must be enhanced by an arterial bubble trap between pump and dialyzer serving as expansion chamber. Recirculation of blood in the Y connection can reach 20% of total blood flow, diminishing solute clearance.

Bleeding, Thrombosis, and Anticoagulation

Patients on hemodialysis are at increased risk for both bleeding and thrombosis. The main factors predisposing to bleeding are uremia-associated defective platelet dysfunction, tissue inflammation (gastrointestinal tract, pericardium), and the use of anticoagulants for hemodialysis. While in children on chronic hemodialysis bleeding is a minor problem, bleeding is a frequent and life-threatening complication in acute kidney injury. Hemorrhagic complications seem to be a predictive rather than a causative factor for mortality [4].

Endogenous arteriovenous fistulas, synthetic arteriovenous grafts, and permanent venous catheters for hemodialysis access are at risk of recurrent thrombosis. All patients on hemodialysis should be tested for underlying thrombophilic conditions. The subclavian hemodialysis access is more prone to thrombotic and stenotic complications than the internal jugular access [5, 6].

Factors potentiating the risk for thrombosis include a high hematocrit (often related to dehydration, high doses of erythropoietin, vigorous ultrafiltration, slowed or interrupted blood flow, blood transfusion upstream the dialyzer and a low dialysate pH. It is important to monitor the anticoagulant status using appropriate tests before and during anticoagulation. Notably, the first signs of clotting occur much more frequently in the air trap than in the dialyzer itself [7].

Contact of blood with tubing material and dialyzer membranes activates two principal mechanisms of thrombus formation: The intrinsic coagulation pathway starts with contact activation factors and leads to the production of thrombin and the formation of cross-linked fibrin clots via an amplifying series of enzymatic reactions. The second mechanism is platelet adhesion and activation which on dialyzer membranes appears not to require von Willebrand factor (vWF) [8].

Anticoagulation is required to prevent clotting for the majority of procedures with extracorporeal circulation. The type and configuration of the extracorporeal blood circuit has implications for the choice and the use of anticoagulants: A patient on intermittent hemodialysis needs only anticoagulants to prevent filter clotting for around 4 h. In continuous venovenous procedures the need for and potential risks of anticoagulants are continuously present. Furthermore, slower blood flow rates and inferior geometry of the blood flow path require more efficient anticoagulation during continuous therapies.

Heparin

Heparin, a heterogeneous mixture of acidic glycosaminoglycans ranging in molecular weight from 3,000 to 60,000 Da, accelerates the formation of molecular complexes between antithrombin III and coagulation factors such as factor Xa and thrombin, enhancing their inactivation. Due to

its convenience and low cost, heparin is the most widely used anticoagulant. Dose requirements show marked interpatient and intrapatient variability, though the clearance and average dosage of unfractionated heparin are not much altered by renal failure [9]. Besides the rare but severe complication of heparin-induced thrombocytopenia (HIT), patients receiving heparin for anticoagulation on dialysis are at increased risk of hyperlipidemia, osteoporosis, and aldosterone suppression.

Heparin coating: Before use, the dialysis system should be flushed with at least 1 L of physiologic saline solution at a flow rate of approximately 100 mL/min to remove any toxic contaminants. To reduce the thrombogenicity of the dialysis system, heparin (5,000 IU/L) or low molecular weight heparin is added to the flushing solution. After heparin coating, the system is rinsed with an equal volume of anticoagulant-free saline solution.

Standard heparin anticoagulation: In children, heparin is typically administered as an initial bolus of 300–1000 IU/m² body surface area (resp. 20–50 IE/kg/h) before connection to the extracorporeal circuit, followed by continuous infusion of 300–800 IU/m²/h (resp. 10–20(–30) IE/kg/h) during hemodialysis. The heparin infusion is discontinued 30–60 min before the end of dialysis in order to avoid excessive delay in obtaining hemostasis after the needles are withdrawn. When an indwelling vascular catheter is used, heparin infusion should be continued until the end of dialysis.

Monitoring of heparin anticoagulation: The whole blood activated clotting time (ACT) is widely used for bedside monitoring of anticoagulation during hemodialysis. To determine the ACT, an activator of surface contact factors such as kaolin (diatomaceous earth) or glass particles is added to accelerate the initial stages of the coagulation cascade tenfold (normal ranges vary for different methods). The target ACT during hemodialysis is about 1.5–2 times the baseline value, typically corresponding to 120–140(–160) s [10]. Alternatively, the whole blood activated partial thromboplastin time (aPTT) could be measured which is based on the same principle with a platelet lipid surrogate added as additional activator. However, the aPTT is unsuitable at this level of heparinization as it is frequently prolonged beyond the measurable range (120–160 s).

Low Molecular Weight (LMW) Heparin

Low molecular weight heparins (3,000–7,000 Da) are heparin derivatives produced by fractionation or depolymerization which primarily inhibit factor Xa. The LMW heparins have half-lives about twice that of unfractionated heparin (2–4 h), which is even more prolonged in renal failure [11]. Most dialysis protocols apply LMW heparin by a single injection at the start of dialysis, few report on giving half the dose initially, and the rest by continuous infusion. Different LMW heparins have been used for HD in adults:

- Enoxaparin (Lovonox, Clexane) 0.68 mg/kg [12]
- Dalteparin (Fragmin) 70 IU/kg [13]
- Nadroparin (Fraxiparine) 70 IU/kg [14]; 150–200 IU/kg [15]
- Reviparin (Clivarin) 85 IU/kg [19]

The overall safety of LMW heparin is comparable to low-dose heparin [16–18]. Standard bedside tests for anticoagulation monitoring are not sensitive enough to control LMW heparin action [19, 20]. Therapeutic monitoring is achieved by checking anti-factor Xa activity, which should be between 0.4 and 0.8 IU/mL 2 h after initial loading [21].

Common side effects of standard heparin anticoagulation, such as hair loss or pruritus, may be reduced by LMW heparin treatment [11]. Lower activation of endothelial lipoprotein lipase may improve lipid metabolism in dialysis patients treated with LMW heparin [22]. The major disadvantage of LMW compared to standard heparin is its higher price.

Direct thrombin inhibitors inhibit thrombin formation, the final step of the coagulation cascade. Thrombin inhibitors are alternative anticoagulants if native or LMW heparin provides inefficient anticoagulation or cause major side effects (most notably heparin induced thrombocytopenia). Thrombin inhibitors are capable of inhibiting clot formation even in patients with mutations

of the prothrombin gene, which lead to heparin-resistant hypercoagulability.

Lepirudin (recombinant hirudin): Hirudin, an anticoagulant originally isolated from the saliva of the medical leech (*Hirudo medicinalis*), is available as a recombinant peptide (lepirudin). Due to its primarily renal route of elimination, dose adjustment to renal function is required. For anticoagulation in hemodialysis, lepirudin is given at a dose of approximately 0.1 (0.08–0.17) mg/kg body weight at the beginning of the dialysis session. Continuous application is not necessary. Due to its long half-life in end-stage renal disease, lepirudin administration with hemodialysis sessions provides effective anticoagulation in the interdialytic interval. The authors have made excellent pilot experience with lepirudin anticoagulation in patients with recurrent fistula clotting, The dose is adjusted to aim at hirudin levels of 0.2–0.5 μg/mL pre-dialysis and 0.8–1.6 μg/mL post-dialysis. Hirudin levels are calculated from the ecarin clotting time. ACT provides only a crude monitoring of hirudin anticoagulation. In case of overdosing, lepirudin can only be eliminated by hemodialysis using a high-flux membrane.

Argatroban is a synthetic direct thrombin inhibitor that binds reversibly to the thrombin enzymatic site. Half-life is 46 min in normal subjects and elimination occurs primarily by hepatic metabolism. Recommended dosing protocols for hemodialysis include a loading dose of 0.1 mg/kg BW followed by continuous infusion of 0.1–0.2 mg/kg BW × h [23], or continuous infusion of 0.12 mg/kg/h without a priming dose. Combined hepatic and renal failure necessitates dose reduction to 0.03 mg/kg/h [24]. The degree of anticoagulation can be monitored readily using the aPTT, with a target between 1.5 and 3.0 times the normal reference values.

Danaparoid (Orgaran), a heparinoid, consists of a mixture of three non-heparin glycosaminoglycans of low molecular weight. Its use has been discontinued in the USA but it is still available in European countries. Since danaparoid does not cause platelet activation, it is used for dialysis in heparin-induced thrombocytopenia.

In patients with intercurrent hemorrhage or after surgery, the bleeding risk associated with hemodialysis can be reduced by several therapeutic principles:

Low-dose heparinization: Minimal heparinization means the administration of about 50% of the usual heparin dose [25, 26]. In patient at high risk of bleeding it is advisable to perform a pre-dialysis ACT. If it is more than 1.2 times the upper limit of normal, no heparin should be given (see below). Otherwise the ACT should be kept at only 1.5 times normal.

Anticoagulant-free dialysis: This method requires high blood flow rates and intermittent flushing of the hemodialyzer with 100–200 mL of isotonic saline every 15–30 min. If pre-dialysis ACT is already high, even the standard circuit priming with heparinized saline should be avoided. When clotting is detected, the whole extracorporeal system should be exchanged prophylactically [27]. Ultrafiltration rate needs to be adjusted for the large volume load administered.

Regional Citrate Anticoagulation

Citrate chelates calcium, which is a necessary cofactor for many steps of the coagulation cascade. Sodium citrate solution (e.g., ACD-A, Baxter: Trisodium citrate, 22 g/L; citric acid, 8 g/L; glucose, 24.5 g/L) is infused into the arterial blood line (initial infusion rate (mL/h) = 2* blood flow rate (mL/min)) to bind ionized calcium in order to inhibit the coagulation cascade. The infusion site should be close to the arterial access using a powerful pump to prevent backflow (Fig. 17.2). Ionized calcium concentration in the extracorporeal circuit (measured post-filter) should be lowered to 0.2–0.3 mmol/L. The dialysate fluid should be calcium-free; CVVH substitution fluid may contain calcium if used in post-dilution mode. To restore and maintain normal systemic ionized calcium levels (1.0–1.3 mmol/L), calcium gluconate 10% (0.23 mmol/L) should be administered at an infusion rate in mL/h equaling 25% of the blood flow rate in mL/min). If possible, calcium should be

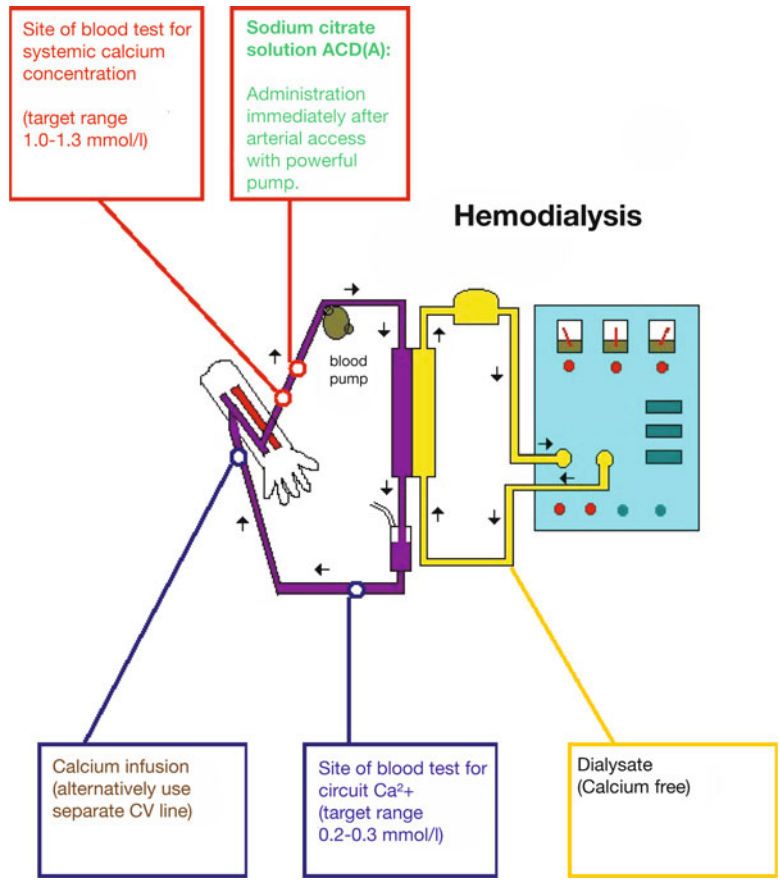


Fig. 17.2 Regional citrate anticoagulation

infused via a separate central line rather than into the venous line of the dialysis circuit in order to avoid clotting in the distal venous segment of the system. Monitoring of patient and circuit calcium levels should be performed every 20 min after starting or changing an infusion rate. Intervals can be extended to 1–2 h as soon as stable levels are achieved. Circuit calcium is regulated by changing the citrate, patient calcium by changing the calcium infusion rate in 20% steps if measured levels fall outside the therapeutic range. Ultrafiltration rates must be continuously adjusted for the amount of fluid administered with the citrate and calcium infusions. The latest generations of acute dialysis devices comprise an integrated citrate pump which synchronizes ultrafiltration to changes in citrate infusion rate. Regional anticoagulation requires frequent monitoring of ionized and total serum calcium, sodium, and acid–base status [28–30]. Citrate is metabolized to bicarbonate in the liver. During citrate degradation, bound calcium is released into the circulation. The metabolism of excess trisodium citrate to sodium bicarbonate can lead to hypernatremia and alkalosis with consequent systemic ionized hypocalcemia. In patients with compromised liver function, inadequate citrate metabolization may lead to metabolic acidosis and high total serum calcium despite low ionized calcium ("calcium lock"). If these potential risks are taken into account regional citrate anticoagulation is a safe and effective procedure, which has replaced heparin as the anticoagulation method of first choice in many adult and pediatric units during the past decade.

Luminal Anticoagulation

In patients with hypercoagulability, instillation of heparin into the catheter after each usage may be not be sufficient to maintain patency. Regular instillation of urokinase or tissue plasminogen

activator (t-PA) every fortnight, is helpful to prevent catheter clotting. Clotted catheters can be opened by Urokinase (5,000 IE/mL) or by t-PA (1 mg/mL) [31]. Citrate has become a popular alternative as a catheter locking agent potentially preventing both catheter clotting and infection. A comparative prospective study of low-dose citrate versus heparin lock in permanent dialysis catheters showed significantly more common clot formation in the citrate group but no differences in the need for urokinase, complete catheter obstruction, or local infection [32]. A 5% citrate lock is equally efficient in preventing catheter dysfunction as a 10% citrate lock [33]. A novel antimicrobial/antithrombotic catheter lock solution has recently been developed (citrate/methylene blue/parabens) [34], but clinical experience especially in the pediatric population is still limited.

Dialysate Circuit

For optimal blood purification, the ratio between dialysis fluid and blood flow rates should be at least 1.5–2. Higher dialysate flow rates achieve only little additional benefit, while lower flow rates result in reduced total clearance rates. A schematic drawing of the dialysis fluid circuit is shown in Fig. 17.3. Most dialysis machines work with a fixed dialysate flow rate of 500 mL/min, requiring 120 L of dialysate during a standard 4 h dialysis session. This huge amount of dialysis fluid is prepared by dilution of concentrated electrolyte and buffer solutions with purified tap water. The dialysate temperature is continuously monitored and kept constant to prevent hypo- or hyperthermic episodes. Degassing

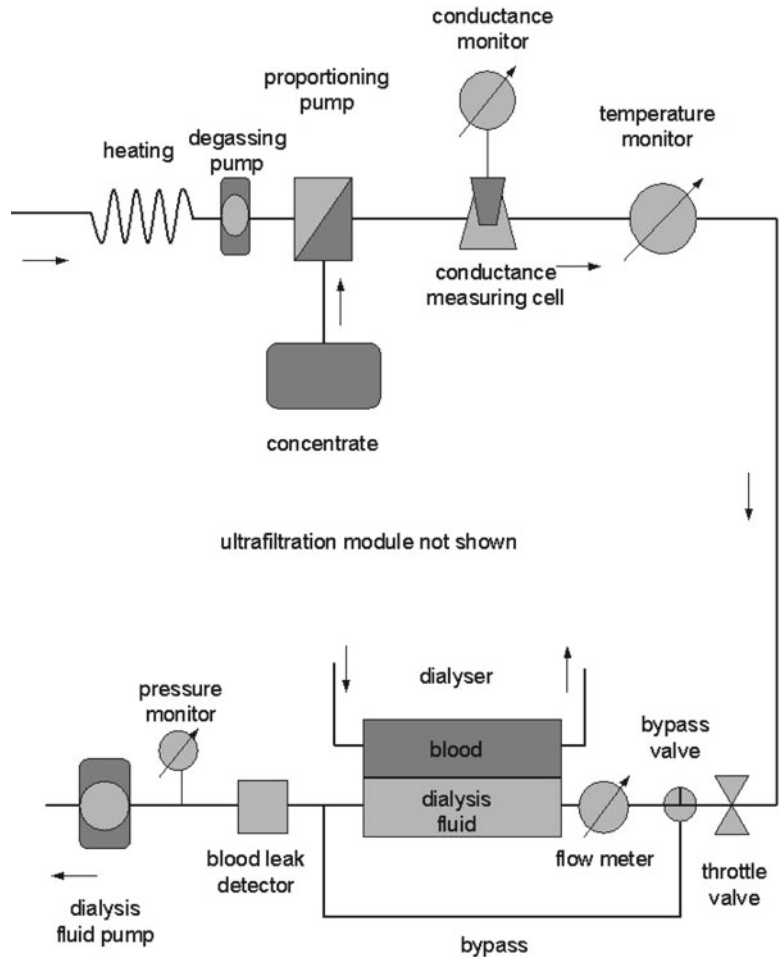


Fig. 17.3 Dialysis fluid circuit

of the dialysis fluid is necessary to prevent formation of gas bubbles at the surface of the dialyzer membrane, which would result in a reduced dialysis efficiency. Furthermore, an ultrafiltration control system permits the removal of the desired amount of water from the patient's blood.

Water Purification

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. Thus the quality of dialysis water is strictly defined by regulatory agencies and regulations are more stringent than those for drinking water. Furthermore, additional purification is essential. A standard water treatment device consists of a water softener, an activated carbon filter, a sediment filter, and a reverse osmosis system [35]. 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 the hard water syndrome, but also protects the reverse osmosis membrane which is used in the final step of water treatment from the buildup 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 particular 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 production of an ultrapure dialysate which is sterile and endotoxin-free allows to perform **'online' hemodiafiltration**. Dialysis machines of the latest generation can filter the dialysate through a high-flux membrane, thereby further increasing microbiological purity and generating fluid which can be infused as substitution fluid.

Quality control of the water for dialysis should be performed at least once per year with respect to its chemical composition. Weekly checks must be applied for bacterial and endotoxin contamination when high-flux membranes are used.

Dialysate Composition

Dialysis fluid is typically prepared by diluting a fluid concentrate with warm degassed, ultrapure water. The dialysate is an isoosmolar solution containing electrolytes, buffers, and often glucose (Table 17.1) [36]. Some dialysis machines which are specifically designed for extracorporeal blood purification in infants use dialysis fluid in ready-made plastic bags. They do not require water purification or degassing.

The most widely used *buffer* in dialysis fluids is sodium bicarbonate. The simultaneous delivery of bicarbonate and together with calcium causes technical difficulties, as both components cannot be maintained in a stable solution. While acetate dialysis requires only single fluid concentrate or solid-phase salt mixture, bicarbonate requires two types of concentrates or solid-phase salt mixtures. The A component (color-coded red) is also termed the acid (a) component, as it usually contains small amounts of acetic acid (pH around 3.4). The B component (color-coded blue) is also termed the base (b) component, as it contains the bicarbonate (pH around 7.8) and is added separately by a second proportioning pump. Dry salt mixtures were first developed for the B component used for bicarbonate dialysis in the form of cartridges or bags, as liquid bicarbonate concentrate is an excellent bacterial growth medium [37]. A saturated bicarbonate solution is produced during the dialysis session by passing warm degassed water through the cartridge [38]. Because of its liquid (acetic acid) and hygroscopic (KCl, $MgCl_2$) components, the A component has been split into a solid component (containing crystalline NaCl) and a fluid component (containing acetic acid,

Table 17.1 Composition of extracellular fluid and standard dialysis fluid solutions

Component	Bicarbonate-based (mmol/L)	Acetate-based (mmol/L)	Plasma (mmol/L)	Ultrafiltrate (mmol/L)
Na^+	137–144	132–145	142	145
K^+	0–4	0–4	4.3	4.4
Ca^{++}	1.25–2.0	1.5–2.0	1.3	1.25
Mg^{++}	0.25–1	0.5–1.0	0.7	0.7
Cl^-	98–112	99–110	104	118
HCO_3^-	27–38	–	24	27.5
CH_3COO^-	2.5–10	31–45	<0.1	<0.1
Glucose	0–11	0–11	4.5	4.8

Source: Adapted from Schneditz D

KCl, and the divalent electrolytes ± glucose). This separation opens the possibility to adjust the concentration of sodium and the other electrolytes separately.

The dialysis fluid is prepared during the dialysis session to minimize bacterial growth. Dialysate can be provided by two systems: the batch system and the single-pass system. In the batch system, a given dialysate volume of up to 100 L is circulated through the dialyzer and returned to the reservoir. It has 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 and risk of bacterial contamination, the batch systems have been largely replaced by single-pass systems. However, the closed batch system has found a revival in the Genius system (Fresenius Medical Care, Bad Homburg, Germany), which operates with much reduced technology. In this mobile system fresh dialysis fluid is taken from the top, and spent dialysate delivered to the bottom part of a 90 L glass tank. The configuration of the system, utilizing the density differences of fresh and used dialysate, largely avoids any mixing of the fluids.

In the single-pass systems, the continuous production of dialysate is achieved by proportioning systems that exactly measure the required amounts of concentrates to be mixed with water. This system has certain advantages when it comes to the delivery of high-efficiency dialysis. 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 and a bypass valve will be activated to prevent contact of this dialysis fluid with the patient's blood. 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; e.g., the decrease of K^+ concentration during dialysis will cause parallel drop in effluent dialysate conductivity.

A dialysate sodium concentration of 138–140 mmol/L is appropriate for most patients [39] since most of the sodium load ingested in the interdialytic interval is removed by ultrafiltration (ultrafiltrate sodium concentrations are usually 5–10 mmol/L below the respective plasma concentrations [40]). Sodium concentrations above 145 mmol/L lead to increased thirst and fluid intake between dialysis sessions. Sodium concentrations below 138 mmol/L may increase the incidence of hypotensive episodes and muscle cramps during the dialysis session.

The dialysate *potassium* concentration is usually 2 mmol/L and can be adjusted to 1 mmol/L in patients with severe hyperkalemia and to 3–4 mmol/L in those with normal predialysis potassium concentrations.

The standard dialysate *calcium* concentration should be 1.25–1.5 mmol/L unless there is substantial hypo- or hypercalcemia. Administration of calcitriol and/or calcium containing phosphate binders can induce hypercalcemia [41]. In these patients, dialysate calcium should be reduced to

0.75–1.25 mmol/L [42–44]. 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 [45, 46].

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 in order to achieve postdialysis serum bicarbonate concentrations of 26–28 mmol/L [47–49]. Slightly higher concentrations may be used in patients with persistent metabolic acidosis but caution is indicated at concentrations exceeding 35 mmol/L since decreasing serum ionized calcium levels may lead to impaired vascular tone and cardiac contractility [50]. A rapid pH increase may be associated with the development of hypokalemia, probably with associated cardiac arrhythmia [51].

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.

Water degassing is necessary to prevent the formation of gas bubbles at the surface of the dialysis membrane. Degassing is achieved either by applying negative pressure or heating in the degassing module of the dialysis machine.

After mixing and degassing, the dialysis fluid is heated. The t*emperature* 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 [52]. Lower dialysate temperatures are also associated with a lower incidence of hypotensive episodes [53, 54].

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.

Prophylaxis of Microbial Contamination and Disinfection

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 occurs 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 formaldehyde, peracetic acid, or other disinfectants. 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 2,000 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 slimeforming bacteria and decalcification. Disinfection can be performed by thermic, chemical, or combined procedures. Thermochemical disinfection with hot citric acid permits simultaneous decalcification.

Dialyzer/Filter

The dialyzer is the key component of the hemodialysis system where blood purification occurs, but the manner in which the membrane interacts with other components of the dialyzer is important for its efficacy. Blood and dialysis fluid pass the dialyzer in countercurrent direction, separated by a semipermeable membrane. Dialysis filter membranes are characterized by material and physical characteristics (clearance, sieving coefficient, ultrafiltration coefficient) as well as by surface and fill volume which are especially important in pediatric hemodialysis (Table 17.2). For optimal efficacy, the filters are designed to minimize diffusion distances by maximizing the ratio of membrane surface to blood volume; the membrane surface area should approximately match the body surface area of the patient. Dialyzers containing hollow-fiber membranes are now used almost exclusively for hemodialysis in children. The high blood-compartment resistance of hollow-fiber membranes enhances the efficiency of therapy because high blood flow rates can be achieved at acceptable axial (arterial-to-venous) pressure drops. Hollow fiber dialyzers consist of a bundle of capillaries potted at both ends into a plastic tubular housing with sealing material. Sealing materials may release solvents or ethylene oxide after gas sterilization, which may cause anaphylactic reactions.

Materials

Currently, two groups of membrane materials are used: Cellulose-based (unmodified and modified) and synthetic ones. Cellulose-based membranes are made of reconstituted cellulose and are relatively inexpensive. Cuprophan® has many hydroxyl residues which are involved in complement activation. In modified cellulosic membranes (for example, tertiary amine as substitution group, Hemophan®), some or all of the hydroxyl residues are esterified to reduce interaction with complement factors. The latter materials, however, lead to a higher activation of the coagulation cascade, making pre-rinsing with heparin advisable. Synthetic membranes are manufactured polymers classified as thermoplasts and made from polysulfone, polyamide, polyethersulfone, polyarylethersulfone/polyamid, or polymethylmethacrylate (PMMA), which show significantly lower complement activation due to protein adsorption. The large pore size and thick wall structure of these membranes allows the high ultrafiltration rates necessary in hemofiltration and high-flux hemodialysis to be achieved 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/polyamid). In the asymmetrical type, a very thin "skin" (about 1 μm) contacting the blood compartment lumen acts as the membrane's separative element with regard to solute removal. Many of synthetic polymers used in manufacturing the above membranes are hydrophobic and require the addition of a hydrophilic agent (PVP) to avoid excessive protein adsorption upon blood exposure.

Physical Characteristics of Hollow-Fiber Membranes

An individual hollow fiber can be viewed as a solid cylinder from which the central region has been removed (cored out) to form the blood compartment. 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. On the other hand according to the Hagen–Poiseuille equation a small decrease in the inner diameter induces a large increase in flow resistance and high axial pressure drop

Table 17.2 Selection of dialyzers suitable for use in pediatric patients

Company	Product	Surface (m^2)	Fill volume (mL)	UF coefficient (mL/h × mmHg)	Membrane material	Sterilization
High-flux dialyzers and hemofilters						
Fresenius	FX paed	0.2	18	7	Helixone® polysulfone	Steam
Baxter	Aquamax HF03	0.3	32	16	Polyethersulfone	ETO
Fresenius	FX 40	0.6	32	20	Helixone® polysulfone	Steam
Gambro	Polyflux 6H	0.6	52	33	Polyamix® (PAES/PVP/PA)	Steam
Fresenius	F40S	0.7	42	20	Polysulfone	Steam
Baxter	Aquamax HF07	0.7	54	33	Polyethersulfone	ETO
Fresenius	FX 50	1.0	53	33	Helixone® polysulfone	Steam
Baxter	Tricea 110G	1.1	65	25.2	Cellulose triacetate	Gamma
Fresenius	F50S	1.1	63	30	Polysulfone	Steam
Baxter	Xenium XPH110	1.1	69	59	Polynephron®polyethersulfone	Gamma
Baxter	AquamaxHF12	1.2	73	51	Polyethersulfone	ETO
Fresenius	F60S	1.3	82	40	Polysulfone	Steam
Baxter	Xenium XPH 130	1.3	83	64	Polynephron® polyethersulfone	Gamma
Fresenius	FX 60	1.4	74	46	Helixone® polysulfone	Steam
Gambro	Polyflux Revaclear	1.4	84	50	PAES/PVP	Steam
Gambro	Polyflux 140H	1.4	94	60	Polyamix® (PAES/PVP/PA)	Steam
Baxter	Tricea 150G	1.5	90	28.9	Cellulose triacetate	Gamma
Baxter	Xenium XPH150	1.5	93	67	Polynephron® polyethersulfone	Gamma
Fresenius	F70S	1.6	98	50	Polysulfone	Steam
Gambro	Polyflux 170H	1.7	115	70	Polyamix® (PAES/PVP/PA)	Steam
Baxter	Xenium XPH170	1.7	106	74	Polynephron® polyethersulfone	Gamma
Fresenius	F80S	1.8	110	55	Polysulfone	Steam
Fresenius	FX 80	1.8	95	59	Helixone® polysulfone	Steam
Gambro	Polyflux Revaclear MAX	1.8	100	60	PAES/PVP	Steam
Baxter	Tricea 190G	1.9	115	37	Cellulose triacetate	Gamma
Baxter	Xenium XPH190	1.9	115	76	Polynephron® polyethersulfone	Gamma
Baxter	Aquamax HF19	1.9	109	80	Polyethersulfone	ETO
Baxter	Tricea 210G	2.1	125	39	Cellulose triacetate	Gamma
Baxter	Xenium XPH210	2.1	128	82	Polynephron® polyethersulfone	Gamma
Gambro	Polyflux 210H	2.1	125	85	Polyamix® (PAES/PVP/PA)	Steam
Fresenius	FX 100	2.2	116	73	Helixone® polysulfone	Steam
Fresenius	HdF100S	2.4	138	60	Polysulfone	Steam
Low-flux dialyzers						
Fresenius	F3	0.4	28	1.7	Polysulfone	ETO
Fresenius	F4	0.7	42	2.8	Polysulfone	ETO
Fresenius	F4HPS	0.8	51	8	Polysulfone	Steam
Fresenius	FX 5	1.0	54	8	Helixone® polysulfone	Steam
Fresenius	F5HPS	1.0	63	10	Polysulfone	Steam
Fresenius	F5	1.0	63	4.0	Polysulfone	ETO
Baxter	XENIUM LF110	1.1	71	3.8	PUREMA polyethersulfone	Gamma
Fresenius	F6HPS	1.3	78	13	Polysulfone	Steam
Fresenius	F6	1.3	82	5.5	Polysulfone	ETO
Baxter	XENIUM LF130	1.3	79	5.4	PUREMA polyethersulfone	Gamma
Fresenius	FX 8	1.4	74	12	Helixone® polysulfone	Steam
Gambro	Polyflux 14L	1.4	81	10.0	Polyamix® (PAES/PVP/PA)	Steam
Baxter	XENIUM LF150	1.5	94	7.4	PUREMA polyethersulfone	Gamma

(continued)

Table 17.2 (continued)

Company	Product	Surface (m^2)	Fill volume (mL)	UF coefficient (mL/h × mmHg)	Membrane material	Sterilization
Fresenius	F7	1.6	98	6.4	Polysulfone	ETO
Fresenius	F7HPS	1.6	96	16	Polysulfone	Steam
Baxter	XENIUM LF170LF	1.7	102	8.8	PUREMA polyethersulfone	Gamma
Gambro	Polyflux 17L	1.7	104	12.5	Polyamix® (PAES/PVP/PA)	Steam
Fresenius	FX 10	1.8	95	14	Helixone® polysulfone	Steam
Fresenius	F8HPS	1.8	113	18	Polysulfone	Steam
Fresenius	F8	1.8	110	7.5	Polysulfone	ETO
Baxter	XENIUM LF190	1.9	116	9.8	PUREMA polyethersulfone	Gamma
Baxter	XENIUM LF210	2.1	126	12.0	PUREMA polyethersulfone	Gamma
Gambro	Polyflux 21L	2.1	123	15.0	Polyamix® (PAES/PVP/PA)	Steam
Fresenius	F10HPS	2.2	132	21	Polysulfone	Steam

PAES, polyarylethersulfone; *PVP*, polyvinylpyrrolidone; *PA*, polyamide

which requires a higher blood-flow rate. The total nominal membrane surface area, which should match approximately the body surface area of the patient, depends on the inner diameter, fiber length, and overall number of fibers (7,000–14,000). The latter two ones are adaptable to create dialyzers for children.

Several properties of HD membranes influence dialyzer performance: the number of pores per unit surface area, pore size, and TMP are the major determinants of plasma ultrafiltrate flow rate. For diffusive transport, membrane wall thickness and pore density (porosity) are additional important determinants. The sieving coefficient of a membrane is influenced by the membrane pore-size distribution [55]. A large number of relatively small pores (approximately 10 kDa) are typical for a high-efficiency membrane, while a membrane with a large number of relatively large pores (approximately 60 kDa) is typical for a high-flux membrane. On the other hand, a membrane with small number of pores and broad distribution of pore size is unfavorable from the perspective of both diffusive transport and sieving.

Dialyzer Performance Characteristics

The performance of dialyzers is characterized by clearance, sieving coefficient, and ultrafiltration coefficient. Although not precisely defined HD treatment efficiency is very closely related to a dialyzer's small solute-removal capabilities. Solute permeability is high if the membrane is thin, with numerous pores of large diameter. A convenient measure of water permeability (water flux) is the ultrafiltration coefficient (K_{UF}: mL/h × mmHg) of the dialyzer, which is defined as the volume of ultrafiltrate produced per hour per mmHg TMP, 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. According to their solute permeability, dialyzers are characterized as low-flux or high-flux dialyzers. High-flux dialyzers, mostly made of synthetic membranes, achieve ultrafiltration coefficients up to 60 mL/min × mmHg. They also have a higher molecular weight cutoff and greater convective permeability to molecules of 5–25 kDa, permitting higher middle molecule clearance.

Backfiltration

The hydrostatic pressure of both blood and dialysis fluid decreases during passage of the dialysis filter. Since blood and dialysis fluid pass the filter in countercurrent 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 dialyzer, the so-called backfiltration. This phenomenon is a routine occurrence during high-flux HD [56], but not in low-flux HD. Therefore, a high internal ultrafiltration rate may increase the convective transport of middle molecules [57, 58].

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.

The biological response during dialysis is believed to impact on long-term patient morbidity and survival and should be minimized. Dialyzers with synthetic membranes induce a much lower activation of complement factors than regenerated cellulose membranes [59]. The alternative complement pathway is activated by blood contact with a dialyzer. 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 [60, 61].

Activation of circulating mononuclear cells by complement and bacterial endotoxins can induce the production of cytokines [62]. 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 in hemodialyzed patients. It has been speculated that suppressing inflammation may be useful in treating an inflammatory-malnutrition syndrome in dialysis patients [63]. The biofilm generation due to protein adsorption of proteins at membranes results in a progressive loss of the diffusive and convective capacity of the membrane. 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 biomaterials. 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 [64]. This has led to severe clinical reactions in patients dialyzed with AN69 membranes who are treated with ACE inhibitors [65] and angiotensin II receptor antagonists [66].

Sterilization

To prevent allergic reactions against ethylene oxide, steam sterilized or gamma-irradiated dialysis tubing systems and filters should be used. All dialyzer filters are declared for single use by the manufacturer. However, the filter can be rinsed and disinfected after use, and reused in the same patient [67]. Based on the available experimental and clinical evidence, filter reuse cannot be recommended for pediatric hemodialysis patients.

Ultrafiltration Control

The control of ultrafiltration can be achieved by 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 which is automatically adjusted to the desired rate by the dialysis machine. In the closed loop system the dialysis fluid circulates in a closed circuit from which an ultrafiltration pump removes the desired fluid volume. The circulating dialysate is intermittently replaced by fresh dialysate. 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. Ultrafiltration is controlled by an additional pump removing fluid from this loop. Mobile machines measure the ultrafiltration rate gravimetrically by comparing the weights of bags filled with fresh and used dialysate.

In order to minimize the risk of dialysis-related hypovolemia, the net ultrafiltration rate should not exceed 1.5–2% of the respective dry weight per hour. In case of marked hypervolemia requiring a large amount of ultrafiltration, the sequential ultrafiltration technique according to Bergström (iso-ultrafiltration) is useful. In this technique, the treatment session is initiated by short period of isolated rapid ultrafiltration (e.g., 1% of dry weight per 15 min or 1.5% of dry weight per 30 min) without concomitant dialysis flow, followed by HD with the usual 1–2% ultrafiltration per hour.

Hemofiltration

The combination of diffusion process and convective mass transport leads to uremic toxin extraction in dialysis. Whereas in HD blood purification depends mostly on a diffusion process secondary to a concentration gradient and clearance correlates directly with blood flow rate, in hemofiltration clearance is achieved by convective mass transport secondary to a pressure gradient only [68]. The dialyzer is replaced by a hemofilter containing a high-flux membrane with an ultrafiltration coefficient of more than 15–60 mL/min/mmHg depending on membrane surface area. Up to 25–30% of the blood volume passing the hemofilter can be ultrafiltered; the ultrafiltration rate is limited by hematocrit and TMP (e.g., blood flow 200 mL/min and hematocrit of 35% → plasma water flow is 120 mL/min → maximum clearance to be attained by

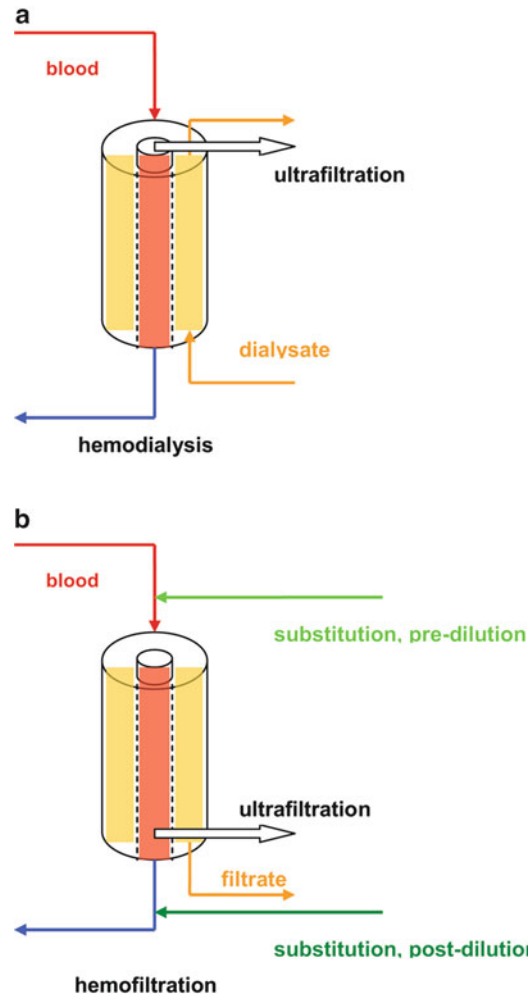


Fig. 17.4 Principles of hemodialysis, hemofiltration, and hemodiafiltration

hemofiltration at filter fraction of 25%: 30 mL/min). The ultrafiltrate containing urea, creatinine, and other waste products is substituted with an equal volume (less the desired fluid withdrawal) of bicarbonate buffered ringer solution or dialysis fluid introduced into either the arterial (predilution) or the venous line (postdilution) (Fig. 17.4). The filtration rate is measured gravimetrically, and fluid substitution is adjusted automatically to the filtration rate. The postdilution substitution mode is a compromise between substance withdrawal and amount of needed substitution resulting in a reduced clearance in the low molecular range. Predilution is helpful if blood flow is limited (rate of substation: in predilution: 30mL/KG/h, postdilution: 20mL/KG/h). The reduced

clearance due to dilution of the blood before filter can be compensated by using high amounts of filtrate and substitute. In postdilution mode the maximum filtrate flow rate is one third of blood flow to limit the risk of excessive hemoconcentration (i.e., blood flow rate should be minimum three times of filtrate flow rate). In the predilution mode, maximum filtrate flow rate should be two thirds of or equal to the blood flow rate.

Adequate hemofiltration requires an exchange volume of around 80–120% of total body water per treatment. Clinical advantages of hemofiltration over hemodialysis include better hemodynamic stability with less hypotensive episodes, and no exposure to dialysis fluid which may contain pyrogens [69]. Hemofiltration achieves a better middle-molecular clearance, whereas the diffusive clearance of small molecules is higher in hemodialysis.

The major drawback for chronic hemofiltration is this relatively low clearance which depends on the turnover rate of ultrafiltration and fluid substitution and is critically limited by hematocrit levels. In contrast to its rare use as chronic renal replacement therapy, hemofiltration is preferred over hemodialysis in patients with cardiovascular instability in the critical care setting.

Hemodiafiltration

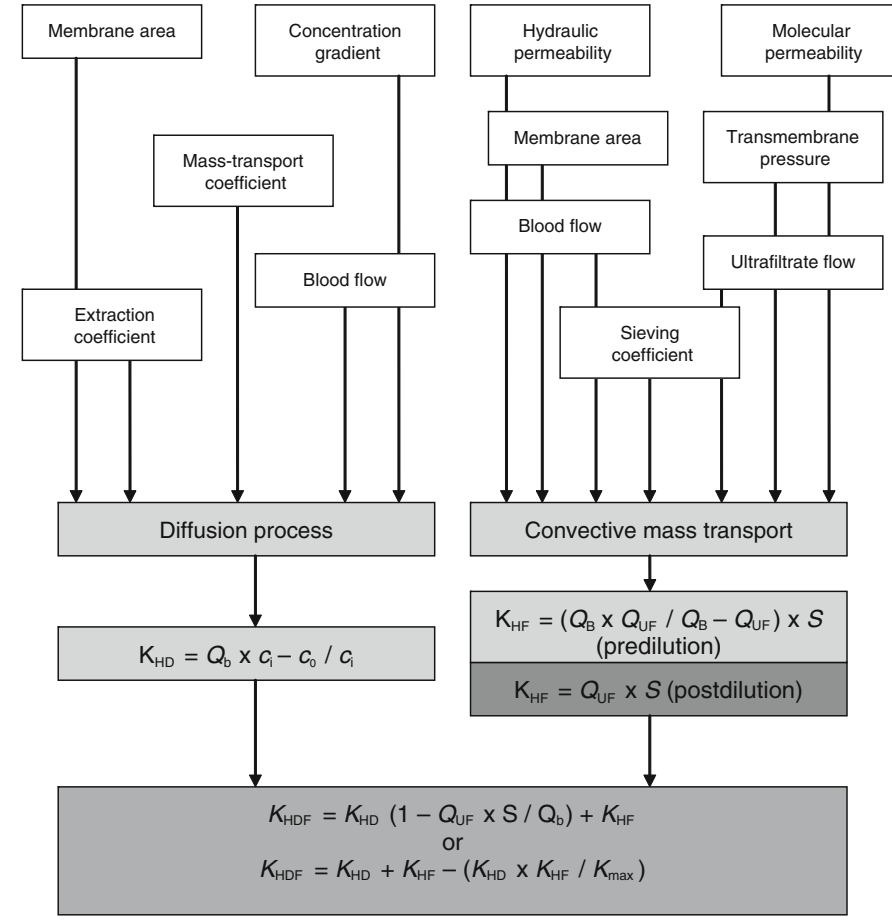
The advantages of high diffusive clearance rates in hemodialysis and the improved cardiovascular stability on hemofiltration have been combined in a hybrid system including both convective and diffusive clearance (Figs. 17.5 and 17.6) [70]. Indications for hemodiafiltration include frequent hypotensive episodes and excessive serum phosphate levels. Online production of substitution fluid by sterile ultrafiltration of dialysis solution has made HDF safer and helped to reduce treatment costs. HDF with high-flux membrane is as efficient as HD for low molecular weight compounds, but is more efficient than HF for low molecular weight compounds [71]. Online HDF, 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 [72].

Optimization of Therapy by Feedback Control

In recent years, several technological advances have made it possible to gain instantaneous information about the fluid and purification status during hemodialysis, providing the opportunity to adapt dialysis settings to ensure efficacy and patient well-being during the procedure. Historically, feedback control used to be limited to the measurement of body weight and blood pressure. The next step of development was *profiled hemodialysis*, which allows modeling of dialysate sodium concentration and ultrafiltration rate yet without any feedback regarding the patient fluid status. These continuous slopes or stepwise gradients of dialysate sodium concentration and ultrafiltration rate can be used separately or in combination. A priori sodium profiling is of limited efficacy in preventing hypotensive episodes as it works on the assumption of a uniform, predetermined vascular response to fluid withdrawal [73, 74]. Modern technology overcomes this concept by online monitoring of chemical and physical signals leading to biofeedback circuits, which allow to individualize treatment sessions according to the patient's actual physical status and ongoing treatment response.

Blood Volume Monitoring and Modeling

In HD, 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 between extra- and intravascular compartments (= vascular refilling) is limited by physiologic factors such as the hydraulic conductivity of the microvascular wall [75]. 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



K_{HD} = hemodialysis clearance
K_{HF} = hemofiltration clearance
K_{max} = maximum achieved clearance
Q_b = blood flow
Q_{UF} = ultrafiltrate flow
S = sieving coefficient = 2 c_{UF} / (c_i + c_0)
c_0 = inlet solute concentration
c_i = outlet solute concentration
$c_i - c_0 / c_i$ = extraction coefficient
c_{UF} = ultrafiltrate solute concentration

Fig. 17.5 Determinants of mass transport in hemodiafiltration (Adapted from Fischbach et al. [72])

reached symptomatic hypotension will occur [76]. To circumvent the need to measure absolute blood volume, the concept of relative blood volume (RBV) or hematocrit has been adopted. The physical principles of RBV measurement utilized in commercially available devices today are sound velocity (BVM, Fresenius Medical Care, Bad Homburg, Germany), and optical density (Crit Line III, Hemametrics, Kaysville, Utah; Hemoscan, Hospal-Dasco, Medolla, Italy).

In the ideal system with a constant ultrafiltration rate, the transition from over- to euhydration is associated with a blood-volume curve that is expected to be concave. Typically, the slope is steeply negative in the initial phase of the session and gradually flattens toward the end of dialysis.

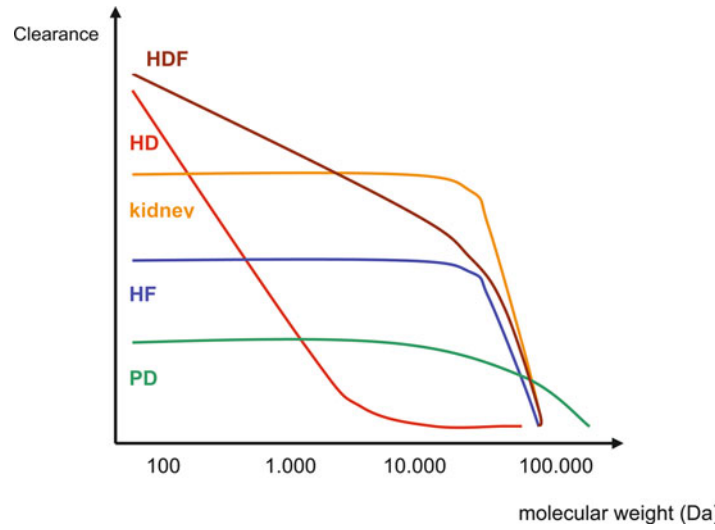


Fig. 17.6 Clearance profiles in different techniques

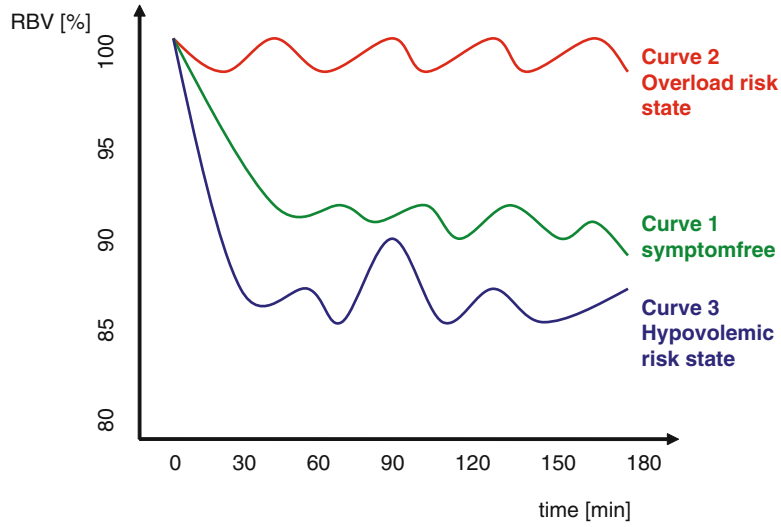


Fig. 17.7 Schematic curve shapes of relative blood volume (RBV) measured by blood volume monitoring (BVM). Three major curve shapes can be distinguished

A sudden steepening of the slope despite constant ultrafiltration indicates reduced vascular filling and an increased risk of intradialytic hypotension, whereas a lacking decrease of the RBV curve indicates persistent fluid overload (Fig. 17.7) [77].

A variety of feedback control algorithms with complex fuzzy logic controllers have been proposed. Whereas the Crit Line device is designed as a stand-alone monitor without automated feedback control options, Hemoscan (Hospal) and BVM (Fresenius Medical Care) are integrated into HD machines and can be used to modulate dialysate sodium and ultrafiltration rate according to the patient's blood volume response. Pediatric experience to date is limited to manual observational studies and manual feedback correction algorithms. The overall impression is that hypotensive events are strongly associated with the steepness of the RBV curve during the first treatment hour. Using the **BVM** system in a large number of hemodialysis sessions in children, Hothi et al. defined critical RBV thresholds associated with hypotensive complications. These were 88% at the end of the first hour, 84% at the end of the second hour, and 82% at the end of the third hour. In contrast, RBV values at the end of

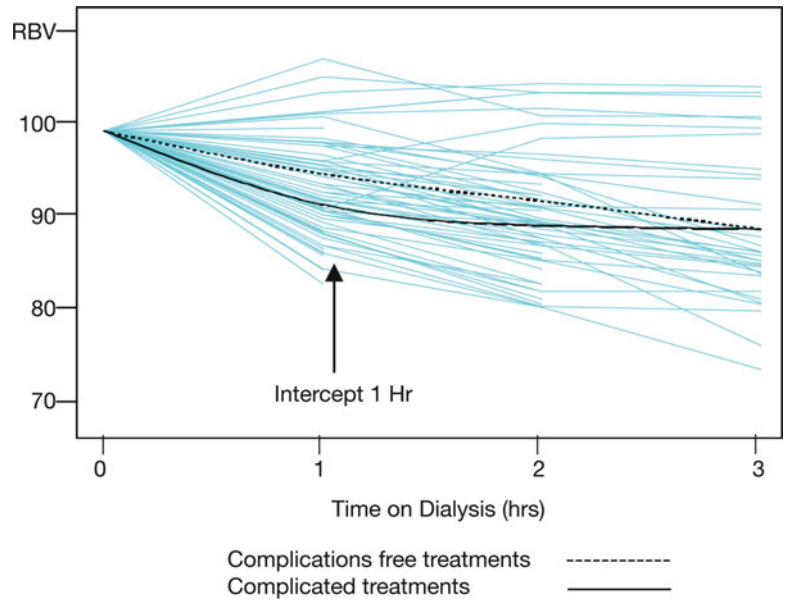


Fig. 17.8 Individual relative blood volume (RBV) curves with group trends for treatments with and without complications. The arrow indicates the dialysis time intercept of 1 h. Seventy four blood volume protocols were analyzed retrospectively with respect to complications (defined as hypotension and/or intradialytic events requiring nurse intervention). Treatments with complications were associated with steeper decline of the RBV curve at the end of the first hour, but not with final RBV measurement. ROC curves presented RBV cutoff thresholds of 88% at end of the first hour of dialysis (From Hothi et al. [78]: original picture (permission is needed))

the fourth treatment hour were not correlated with intradialytic hypotension (Fig. 17.8) [78]. For the **Crit Line**, pediatric validation studies targeted the first 50% of the total ultrafiltration goal to be removed during the first hour of dialysis with a maximum blood volume change of 8–12% in the first hour, and the second half to be removed during the remaining treatment time with a maximum blood volume change of 5% per hour subsequently [79]. After 6 months of treatment with this algorithm, ultrafiltration-associated symptoms and the burden of antihypertensive medication had decreased substantially.

Regarding automated feedback control circuits, the **Hospal system** controls the trajectory of RBV changes by adjusting dialysate composition and ultrafiltration rate. Controlled fluid removal is achieved by target definitions for weight reduction, blood volume change, and dialysate conductivity based on the effects of sodium concentration on extracellular volume. The **Fresenius BVM system** allows to define a critical relative blood volume (RBV_{crit}) and responds by adapting ultrafiltration rates. The feedback loop system continuously adapts ultrafiltration according to the following rules: (1) total volume must be removed within predefined treatment time, (2) initial UF rate is set at twice the constant UF rate, and (3) whenever RBV drops by more than 50% of the distance between the current (= 100%) and the critical RBV threshold, the UF rate is linearly decreased. The BVM module can be operated in combination with the Fresenius BTM system to optimize intradialytic cardiovascular stability (see below).

Ionic Dialysance Monitoring

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 [80, 81]. Based on the observation that dialysance of ionized sodium is almost identical to urea clearance and that dialysate conductivity over the

range of clinical conductivities (12–18 S/cm) is a fairly linear function of dialysate sodium, online conductivity measurements have been included in several latest-generation dialysis machines to determine a surrogate for urea clearance without need for additional equipment or blood sampling (Diascan Quality Control Monitor, Gambro Renal Products, Lakewood, Colorado; On-line clearance monitoring (OCM) for 4,008 S and 5,008, Fresenius Medical Care, Bad Homburg, Germany). To determine the current clearance the sodium concentration at the dialysate inlet is enhanced for 2 min and changes in conductivity are measured at the dialysate outlet. The monitor shows *K* over treatment time, so *Kt* is equivalent to the amount of blood which is purified since starting of the session. To complete the *Kt/V* urea index obtained from urea kinetic modeling, the volume of urea distribution (*V*, = total body water) must be given. *V* can be measured by bioimpedance analysis or formal urea kinetic modeling, or predicted from height and weight. The following anthropometric TBW prediction equations have been validated for children [82]:

$$\text{Boys: } \text{TBW} = 0.1 \times (\text{Height} * \text{Weight})^{0.68} - 0.37 \times \text{weight}$$
$$\text{Girls: } \text{TBW} = 0.14 \times (\text{Height} * \text{Weight})^{0.68} - 0.35 \times \text{weight}$$

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 both in adults and children [83].

The implementation of the conductivity kinetic model also permits to achieve a neutral sodium balance at each HD session [84], representing major progress compared to previous approaches to sodium kinetic modeling which were unsuitable for routine application as they required blood sampling. The conductivity kinetic model has been demonstrated to improve intra-HD cardiovascular stability in adult hypotension-prone patients [85]. Ionic dialysance can also be used to monitor the blood flow through the vascular access [86].

Urea Monitoring

An alternative approach for online urea kinetic modeling is to measure urea directly in the spent dialysate or the ultrafiltrate. However, dialysate-based urea monitoring devices are not in widespread use due to their high cost and maintenance effort.

Thermal Energy Flow and Blood Temperature Monitoring

The temperatures of the dialysis fluid and the extracorporeal circuit determine thermal balance during hemodialysis. The dialyzer acts as a heat exchanger. Blood leaving the dialyzer has the temperature of the dialysate, but venous line cooling is inevitable even with insulated lines. Therefore the actual dialysate temperature would require to be increased above body temperature to maintain body temperature. On the other hand, ultrafiltration tends to raise body temperature in part by the compensatory vasoconstriction it induces, leading to retention of body heat. Cooler dialysate has been clearly demonstrated to reduce the incidence of hypotension. Online measurement of extracorporeal blood temperatures without inserting a thermistor probe into the blood stream has become possible by the Blood Temperature Monitor (BTM, Fresenius Medical Care, Bad Homburg, Germany). By using a BTM module isothermic dialysis can be performed and it seems to be a good approach for reducing the core temperature without discomfort to the patient [87]. A second useful application of the BTM is the assessment of access recirculation (see below).

Access Recirculation

Recirculation of blood from the venous to the arterial blood line leads to reduced hemodialysis efficacy. The recirculation rate is increased by a small distance between the sites of blood withdrawal and return, a low blood flow in the arteriovenous fistula and by wrong positioning of the needles (blood return upstream of blood withdrawal site). Recirculation should not account for more than 10% of the total blood flow rate [88].

Recirculation is classically measured by the indicator dilution technique. The indicator is diluted by extracorporeal blood flow, enters the access, and – in case of access recirculation – reappears in the arterial blood line with a delay of a few seconds. A common way to measure the recirculation rate is by using urea concentrations in blood samples taken from the arterial and venous blood line and a third sample from a peripheral vein according to the formula:

$$\text{Recirculation}\ (\%) = Q_R / Q_B = ([\text{Urea}]_S - [\text{Urea}]_A)/([\text{Urea}]_S - [\text{Urea}]_V),$$

where Q_R is the recirculating blood flow, Q_B is the total blood flow, $[\text{Urea}]_S$ is the urea concentration in the systemic circulation, $[\text{Urea}]_A$ is the urea concentration in the arterial blood line, and $[\text{Urea}]_V$ is the urea concentration in the venous blood line.

Alternatively, the blood sample from the arterial line may be withdrawn after reduction of the blood flow rate to 20–30 mL/min for 30 s, assuming that the urea concentration of this sample is representative for the systemic circulation.

In recent years, several automated systems have been developed that allow online recirculation monitoring. The hemodialysis monitor (HDM01, Transonic Systems, Inc., Ithaca, New York) utilizes changes in ultrasound velocity caused by the dilution of blood with isotonic saline. The Crit-Line Monitor (Crit-Line III, HemaMetrics, Kaysville, Utah) is using the decrease in optical density caused by dilution of blood with isotonic saline. The change in blood conductivity (Λ) caused by dilution with hypertonic saline can be measured noninvasively by utilizing electromagnetic sensors (Hemodynamic Monitor (HDM), Gambro Healthcare, Lakewood, Colorado) or conductivity cells (Multimat, Bellco SNIA Group, Mirandola, Italy). Finally, the blood temperature monitor (BTM, Fresenius Medical Care, Bad Homburg, Germany) allows to assess recirculation based on the principle of thermal dilution technique using temperature sensors. Blood temperatures are measured without inserting a thermistor probe into the bloodstream. The sensors housed in small boxes are touching the outside of the blood line with a distance to the access of approximately 1.5 m. Recirculation is determined by the arteriovenous gradient: $R = \Delta A/\Delta V$. Taking environmental conditions into account the precision of the temperature measurements is better than 0.1°C for blood flows above 120 mL/min and yields results which are consistent with the HDM ultrasound dilution method [89]. This test is limited by a component related to the cardiopulmonary recirculation due to the duration of the test.

References

1. 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.
2. Besarab A, Al-Saghir F, Alnabhan N, Lubkowski T, Frinak S. Simplified measurement of intra-access pressure. ASAIO J. 1996;42(5):M682–7.
3. 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.
4. Kreuzer M, Ehrich JH, Pape L. Haemorrhagic complications in paediatric dialysis-dependent acute kidney injury: incidence and impact on outcome. Nephrol Dial Transplant. 2010;25(4):1140–6.
5. Agraharkar M, Isaacson S, Mendelssohn D, Muralidharan J, Mustata S, Zevallos G, Besley M, Uldall R. Percutaneously inserted silastic jugular hemodialysis catheters seldom cause jugular vein thrombosis. ASAIO J. 1995;41(2):169–72.

6. Vanherweghem JL, Yassine T, Goldman M, Vandenbosch G, Delcour C, Struyven J, Kinnaert P. Subclavian vein thrombosis: a frequent complication of subclavian vein cannulation for hemodialysis. Clin Nephrol. 1986;26(5):235–8.
7. Keller F, Seemann J, Preuschof L, Offermann G. Risk factors of system clotting in heparin-free haemodialysis. Nephrol Dial Transplant. 1990;5(9):802–7.
8. Hakim RM, Schafer AI. Hemodialysis-associated platelet activation and thrombocytopenia. Am J Med. 1985;78(4):575–80.
9. Kandrotas RJ, Gal P, Douglas JB, Deterding J. Pharmacokinetics and pharmacodynamics of heparin during hemodialysis: interpatient and intrapatient variability. Pharmacotherapy. 1990;10(5):349–55.
10. Farrell PC, Ward RA, Schindhelm K, Gotch FA. Precise anticoagulation for routine hemodialysis. J Lab Clin Med. 1978;92:164–76.
11. Goudable C, Saivin S, Houin G, et al. Pharmacokinetics of a low molecular weight heparin (fraxiparine) in various stages of chronic renal failure. Nephron. 1991;59:543–5.
12. Naumnik B, Borawski J, Myśliwiec M. Different effects of enoxaparin and unfractionated heparin on extrinsic blood coagulation during haemodialysis: a prospective study. Nephrol Dial Transplant. 2003; 18(7):1376–82.
13. Sagedal S, Hartmann A, Sundstrøm K, Bjørnsen S, Fauchald P, Brosstad F. A single dose of dalteparin effectively prevents clotting during haemodialysis. Nephrol Dial Transplant. 1999;14(8):1943–7.
14. Reach I, Luong N, Chastang C, Chakroun M, Mirshahi S, Mirshahi MC, Soria J, Desmichels D, Baumelou A. Dose effect relationship of reviparin in chronic hemodialysis: a crossover study versus nadroparin. Artif Organs. 2001;25(7):591–5.
15. Nurmohamed MT, ten Cate J, Stevens P, Hoek JA, Lins RL, ten Cate JW. Long-term efficacy and safety of a low molecular weight heparin in chronic hemodialysis patients. A comparison with standard heparin. ASAIO Trans. 1991;37(3):M459–61.
16. Schrader J, Stibbe W, Armstrong VW, et al. Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. Kidney Int. 1988;33:890–6.
17. Hory B. Hemodialysis with low-molecular-weight heparin in high-risk hemorrhagic patients with acute renal failure. Am J Med. 1988;84:566.
18. Farooq V, Hegarty J, Chandrasekar T, Lamerton EH, Mitra S, Houghton JB, Kalra PA, Waldek S, O'Donoghue DJ, Wood GN. Serious adverse incidents with the usage of low molecular weight heparins in patients with chronic kidney disease. Am J Kidney Dis. 2004;43(3):531–7.
19. Briel RC, Zielke E, Zwirner M. Untersuchungen zur korrelation der anti-faktor-Xa-aktivität von niedermolekularem heparin (fragmin) und der aktivierten vollblutgerinnungszeit im AC-tester. Ärztl Lab. 1987;33:237.
20. Greiber S, Weber U, Galle J, et al. Activated clotting time is not a sensitive parameter to monitor anticoagulation with low molecular weight heparin in hemodialysis. Nephron. 1997;76:15–9.
21. Grau E, Sigüenza F, Maduell F, et al. Low molecular weight heparin (CY 216) versus unfractionated heparin in chronic hemodialysis. Nephron. 1992;62:13–7.
22. Schmitt Y, Schneider H. Low-molecular-weight heparin (LMWH): influence on blood lipids in patients on chronic hemodialysis. Nephrol Dial Transplant. 1993;8:438–42.
23. Yamamoto S, Koide M, Matsuo M, Suzuki S, Ohtaka M, Saika S, Matsuo T. Heparin-induced thrombocytopenia in hemodialysis patients. Am J Kidney Dis. 1996;28(1):82–5.
24. Reddy BV. Argatroban use in dialysis patients. Semin Dial. 2004;17(1):73.
25. Klingel R, Wandel E, Hafner G, et al. Minimal heparinization in dialysis patients with increased risk of bleeding. Dtsch Med Wochenschr. 1993;118: 1878–83.
26. Janssen MJ, Van der Meulen J. The bleeding risk in chronic hemodialysis: preventive strategies in high-risk patients. Neth J Med. 1996;48:198–207.
27. Preuschof L, Keller F, Seemann J, Offermann G. Heparin-free hemodialysis with prophylactic change of dialyzer and blood lines. Int J Artif Organs. 1988;11:255–8.
28. Pinnick RU, Wiegmann TB, Diederich DA. Regional citrate anticoagulation for hemodialysis in the patient at high risk for bleeding. N Engl J Med. 1983;308: 258–61.
29. Lohr JW, Slusher S, Diederich D. Safety of regional citrate hemodialysis in acute renal failure. Am J Kidney Dis. 1989;13:104–7.
30. Wiegmand TB, MacDougall ML, Diederich DA. Long-term comparisons of citrate and heparin as anticoagulants for hemodialysis. Am J Kidney Dis. 1987;5:430–5.
31. Paulsen D, Reisoether A, Aasen M, Fauchald P. Use of tissue plasminogen activator for reopening of clotted dialysis catheters. Nephron. 1993;64(3):468–70.
32. Hendrickx L, Kuypers D, Evenepoel P, Maes B, Messiaen T, Vanrenterghem Y. A comparative prospective study on the use of low concentrate citrate lock versus heparin lock in permanent dialysis catheters. Int J Artif Organs. 2001;24(4):208–11.
33. Meeus G, Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. A prospective, randomized, double-blind crossover study on the use of 5% citrate lock versus 10% citrate lock in permanent hemodialysis catheters. Blood Purif. 2005;23(2):101–5.
34. Steczko J, Ash SR, Nivens DE, Brewer L, Winger RK. Microbial inactivation properties of a new antimicrobial/antithrombotic catheter lock solution (citrate/methylene blue/parabens). Nephrol Dial Transplant. 2009;24(6):1937–45.
35. OIbricht C, Lonnemann G, Frei U, Koch KM. Hemodialysis, haemofiltration, and complications of

technique. In: Davison AM, Cameron JS, Grünfeld JP, Kerr DNS, Ritz E, Winearls CG, editors. Oxford textbook of clinical nephrology. Oxford: Oxford University Press; 1998. p. 2025.
36. Schneditz D. Technologic aspects of hemodialysis and peritoneal dialysis. In: Nissenson AR, Fine RN, editors. Clinical dialysis. 4th ed. The McGraw-Hill Companies: Inc; 2005. p. 47–84.
37. Stragier A, Wenderickx D. Bacterial growth prevention in liquid bicarbonate concentrate. EDTNA ERCA J. 1998;24:40–2.
38. Delin K, Attmann PO, Dahlberg M, Awell M. A clinical test of a new device for on-line preparation of dialysis fluid from bicarbonate powder: the Gambro BiCart. Nephrol Dial Transplant. 1994;9:468–9.
39. Redaelli B, Sforzini S, Bonoldi G, et al. Hemodialysis with "adequate" sodium concentration in dialysate. Int J Artif Organs. 1979;2:133–40.
40. Locatelli F, Ponti R, Pedrini L, et al. Sodium kinetics across dialysis membranes. Nephron. 1984;38:174–7.
41. Hercz G, Kraut JA, Andress DL, et al. Use of calcium carbonate as a phosphate binder in dialysis patients. Miner Electrolyte Metab. 1986;12:314–9.
42. Mactier RA, VanStone J, Cox A, et al. Calcium carbonate is an effective phosphate binder when dialysate calcium concentration is adjusted to control hypercalcemia. Clin Nephrol. 1987;28:222–6.
43. Sawyer N, Noonan K, Altman P, et al. High-dose calcium carbonate with stepwise reduction in dialysate calcium concentration: effective phosphate control and aluminium avoidance in hemodialysis patients. Nephrol Dial Transplant. 1989;4:105–9.
44. Slatopolsky E, Weerts C, Norwood K, et al. Long-term effects of calcium carbonate and 2.5 mEq/liter calcium dialysate on mineral metabolism. Kidney Int. 1989;36:897–903.
45. Mountokalakis TD. Magnesium metabolism in chronic renal failure. Magnes Res. 1990;3:121–7.
46. Markell MS, Altura BT, Sarn Y, et al. Deficiency of serum ionized magnesium in patients receiving hemodialysis or peritoneal dialysis. ASAIO J. 1993;39: M801–4.
47. Von Wagner L, Decker G, Zuber K, Strauch M. Die zusammensetzung der dialysatflüssigkeit bei der bikarbonatdialyse. Nieren- Hochdruckkrankheiten. 1984;13:124–8.
48. Gennari FJ. Acid-base balance in dialysis patients. Kidney Int. 1985;28:678–88.
49. Gennari FJ. Acid-base balance in dialysis patients. Semin Dial. 2000;13:235–9.
50. Leunissen K, van den Berg BW, van Hooff JP. Ionized calcium plays a pivotal role in controlling blood pressure during hemodialysis. Blood Purif. 1989;7:233–9.
51. Wiegand C, Davin T, Raji L, Kjellstrand C. Life threatening hypokalemia during hemodialysis. Trans Am Soc Artif Intern Organs. 1979;25:416–8.
52. Hegbrant J, Sternby J, Larsson A, et al. Beneficial effect of cold dialysate for the prevention of hemodialysis-induced hypoxia. Blood Purif. 1997;15:15–24.
53. Hegbrant J, Martensson L, Ekman R, et al. Dialysis fluid temperature and vasoactive substances during routine hemodialysis. ASAIO J. 1994;40:M678–82.
54. Sherman RA, Rubin MP, Cody RP, Eisinger RP. Amelioration of hemodialysis-associated hypotension by the use of cool dialysate. Am J Kidney Dis. 1985;5:124–7.
55. Ronco C, Ballestri M, Cappelli G. Dialysis membranes in convective treatments. Nephrol Dial Transplant. 2000;15(Suppl 2):31–6.
56. Ronco C. Backfiltration: a controversial issue in modern dialysis. Int J Artif Organs. 1988;11(2):69–74.
57. Ronco C, Brendolan A, Lupi A, et al. Effects of a reduced inner diameter of hollow fibers in hemodialyzers. Kidney Int. 2000;58:809–17.
58. Ronco C, Orlandini G, Brendolan A, et al. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. Kidney Int. 1998;54:979–85.
59. Hoenich NA, Woffindin C, Matthews JN, et al. Clinical comparison of high-flux cellulose acetate and synthetic membranes. Nephrol Dial Transplant. 1994;9:60–6.
60. Craddock PR, Fehr J, Dalmasso AP, et al. Hemodialysis leukopenia: pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membrane. J Clin Invest. 1977;59:879–88.
61. Chenoweth DE. Complement activation produced by biomaterials. Artif Organs. 1991;12:502–4.
62. Herbelin A, Nguyen AT, Zingraff J, et al. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. Kidney Int. 1990;37: 116–25.
63. Kaysen GA. Role of inflammation and its treatment in ESRD patients. Blood Purif. 2002;20:70–80.
64. Verresen L, Fink E, Lemke HD, Vanrenterghem Y. Bradykinin is a mediator of anaphylactoid reactions during hemodialysis with AN69 membranes. Kidney Int. 1994;45:1497–503.
65. Kammerl MC, Schaefer RM, Schweda F, et al. Extracorporal therapy with AN69 membranes in combination with ACE inhibition causing severe anaphylactoid reactions: still a current problem? Clin Nephrol. 2000;53:486–8.
66. John B, Anijeet HK, Ahmad R. Anaphylactic reaction during hemodialysis on AN69 membrane in a patient receiving angiotensin II receptor antagonist. Nephrol Dial Transplant. 2001;16:1955–6.
67. Stellungnahme der Kommission für Gerätetechnik zur Wiederverwendung von Dialysatoren. In Mitteilungen der Deutschen Arbeitsgemeinschaft für klinische Nephrologie. AnonymousGöttingen, Vandenhoeck & Ruprecht: 1994:243.
68. Shaldon S, Beau MC, Deschodt G, et al. Vascular stability during hemofiltration. Trans ASAIO. 1980;26: 391–4.
69. Baldamus CA, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. Nephron. 1982;31:324–32.

70. Schmidt M, Schmidt M. Hemodiafiltration. In: Henderson LW, Quellhorst E, Baldamus CA, Lysaght MJ, editors. Hemofiltration. Berlin: Springer; 1986. p. 265.
71. 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.
72. Fischbach M, Edefonti A, Schröder C, Watson A, European pediatric dialysis working group. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.
73. Sadowski RH, Allred EN, Jabs K. Sodium modeling ameliorates intradialytic and interdialytic symptoms in young hemodialysis patients. J Am Soc Nephrol. 1993;4:1192–8.
74. Hothi DK, Harvey E, Goia CM. Geary DF; evaluating methods for improving ultrafiltration in pediatric hemodialysis. Pediatr Nephrol. 2008;23(4):631–8.
75. Schneditz D, Roob J, Oswald M, Pogglitsch H, Moser M, Kenner T, Binswanger U. Nature and rate of vascular refilling during hemodialysis and ultrafiltration. Kidney Int. 1992;42(6):1425–33.
76. Kim KE, Neff M, Cohen B, Somerstein M, Chinitz J, Onesti G, Swartz C. Blood volume changes and hypotension during hemodialysis. Trans Am Soc Artif Intern Organs. 1970;16:508–14.
77. 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.
78. Hothi DK, Harvey E, Goia CM, Geary D. Blood-volume monitoring in paediatric haemodialysis. Pediatr Nephrol. 2008;23:813–20.
79. Patel HP, Goldstein SL, Mahan JD, Smith B, Fried CB, Currier H, Flynn JT. A standard, noninvasive monitoring of hematocrit algorithm improves blood pressure control in pediatric hemodialysis patients. Clin J Am Soc Nephrol. 2007;2:252–7.
80. Petitclerc T, Goux N, Reynier AL, Béné 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.
81. Polaschegg HD. Automatic, noninvasive intradialytic clearance measurement. Int J Artif Organs. 1993;16(4):185–91.
82. Morgenstern BZ, Wühl E, Sreekumaran Nair K, Warady B, Schaefer F. Anthropometric prediction of total body water in children who are on pediatric peritoneal dialysis. J Am Soc Nephrol. 2006;17:285–93.
83. Grzegorzewska AE, Banachowicz W. Evaluation of hemodialysis adequacy using online Kt/V and single-pool variable-volume urea Kt/V. Int Urol Nephrol. 2008;40:771–8.
84. Locatelli F, Buoncristiani U, Canaud B, Köhler H, Petitclerc T, Zucchelli P. Haemodialysis with on-line monitoring equipment: tools or toys? Nephrol Dial Transplant. 2005;20(1):22–33.
85. Locatelli F, Andrulli S, Di Filippo S, Redaelli B, Mangano S, Navino C, Ariano R, Tagliaferri M, Fidelio T, Corti M, Civardi S, Tetta C. Effect of on-line conductivity plasma ultrafiltrate kinetic modeling on cardiovascular stability of hemodialysis patients. Kidney Int. 1998;53(4):1052–60.
86. Mercadal L, Challier E, Cluzel P, Hamani A, Boulechfar H, Boukhalfa Z, Izzedine H, Bassilios N, Barrou B, Deray G, Petitclerc T. Detection of vascular access stenosis by measurement of access blood flow from ionic dialysance. Blood Purif. 2002;20:177–81.
87. Schneditz D, Ronco C, Levin N. Temperature control by the blood temperature monitor. Semin Dial. 2003;16(6):477–82.
88. Ogden DA, Cohen IM. Blood recirculation during hemodialysis with a coaxial counterflow single needle blood access catheter. Trans Am Soc Artif Intern Organs. 1979;25:324–7.
89. Schneditz D, Wang E, Levin NW. Validation of haemodialysis recirculation and access blood flow measured by thermodilution. Nephrol Dial Transplant. 1999;14:376–83.

Prescribing and Monitoring Hemodialysis for Pediatric Patients

18

Stuart L. Goldstein

Keywords
Hemodialysis monitoring • Pediatric dialysis • Children • Hemdoailysis prescribing

Introduction

The hemodialysis adequacy concept was born over 30 years ago when nephrologists began to view the hemodialysis treatment in terms of a quantifiable dose of toxin clearance delivered, which could be prescribed by manipulating dialyzer size, blood pump flow rates, and treatment time. Since that time, numerous studies have attempted to delineate the most accurate method of dose quantification and to correlate dialysis dose with patient outcome. While sometimes beset by complex mathematical formulas that can obscure the basic concepts of dialysis dose and resultant outcome, these research endeavors have lead to improvements in patient outcome by focusing nephrologists' attention on the variables governing their patients' hemodialysis treatments and by creation of national initiatives which define minimum standards for the dose of delivered hemodialysis.

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Definitions

Adequate Hemodialysis

The term hemodialysis adequacy is derived from the National Cooperative Dialysis Study (NCDS), which aimed to control for dialysis treatment dose in adult patients and correlate a particular dose with patient outcome [1]. The NCDS controlled for the hemodialysis dose based on either the treatment time or the time averaged blood urea nitrogen (BUN) concentration between hemodialysis treatments. The mechanistic analysis of the NCDS, performed by Gotch and Sargent, revealed that the relationship between dialysis dose and outcome was not linear, but rather a nearly fourfold increase in hospitalization/death rates occurred in patients receiving less than 50% urea clearance compared to patients receiving greater than 50% urea clearance during each dialysis treatment. Thus, the resultant concept of "adequate" dialysis was created to define a *minimum* hemodialysis dose below which occurs a clinically unacceptable rate of negative outcome.

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Optimal Hemodialysis

"Optimal" dialysis refers to a hemodialysis dose above which no significant reduction in negative outcomes or improvement in positive outcomes occurs. No data exist to define the optimal dialysis dose for either children or adults. Determination of optimal dialysis dose remains a difficult task, since economic and psychosocial factors may tend to decrease patient time on dialysis. In fact, while more prolonged dialysis times have recently been shown to improve pediatric patient growth [2, 3], they could conceivably increase patient isolation from activity with peers. A conceptual framework for determining optimal hemodialysis is provided at the end of the chapter.

Initiation of Hemodialysis

Patients initiating hemodialysis either for the first time or after the loss of a kidney transplant may suffer from malnutrition, fluid overload, and hypertension. Therefore, prior to addressing chronic hemodialysis adequacy measurement, patient transition from chronic kidney disease to maintenance dialysis requires special attention. The principles for a safe hemodialysis initiation prescription form the basis for chronic dialysis adequacy measurement. The goals for the first month of hemodialysis therapy should include establishment of a target post-hemodialysis treatment weight, blood pressure normalization, and hemodialysis prescription refinement to allow for predictable and sufficient urea clearance.

During the first few hemodialysis treatments, the amount of urea reduction can be prescribe using the following mass transfer equation:

$$Kt/V \approx -\ln (Ct/C0)$$

where Ct is the concentration of BUN after t minutes of dialysis, C0 is the initial concentration, K is the urea clearance (mL/min), t is the duration of dialysis (minutes), and V is the urea volume of distribution (mL). The urea volume of distribution is equivalent to the total body water (TBW), which is approximately 60% of the patient's weight. Examination of this equation reveals that urea clearances can be increased by three possible interventions: increasing the dialyzer clearance coefficient (accomplished by increasing dialyzer surface area or the blood pump flow rate), increasing the individual hemodialysis treatment time or decreasing the patient's TBW.

Repeated iteration of this formula leads to accurate assessment of the patient TBW volume and optimization of the dialysis prescription. For example, suppose a patient new to dialysis presents with a weight of 50 kg and a baseline BUN of 130 mg/dL. To prevent urea disequilibrium syndrome, we desire to affect a 30% urea reduction with the first hemodialysis treatment. Thus, the resulting Ct/C0 = 0.7. To keep the extracorporeal hemodialysis blood circuit volume less than 10% of the patient's blood volume, we opt for a dialyzer with a K of 200 mL/min at a blood pump flow rate of 250 mL/min. Using these data, one can solve for the approximate hemodialysis treatment time needed to affect a 30% urea reduction:

$$-\ln (0.7) = 200 \text{ mL/min} * t/(600 \text{ mL/kg} * 50 \text{ kg}) \text{ OR}$$

$$t = -\ln(0.7) * 30{,}000 \text{ mL}/200 \text{ mL/min SO}$$

$$t = 54 \text{ min}$$

The next step requires measurement of the pre- and post-dialysis BUN associated with actual delivery of the treatment prescribed above. To continue the example, let's assume the patient received 54 min of hemodialysis and the predialysis BUN was 130 mg/dL and the post dialysis BUN was 99 mg/dL. If all of the initial assumptions had been correct, a 30% urea clearance should have yielded a post-BUN of 91 mg/dL. The lower than expected urea clearance likely reflects a higher patient TBW than assumed (i.e., >60% of weight), which is not unusual given that patients initiating dialysis therapy are often fluid overloaded. Using the initiation formula,

$$-\ln (99/130) = 200 \text{ mL min} * 54 \text{ min}/V \text{ OR}$$

$$V = 200 \text{ mL/min} * 54 \text{ min}/0.27 \text{ SO}$$

$$V = 39{,}259 \text{ mL}$$

reveals that patient's TBW (V) was underestimated by 9,259 mL. Other factors including access recirculation and dialyzer clearance variation can

also contribute to the lower than expected urea clearance. Nonetheless, use of the "new" V assists in optimizing the next dialysis treatment prescription. For example, if one wanted to prescribe for 50% urea clearance using the same dialyzer, the initiation formula yields:

$$-\ln(0.5) = 200\ \text{mL/min} * t/39{,}329\ \text{mL or } t = 136\ \text{min}$$

The second treatment is provided with pre- and post-dialysis BUN samples drawn to further refine the assessment of the patient's TBW. Once the patient demonstrates a stable post-dialysis target weight, has good blood pressure control, and 65–70% urea clearance can be accurately predicted and reliably delivered, the focus of the dialysis prescription changes to assessment of maintenance hemodialysis adequacy.

Urea Clearance and Metabolism

All methods of hemodialysis adequacy measurement base the assessment of dialysis dose on a variation of the fractional urea reduction affected by the hemodialysis treatment. Understanding urea generation, distribution, and movement during and between dialysis treatments is essential to any discussion of hemodialysis adequacy.

Clearance and Nutrition

Prior to the initiation of a hemodialysis treatment, urea is evenly distributed across a patient's TBW, i.e. within both the intracellular and extracellular fluid (ECF) compartments. During the hemodialysis treatment, urea is removed immediately and efficiently from the intravascular space since the hemodialysis circuit is connected only to the patient's vascular access. As urea diffuses easily across the vascular wall, equilibration between the extravascular and intravascular components of the extracellular space occurs nearly instantaneously. In contrast, urea movement from the intracellular fluid (ICF) to the ECF space is limited by cellular transport characteristics of urea, which results in a urea concentration disequilibrium, with the ICF urea concentration greater than the ECF urea concentration. The ICF to ECF urea concentration difference persists throughout the hemodialysis treatment and can last for up to 1 h after treatment termination. Failing to account for this urea disequilibrium can lead to an overestimation of the true urea mass removed during dialysis, and therefore an inflated assessment of hemodialysis dose. These concepts will be addressed later in the chapter under the discussion of double-pool urea kinetics.

The two fundamental clinical variables assessed by hemodialysis adequacy measurement are dialysis treatment urea clearance and patient protein nutrition status. While most hemodialysis adequacy research has focused solely on urea clearance, the mechanistic analysis of the NCDS strongly suggested that patients with poor nutrition status demonstrated higher hospitalization/death rates, irrespective of the delivered hemodialysis dose [1]. Provision of adequate hemodialysis thus requires attention to urea clearance during dialysis and urea generation between dialysis treatments.

Formal Urea Kinetic Modeling

The urea kinetic model was validated by the mechanistic analysis of the NCDS in which both urea clearance and nutrition status as assessed by the model were shown to be associated with patient outcome. The strength of urea kinetic modeling (UKM) resides in the ability to assess both urea clearance and patient nutrition status. Although UKM has been considered the gold standard for hemodialysis adequacy measurement, the advanced mathematical calculations required for computation made UKM unavailable to many practitioners in the late 1980s and early 1990s. The advent of online calculators and personal computers should have led to wider UKM use; however, many nephrologists still do not employ UKM in their routine practice.

Formal UKM solves two unique, but interrelated differential equations for two variables: patient TBW (V, in milliliters) and urea generation rate (G, in milligrams per minute). Values for V and G are then used to calculate normalized urea clearance during a dialysis treatment and patient protein catabolic rate (PCR). The PCR is then divided by post-dialysis patient weight in

kilograms to yield a normalized protein catabolic rate (nPCR).

Single-Pool Kt/V

The fractional urea mass removed during hemodialysis is affected by the following factors: dialyzer urea clearance coefficient (K, in milliliters per minute), pre- and posttreatment BUN (mg/dL), treatment duration (t, in minutes), patient TBW (V, in milliliters), the amount of plasma water removed during dialysis (ultrafiltrate), and the intradialytic urea generation rate (G). As with the hemodialysis initiation equation, fractional urea clearance can be described in terms of Kt/V. Pre- and post-dialysis measured BUNs, the dialyzer K for urea at the delivered blood pump flow rate, time of treatment, and pre-and post-dialysis patient weight are provided to the UKM algorithm. The difference between the pre- and post-dialysis weights yields the ultrafiltration volume obtained during the treatment. The UKM model is solved for V and G based on the above variables.

To determine single-pool Kt/V, which does not account for the urea ICF to ECF disequilibrium caused by hemodialysis, the post-BUN sample is drawn 30 s after the termination of dialysis. Methods accounting for double-pool urea distribution will be discussed later in the chapter.

Normalized Protein Catabolic Rate

The amount of protein catabolized to yield G between dialysis treatments can be calculated using the modified Borah equation. For a patient without significant unmeasured protein losses (e.g., burns) or without significant protein catabolism from other causes (e.g., infection), the PCR calculated from G reflects patient protein intake. Thus, nPCR can reflect a component of the nutrition status of a patient receiving hemodialysis [4–7]. Work demonstrating the utility of nPCR assessment and interpretation will be presented later in the chapter.

Algebraic Approximation Equations

Second-Generation Natural Logarithm Method spKt/V

The sophisticated mathematic formulas required for UKM calculation often preclude routine UKM in many centers. As a result, substantial investigation has been performed to develop and validate simpler Kt/V measurement methods [8]. Of these, only the natural logarithm formula of Daugirdas garnered acceptance for spKt/V approximation in adults and children [9]. The Daugirdas natural logarithm formula (Daugirdas II) is

$$\mathrm{spKt/V} = -\ln(\mathrm{C1/C0} - 0.008 * \mathrm{t}) + \left(4 - 3.5 * \mathrm{C1/C0}\right) * \mathrm{UF/W}$$

where C0 is the pre-dialysis BUN (mg/dL), C1 is the post-dialysis BUN (mg/dL), t is the session length (h), UF is the ultrafiltrate (kg), and W is the post-dialysis weight (kg). The accuracy of Daugirdas II resides in accounting for dialysis treatment duration and urea removed by ultrafiltration, neither of which is incorporated into the hemodialysis initiation equation discussed previously in the chapter.

Daugirdas II is a reliable and practical alternative to formal UKM for Kt/V estimation in children. A 368 dual Kt/V analysis comparing UKM Kt/V to Daugirdas II Kt/V demonstrated less than 6% difference in every treatment and the percentage difference did not vary with patient size [10]. NKF-K/DOQI guidelines recommend a Kt/V prescription of 1.3 to ensure Kt/V delivery of 1.2, which is an 8% difference [11]. Thus, the 6% maximal difference seen between UKM and Daugirdas II Kt/V observed in children is clinically acceptable.

Normalized Protein Catabolic Rate Approximation

In this same study of 368 dual analyses [10], UKM derived nPCR was also reliably and accurately

estimated using a urea generation rate derived from the difference between the post- and pre-treatment BUN concentrations:

$$\text{estG(mg/min)} = [(C2 * V2) - (C1 * V1)]/t$$

where C1 is the post-dialysis BUN (mg/dL), C2 is the pre-dialysis BUN (mg/dL), V1 is the post-dialysis TBW (dL; V1 = 5.8 dL/kg* post-dialysis weight in kg), V2 is the pre-dialysis TBW (dL, V2 = 5.8 dL/kg* pre-dialysis weight in kg), and t is the time (min) from the end of the dialysis treatment to the beginning of the following treatment. Then estnPCR was calculated using the following modified Borah [12] equation:

$$\text{estnPCR} = 5.43 * \text{estG/V1} + 0.17$$

where V1 is the total body water (L) post-dialysis (0.58* post-dialysis weight in kg). Results from these analyses revealed UKM nPCR and estnPCR differed by more than 0.1 g/kg/day in only 12/368 treatments, which is a clinically acceptable degree of error.

Practical Examples Using Algebraic Approximation

The following three examples illustrate the utility of Kt/V and nPCR assessment in evaluation of a patient's maintenance hemodialysis prescription. Each example details the single-pool Kt/V (spKt/V) and nPCR values for three consecutive months for a 10-year-old patient.

Example 1: Real weight gain

Month	Weight (kg)	spKt/V	nPCR
1	34.3	1.40	1.20
2	35.2	1.32	1.15
3	36.1	1.20	1.18

In this example, the patient has steadily increasing weight, an acceptable nPCR, and a decreasing Kt/V. Since the patient's nPCR reflects adequate protein intake, this patient's weight gain likely represents true body mass accretion. As a result, the patient's TBW (V) has increased proportionally, leading to a decrease in Kt/V since neither the dialyzer K nor the treatment time was altered. Thus, the patient in this example is outgrowing the current dialysis prescription, and the appropriate action will be to increase the dialysis dose, which can be accomplished by increasing K (by increasing the blood pump flow rate or dialyzer size) or by increasing the dialysis treatment duration.

Example 2: Fluid weight gain

Month	Weight (kg)	spKt/V	nPCR
1	34.3	1.40	1.20
2	35.2	1.32	0.96
3	36.1	1.20	0.65

In this example, the patient demonstrates the same progressive weight gain and Kt/V decrease as the patient in Example 1. However, the current patient's nPCR has dropped precipitously, indicating poor protein intake. Thus, the patient's weight gain does not result from true visceral body mass accretion, but rather from progressive fluid accumulation. UKM modeling yielding these values would provide a calculation showing that V accounted for an abnormally high percentage of body weight (e.g., >70%), a calculation not provided by Daugirdas II. Nonetheless, this example shows that combination of both algebraic KtV and nPCR measurement can lead to the same clinical conclusions. The appropriate management of the case in Example 2 is to provide aggressive nutritional intervention and decrease the patient's target weight via ultrafiltration.

Example 3: Weight loss

Month	Weight (kg)	spKt/V	nPCR
1	34.3	1.40	0.98
2	32.5	1.32	0.98
3	31.3	1.45	0.88

In this example, the patient has progressive weight loss and decreasing nPCR, indicating poor nutritional status and a visceral protein catabolic state. Notice that the patient had adequate urea clearance in spite of the progressive weight loss, once again illustrating that complete hemodialysis adequacy assessment should account for both clearance and nutrition status.

Urea Reduction Ratio

The urea reduction ratio (URR) uses only the pre- and post-dialysis BUN samples to calculate the fractional excretion of urea caused by dialysis:

$$\text{URR} = (\text{pre - BUN} - \text{post - BUN})/\text{pre - BUN} * 100$$

Since URR does not account for intradialytic urea generation or urea removed by ultrafiltration, corresponding Kt/V values may vary by as much as 20% for treatments with the same URR value. In addition, URR does not yield any information regarding nutrition status. While URR is easy to calculate, it is recognized as the least favorable method for hemodialysis adequacy measurement and should not be used to control for dialysis dose in clinical outcome studies.

Urea Rebound and Double-Pool Kt/V

Concepts

Kt/V calculation is based upon the pre- and posttreatment BUN concentrations. In children, the posttreatment BUN concentration rises in a first-order logarithmic fashion until re-equilibration between ICF and ECF BUN concentrations occurs 30–60 min after the treatment ends [13, 14]. This rise in BUN concentration has been termed urea rebound. As the BUN rebounds after hemodialysis treatment termination, the resultant calculation of Kt/V will yield lower values.

Calculation of Kt/V by spKt/V using the immediate, 30s post-dialysis BUN (BUN30s) sample does not take urea rebound into account and leads to overestimation of the true urea mass removed by dialysis. Calculation of Kt/V by double-pool or equilibrated Kt/V (eqKt/V) is based on a post-dialysis BUN concentration actually drawn, or estimated, after the completion of urea rebound. Numerous studies in both children and adults show that urea rebound ranges from 7.6% to 24% and accounts for a 12.3–16.8% difference between spKt/V and eqKt/V values [13–19].

Double-Pool Kt/V Estimation Formulas

It is impractical to wait for 1 h after a treatment to obtain an equilibrated BUN (eqBUN) for eqKt/V calculation. Many formulas have been devised to estimated eqKt/V (estKt/V) by applying a cofactor to spKt/V and relying solely on a pre-BUN and post-BUN30s. Of these, the rate equation by Daugirdas [20] is the most accurate.

$$\text{estKt/V(Daugirdas)} = \text{spKt/V} * (1 - 0.6/t) + 0.03$$

where t is the treatment time in hours.

Since urea rebound is primarily characterized by a first-order logarithmic, concentration dependent ICF to ECF urea movement, a more recent method for estimating eqBUN by extrapolating the rise in BUN from 30 s to 15 min post-dialysis (ΔBUN) has been validated [13, 14]. Since urea rebound is 69% complete at 15 min post-dialysis, eqBUN can be estimated using the following formula:

$$\text{estBUN} = (\Delta\text{BUN}/0.69) + \text{BUN30s}$$

To estimate double-pool eqKt/V, estBUN is used for the C1 in the Daugirdas II estimation formula. Use of Daugirdas II in this manner is logical, since estBUN reflects BUN that has equilibrated across the single pool of the TBW. Logarithmic extrapolation yields an extremely accurate estimation of eqBUN, since two BUN values are assessed post-dialysis. The maximum difference between eqBUN and estBUN is 1.55 mg/dL, which is less than the standard error of the BUN lab measurement itself. As a result, the difference between eqKt/V using a measured eqBUN and estimated eqKt/V using the estBUN by logarithmic extrapolation was less than that of other published eqKt/V estimation methods.

Hemodialysis Adequacy and Clinical Outcome Study

Recent pediatric data demonstrate the value of assessing and controlling for hemodialysis adequacy in pediatric patients receiving hemodialysis. Tom and colleagues correlated increased protein administration and increased urea clearance (spKt/V > 2) with improved growth in well-nourished children receiving hemodialysis, even in the absence of growth hormone [3]. Fischbach and colleagues have also demonstrated improved growth over and above what can be achieved with growth hormone when an

intensified hemodialysis treatment regimen (spKt/V > 1.5 for 5 times per week) is provided [2]. We have repeatedly demonstrated nPCR to be a superior marker of nutrition status in malnourished patients who received intradialytic parenteral nutrition (IDPN) [7, 21]. After IDPN initiation, patient weight and body mass accretion were associated with significant increase in nPCR but not in serum albumin. In another study, nPCR < 1 g/kg/day was predictive of persistent weight loss over the next 3 months in adolescent patients [22]. Other pediatric work showed no correlation between spKt/V and other ESRD lab indicators, such as anemia status or serum albumin [23].

Even more recent work shows eqKt/V to be more closely associated with improvements in inflammation status [24, 25], suggesting that eqKt/V should be used in future outcomes studies to control for the true mass of urea removed. Hemodialysis outcome study validity requires a control for HD dose, so the application of simpler, more accessible HD adequacy measurement methods should lead to an increase in pediatric HD outcome study research. Initial single-center and multicenter pediatric studies are starting to assess the impact of dialysis dose on outcome [3, 23]. However, a recent pediatric study from the Center for Medicare & Medicaid Services (CMS) Clinical Performance Measures Project demonstrated that little difference in hemodialysis prescription management would result when comparing single-pool Kt/V versus equilibrated Kt/V values from the same treatment [26]. As a result, K/DOQI states that spKt/V assessment is appropriate for patient management, while equilibrated Kt/V values should be used for outcome study [11].

Frequent Hemodialysis Adequacy Measurement

The formulas and concepts detailed above apply to thrice-weekly hemodialysis, which currently remains the standard of care. More recently, frequent dialysis regimens of up to 6 times per week treatments or nocturnal extended treatment times have been evaluated in children. As a result, newer formulas have been proposed to derive comparable delivered hemodialysis doses, irrespective of the regimen prescribed. The recent revision of the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K-DOQI) Hemodialysis Adequacy Guidelines addressed the issue of how to monitor delivered dialysis dose in patients receiving hemodialysis more than thrice weekly [11]. The Work Group advocated for the use of standard Kt/V (stdKt/V), which normalizes the dose to attain the same pre-dialysis treatment BUN level, irrespective of the number of prescribed weekly treatments. An adult patient feasibility and efficacy trial assessing the NxStage™ System employed formulas to calculate an equilibrated Kt/V (eKt/V) for one treatment session and then used that value in a stdKt/V calculation [27]. The eKt/V formula has been validated separately [28]. The formulas are listed below:

1. $eKt/V = 0.924*spKt/V - 0.395*spKt/V/t + 0.056$

where spKt/V is the single-pool Kt/V calculated by Daugirdas II [8, 9] and t is the treatment time in hours

2. $stdKt/V = 168*(1-\exp[-eKt/V])/t/[(1-\exp[-eKt/V]/(eKt/V) + 168/(N*t)-1]$

where N is the number of weekly treatments.

As varied hemodialysis prescription options become more prevalent, it will be important to be able to compare delivered dose across pediatric centers. Preliminary data demonstrate excellent outcomes in children who receive 6 times per week dialysis with the NxStage™ [29]. We recently performed an analysis of spKt/V by logarithmic extrapolation with stdKt/V derived as described above and found that one should deliver a $stdKt/V \geq 2.0$ for thrice-weekly pediatric HD in order to achieve a $spKt/V \geq 1.2$ and a $stdKt/V \geq 2.2$ if one wishes to ensure a $spKt/V \geq 1.4$ [30]

References

1. Gotch FA, Sargent JA. A mechanistic analysis of the national cooperative dialysis study (NCDS). Kidney Int. 1985;28:526–34.
2. Fischbach M, et al. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21:1746–52.

3. Tom A, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134:464–71.
4. Combe C, et al. Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. Am J Kidney Dis. 2001;37:S81–8.
5. Cappy CS, Jablonka J, Schroeder ET. The effects of exercise during hemodialysis on physical performance and nutrition assessment. J Ren Nutr. 1999;9:63–70.
6. Grupe WE, Harmon WE, Spinozzi NS. Protein and energy requirements in children receiving chronic hemodialysis. Kidney Int Suppl. 1983;15:S6–S10.
7. Goldstein SL, Baronette S, Gambrell TV, Currier H, Brewer ED. NPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. Pediatr Nephrol. 2002;17:531–4.
8. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–13.
9. Goldstein SL, Sorof JM, Brewer ED. Natural logarithmic estimates of Kt/V in the pediatric hemodialysis population. Am J Kidney Dis. 1999;33:518–22.
10. Goldstein SL. Hemodialysis in the pediatric patient: state of the art. Adv Ren Replace Ther. 2001;8:173–9.
11. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. Am J Kidney Dis. 2006;48:S1–S322.
12. Borah MF, et al. Nitrogen balance during intermittent dialysis therapy of uremia. Kidney Int. 1978;14:491–500.
13. Goldstein SL, Sorof JM, Brewer ED. Evaluation and prediction of urea rebound and equilibrated Kt/V in the pediatric hemodialysis population. Am J Kidney Dis. 1999;34:49–54.
14. Goldstein SL, Brewer ED. Logarithmic extrapolation of a 15 min postdialysis BUN to predict equilibrated BUN and calculate double-pool Kt/V in the pediatric hemodialysis population. Am J Kidney Dis. 2000;36:98–104.
15. Maduell F, et al. Validation of different methods to calculate Kt/V considering postdialysis rebound. Nephrol Dial Transplant. 1997;12:1928–33.
16. Pedrini LA, Zereik S, Rasmy S. Causes, kinetics and clinical implications of post-hemodialysis urea rebound. Kidney Int. 1988;34:817–24.
17. Marsenic O, Pavlicic D, Bigovic G, Peco-Antic A, Jovanovic O. Effects of postdialysis urea rebound on the quantification of pediatric hemodialysis. Nephron. 2000;84:124–9.
18. Tattersall JE, DeTakats D, Chamney P, Greenwood RN, Farrington K. The post-hemodialysis rebound: predicting and quantifying its effect on Kt/V. Kidney Int. 1996;50:2094–102.
19. Smye SW, Evans JH, Will E, Brocklebank JT. Paediatric haemodialysis: estimation of treatment efficiency in the presence of urea rebound. Clin Phys Physiol Meas. 1992;13:51–62.
20. Daugirdas JT, Schneditz D. Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. ASAIO J. 1995;41:M719–24.
21. 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;15:312–7.
22. Juarez-Congelosi M, Orellana P, Goldstein SL. Normalized protein catabolic rate versus serum albumin as a nutrition status marker in pediatric patients receiving hemodialysis. J Ren Nutr. 2007;17:269–74.
23. Brem AS, Lambert C, Hill C, Kitsen J, Shemin DG. Clinical morbidity in pediatric dialysis patients: data from the network 1 clinical indicators project. Pediatr Nephrol. 2001;16:854–7.
24. Goldstein SL, Leung JC, Silverstein DM. Pro- and anti-inflammatory cytokines in chronic pediatric dialysis patients: effect of aspirin. Clin J Am Soc Nephrol. 2006;1:979–986.
25. Goldstein SL, et al. Acute and chronic inflammation in pediatric patients receiving hemodialysis. J Pediatr. 2003;143:653–7.
26. Goldstein SL, Brem A, Warady BA, Fivush B, Frankenfield D. Comparison of single-pool and equilibrated Kt/V values for pediatric hemodialysis prescription management: analysis from the centers for Medicare & Medicaid services clinical performance measures project. Pediatr Nephrol. 2006;21:1161–6.
27. Jaber BL, et al. Daily hemofiltration for end-stage renal disease: a feasibility and efficacy trial. Blood Purif. 2004;22:481–9.
28. Leypoldt JK, Jaber BL, Zimmerman DL. Predicting treatment dose for novel therapies using urea standard Kt/V. Semin Dial. 2004;17:142–5.
29. Goldstein SL, et al. Frequent hemodialysis with NxStage system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008;23:129–35.
30. Mammen C, Goldstein SL, Milner R, White CT. Standard Kt/V thresholds to accurately predict single-pool Kt/V targets for children receiving thrice-weekly maintenance haemodialysis. Nephrol Dial Transplant. 2010;25(9):3044–50.

Maintenance Hemodialysis During Infancy

19

Tim Ulinski and Pierre Cochat

Keywords
Hemodialysis • Maintenance hemodialysis • Infancy

Recent reports have indicated an increased incidence of very young patients diagnosed with and treated for end-stage renal disease (ESRD). The main diagnostic categories contributing to this increase are hereditary and congenital disorders and hemolytic uremic syndrome [1].

In most infants (i.e., children under 24 months of age) with ESRD, the treatment of choice is peritoneal dialysis (PD). However, maintenance hemodialysis (HD) may be required in certain patients dependent on the underlying renal disease, the presence of extrarenal involvement, and/or individual conditions. Chronic extracorporeal therapies in young infants should be performed only in specialized centers. Since the body of literature on maintenance HD in infants is small, we provide our personal opinion in addition to published reports [2–8].

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Maintenance HD in infants raises major problems both in the short term – such as the choice of permanent vascular access, hemodynamic tolerability, infections – and in the long term, e.g., with respect to nutrition, neurocognitive development, and statural growth. Moreover, ethical problems need to be taken into account, particularly if severe comorbidities are present.

Population

In the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), 11–12.5% of dialysis patients were less than 2 years of age at the time of initiation of index dialysis [5, 9]. However, PD was the preferred treatment modality in this age group; only about 10% of patients received HD [10, 11]. The use of HD in this age group used to be more common in Europe as about 30% of infants were treated by HD in the European Dialysis and Transplant Association Registry [12].

The following conditions may lead to selection of the HD treatment modality in infants:

Patients with loss of peritoneal function (repeated peritonitis episodes, progressive sclerosing peritonitis), leakage or nonfunction of the Tenckhoff catheter, and peritoneal damage (digestive or urinary diversion, laparoschisis, multiple frustraneous

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attempts to implant PD catheters, any other major abdominal surgery) [2, 6].

Patients with lung disease (e.g., pulmonary hypo/dysplasia) when compression of the diaphragm may be deleterious.

Patients with thoracic malformation such as in Jeune syndrome.

Children with massive liver enlargement due to either autosomal recessive polycystic kidney disease or nephronophthisis-related disease (e.g., chronic tubulointerstitial nephritis with glomerular cysts and congenital liver fibrosis).

Infants who underwent bilateral nephrectomy while awaiting subcutaneous access maturation for PD [6].

Children with compromised mesenteric blood flow.

Patients with Prune-Belly syndrome, presenting with complete abdominal muscle hypoplasia.

Patients with infantile form of primary hyperoxaluria type I, in order to achieve sufficient amount of oxalate and thereby limit oxalate burden prior to combined liver–kidney transplantation [13]. In such patients, HD may be associated with concomitant PD in order to improve oxalate removal but PD by itself is not efficient enough.

Extracorporeal Blood Circulation

For obvious reasons, infants on HD must be treated in hospital-based experienced pediatric centers, whereas those on PD can be managed at home. However, the technical approach to infants on HD is often inadequate because of technical limitations. Due to low return on investment for companies, the availability of suitable catheters, blood lines, dialyzers, and machines remains poor.

Vascular Access

Percutaneous dialysis catheters are used by most centers offering infant HD [6]. In order to avoid endothelial damage and later venous stenosis, catheters should be inserted at the lower part of the right internal jugular vein toward the superior vena cava and right atrial junction. Ligation of jugular veins should be avoided. Subclavian and femoral veins may also be used.

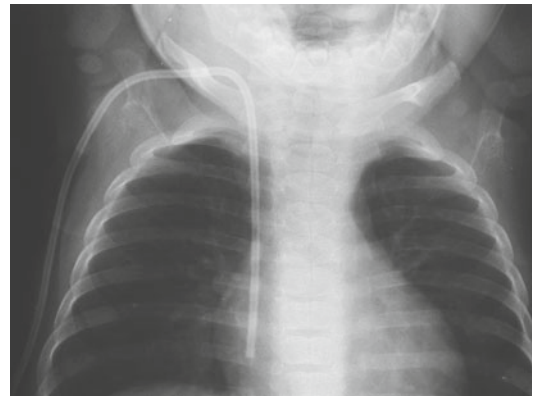

Fig. 19.1 Single-lumen catheter in a 10-month-old boy

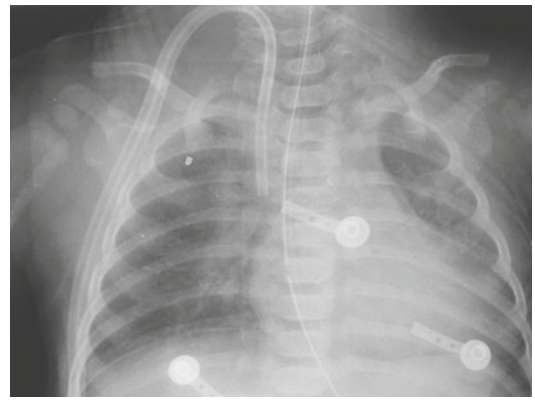

Fig. 19.2 Dual-lumen catheter in an 8-month-old girl

Table 19.1 Advantages and drawbacks of single- and dual-lumen catheters in infants

	Single lumen	Double lumen
Usual catheter size	4–6 Fr	6.5–8 Fr (10–18 cm)
Recirculation	High	Low
Blood flow rate	High	Low
Vessel:catheter diameter ratio	High	Low
Resistance	Low	High
	See Fig. 19.1	See Fig. 19.2

According to Poiseuille's law ("fluid flow through a tube varies with the fourth power of its radius, r^4"), best access is short and of wide diameter, so that a single-lumen catheter with a Y-connector close to the cannula allows greater blood flow and should therefore be preferred to dual-lumen device despite recirculation (Figs. 19.1 and 19.2) (Table 19.1) [14]

Table 19.2 Characteristics of dialyzers adapted to infants

Dialyzer	Membrane material	Effective membrane area (m²)	Priming volume (TMP = 200 mmHg) (mL)
100 HG Cobe	Hemophane	0.2	18
Polyflux 2H	Polyamix	0.2	17
FX paed	Polysulfone	0.2	18
Sureflux 30L	Triacetate	0.3	35
LunDia Pro 200	Polycarbonate	0.5	45
Sureflux 50L	Triacetate	0.5	45
FX40 Fresenius	Polysulfone	0.6	32
200 HG Cobe	Hemophane	0.6	34
Polyflux 6H	Polyamix	0.6	52

The average catheter durability is 3–4 months. Major complications include infection, clotting, and kinking [2, 6, 15]. The risk of infection is lower with cuffed catheters [16]. Partial catheter thrombosis may require local urokinase (or rtPA) and/or catheter exchange via a guide wire. Complete thrombosis leads to catheter failure and necessitates removal. *The creation of an* arteriovenous fistula is a challenging procedure in infants, due to the delicate vessel size and structure. However, highly specialized programs have provided encouraging reports regarding the placement and use of arteriovenous fistulae in young infants [17].

In selected patients, mostly in those weighing more than 10 kg, arteriovenous fistula can be performed using microsurgery. However, only few surgeons worldwide have got adequate training and experience in creating dialysis fistulas in infants [17–19]. A maturation period of 6–12 weeks is usually required before the fistula can be used, starting with single-needle access (diameter ≤17 G). Dual-needle punctures should only be started 8–12 weeks after initial surgery and after careful reevaluation by the specialized surgeon. Surgical revision of fistulae, such as superficialization (and lipectomy) is very often required [11, 20].

Extracorporeal Blood Flow Rate

A widely used formula determines extracorporeal flow rate (Q_D) by body weight (BW, in kg): $Q_D\ (mL/min) = (BW + 10) \times 2.5$. In our experience, this equation gives inadequately low blood flow rate targets. In 23 infants undergoing chronic HD in our unit over the past 10 years, a much higher extracorporeal blood flow rate was achieved on average: 16 ± 5 mL/kg/min. The optimal blood flow rate should be established gradually, both over the course of multiple sessions (within several weeks) and during each HD session. It should be determined individually, taking all technical, surgical, and medical aspects into consideration.

Extracorporeal Circuit

The total extracorporeal blood volume should not exceed 7–10% of the child's blood volume, which approximates 80 mL/kg BW. In addition, at least during the first HD sessions, it is recommended to use priming with either normal saline or 4–5% albumin and connect arterial and venous lines simultaneously.

Dialyzers

The choice of dialyzers adapted for use in infants is limited due to technical and financial constraints (Table 19.2). The membrane surface area should be approximately 75–100% of the patient's body surface area.

Anticoagulation

Anticoagulation is achieved by standard heparin (continuous infusion, 10–30 IU/kg BW per hour; bolus, 10–20 IU/kg BW) or low-molecular-weight heparin (0.5–1 mg/kg, single injection at the beginning of the session).

In order to avoid obstruction of the catheter lumen, heparin (1,000–2,000 IU/mL) should be instilled at the end of each HD session.

Blood Lines

The use of special pediatric tubing systems with fill volumes starting at 20 mL is required to limit the volume of the extracorporeal circuit. The dialysis membrane is best protected by an arterial expansion chamber, which is not incorporated in the line of small children to reduce extracorporeal volume [21].

Adjustment of Post Dialysis Dry Weight

The estimation of dry weight is challenging. Serum protein levels and their change during the dialysis session are poor indices as serum protein is strongly influenced by residual renal function and nutritional status. Bioelectrical impedance analysis and online measurement of changes in hematocrit are not widely available. The adjustment of dry weight could therefore combine (1) the blood pressure profile during ultrafiltration, (2) echocardiographic parameters, (3) inferior vena cava diameter measurement by ultrasound (normal: 8–11.5 mm/m², collapse index (reduction vena cava diameter during inspiration) = 40–75%), and (4) intradialytic heart rate change.

Dialysis Adequacy

Urea kinetic modeling has not found wide acceptance in infants for practical reasons: variations of the duration of dialysis session due to poor dialysis tolerance or vascular access problems, frequent changes in blood urea nitrogen concentration, e.g., due to nutritional status, characteristics of distribution volume in this age group, frequent changes in extracorporeal blood flow rate during HD session, etc. However, the natural logarithm formula for Kt/V proposed by Daugirdas has been applied to infants with an acceptable error [22, 23]. Despite the absence of outcome studies on the minimally acceptable Kt/V in infants and the above-mentioned difficulties, in several countries (e.g., US and Germany), Kt/V measure is mandatory in children of any age as a performance quality.

Prescription and Monitoring During the Session

Short daily dialysis (1.5–3 h sessions, 4–6 times per week) seems to be the most appropriate HD modality in infants, particularly in those with malnutrition, chronic overhydration, intractable hypertension, left ventricular hypertrophy, growth retardation [10], and primary hyperoxaluria requiring efficient oxalate clearance [11, 24]. However, this is only possible for patients living in an acceptable distance from the dialysis center.

During the session, attention should be paid to possible excessive ultrafiltration, the risk of which should be minimized by close monitoring. The ultrafiltration error rate of most HD machines is ±50 mL/h, accumulating to an error margin of ±150–250 mL by the end of a session. While entirely acceptable in adults and older children, these error rates can lead to severe fluid imbalance in young infants. The use of infant scales during HD does not solve this problem completely as scale measurements may again be influenced by a variety of factors.

The best option is therefore to have a good knowledge of ultrafiltration accuracy for individual machines used in infants and to monitor closely the changes in hemodynamic parameters.

Intradialytic hypotension should be managed with saline or 4% albumin as volume replacement.

States of osmotic disequilibrium are frequent in infants and may be prevented by a low blood flow rate during the first few dialysis sessions (3–5 mL/kg BW), by a short duration of the first sessions and, if needed, by the administration of 10% or 20% mannitol (1 g/kg infusion over 1–2 h).

Temperature control may be difficult due to significant extracorporeal blood volume and relatively slow blood flow rate, so that normothermia is recommended by adjusting dialysate bath temperature [25].

Table 19.3 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

Anemia Management

The fraction of hemodialyzed infants requiring recombinant human erythropoietin (rhEPO) is comparable to other age groups, i.e., 88% of infants in the NAPRTCS report including both HD and PD patients [5]. The average weight-related maintenance dose of rhEPO is higher in young patients, up to 200–650 IU/kg per week from our experience and has to be frequently adapted to the rapidly changing hemoglobin normal values (Table 19.3).

Just as in older children, intravenous administration is preferred in infants on HD to avoid subcutaneous injection pain. In case of unstable hemoglobin levels or excessive rhEPO requirements, darbepoetin alpha [26] can help to normalize and stabilize hemoglobin levels.

Due to poor enteric absorption, it is recommended to give iron by the intravenous route. Ferrogluconate, administered at a once-weekly dose of 1 mg/kg, reliably maintains sufficient iron stores in infants on chronic HD.

Renal Osteodystrophy

Hyperparathyroidism is an early and frequent complication in infants with chronic renal failure and its careful management is vital while on HD to avoid rhEPO resistance, skeletal pain, bone deformities, pathological fractures, and even long-term vascular complications. The parathyroid hormone (PTH) level should be checked at least once per month.

In infants on short daily HD, there is a risk of phosphate depletion leading to bone disease and fracture. It is therefore recommended to add phosphorus either by diet or by medication in order to avoid hypophosphatemia (<1.5 mmol/L), while at the same time maintaining adequate PTH control. As calcium requirements have to be adjusted to the rapidly growing bones in infants, calcium concentration in the dialysate bath should not be lower than 1.5 mmol/L. In case of intensified dialysis regimen, addition of phosphate to the dialysate might be necessary.

Metabolic acidosis exerts a detrimental effect on the growth and nutritional status of hemodialyzed infants [29–32]. Therefore, serum bicarbonate levels should be closely monitored and maintained above 22 mmol/L. Oral administration of sodium bicarbonate and the use of higher sodium bicarbonate dialysate concentration are equally applicable measures.

Practical Approach to the Course of a Dialysis Session

Pain and Psychological Care

The psychological assessment and preparation of infants is difficult as it is often impossible to explain the care which is scheduled or in process. Instead of such information, the environment may be adapted using music, movies, games, and affection.

The preference for catheters in infant HD largely eliminates pain and anxiety related to the initiation of the HD procedure. In patients with arteriovenous fistulas, pain minimization by use of a topical anesthetic cream (Emla) is an essential prerequisite.

Even with the short daily HD strategy, each session is conceived long-lasting by the child. Moreover, the child is largely unable to stand, turn over, or toddle while on HD. Hence, the timing of the sessions should either be synchronized with the child's sleeping time or trained staff members such as a play specialist, psychologist, speech therapist, or a specially trained kindergarten mistress should be available to spend quality time with the child.

In most centers, parents are present and often involved at any stage of the session. However, it can become important to set limits to parent involvement in order to preserve stress-free interaction between the child, the parents, and the medical team.

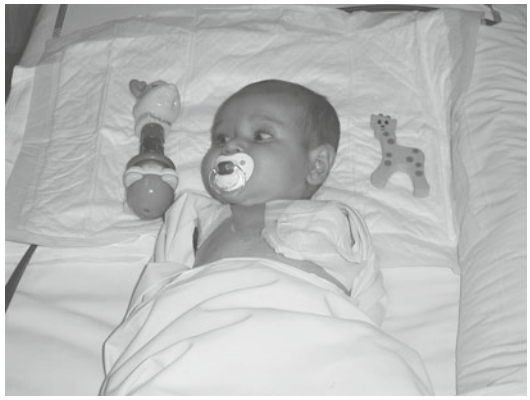

Fig. 19.3 Child's retention using cloth prior to catheter connection

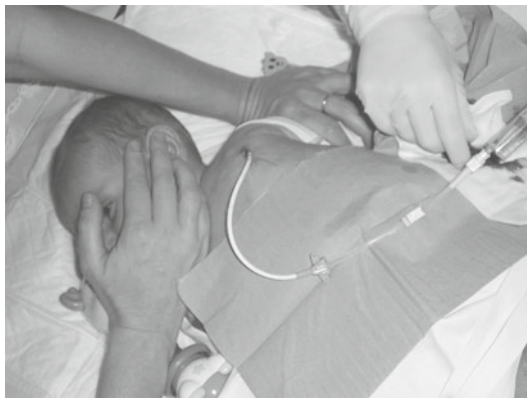

Fig. 19.4 Gentle manual retention of the child at the time of catheter connection

Infant HD requires the continuous presence of a caregiver throughout the dialysis session. Therefore, a 1:1 or 2:1 nurse-to-patient ratio is usually needed.

Beginning of the Session

When connecting the child's permanent vascular access to the dialysis circuit, nurses meet several difficulties (i.e., patient's retention, catheter dysfunction due to obstruction or mobilization, etc.) with an associated risk of infection, technical misuse, catheter removal, etc. (Figs. 19.3 and 19.4).

Intradialytic Hypotension

Intradialytic hypotension is more frequent and occurs more commonly unexpected in infants than in older children. Clinical features include pallor (sometimes with cyanosis), vomiting, irritability, drowsiness, sudden awakening during sleep, sudden crying while resting, sweating, headache, and sometimes seizures. Oxygen masks are poorly accepted because of restlessness; it seems preferable to provide oxygen from a pipe.

Infections

Due to the very frequent use of central venous catheters, the number of infections in infants on HD is higher than in older children. Rapid antibiotic treatment is often required even before the identification of the causative agent. A reliable early marker of bacterial infection is not available. Procalcitonin is about twofold increased in HD children due to deficient renal clearance [27] and fails to distinguish viral from bacterial infections in this patient group.

Outcomes

Patient survival is generally decreased in the youngest age group of dialysis patients. One-year survival rates of 83–89% have been reported both with PD and HD in children starting dialysis with less than 1 year of age [5, 8]. In most series, the major cause of death is infection [7, 8, 12].

Intellectual development is a major issue in infants undergoing chronic HD. Apart from general factors related to infantile ESRD such as energy and protein malnutrition, the frequency and duration of hospitalizations and parental overprotection, brain damage may result from the HD procedure due to repeated hypotensive episodes and hypoxemia during HD sessions [2, 28]. This possibility has neither been verified nor refuted in clinical trials.

Conclusion

Although the ultimate goal is renal transplantation, maintenance HD can provide an excellent primary or alternative treatment in infants when PD has failed or is not an option. The use of HD in infants should be limited to experienced pediatric nephrology centers and requires very frequent adaptation of all dialysis parameters.

References

1. van der Heijden BJ, van Dijk PC, Verrier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004;19:213–21.
2. 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.
3. Bunchman TE. Infant dialysis: the future is now. J Pediatr. 2000;136:1–2.
4. 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.
5. 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.
6. 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.
7. Sousa CN, Gama M, Andrade M, Faria MS, Pereira E. Haemodialysis for children under the age of 2 years. J Ren Care. 2008;34:9–13.
8. Wood EG, Hand M, Briscoe DM, Donaldson LA, Yiu V, Harley FL, Warady BA, Ellis EN. Risk factors for mortality in infants and young children on dialysis. Am J Kidney Dis. 2001;37:573–9.
9. Lerner GR, Warady BA, Sullivan EK, Alexander SR. Chronic dialysis in children and adolescents. The 1996 annual report of the North American pediatric renal transplant cooperative study. Pediatr Nephrol. 1999;13:404–17.
10. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14:297–303.
11. Bunchman TE. Pediatric hemodialysis: lessons from the past, ideas for the future. Kidney Int Suppl. 1996;53:S64–67.
12. Ehrich JH, Rizzoni G, Brunner FP, Fassbinder W, Geerlings W, Mallick NP, Raine AE, Selwood NH, Tufveson G. Renal replacement therapy for end-stage renal failure before 2 years of age. Nephrol Dial Transplant. 1992;7:1171–7.
13. Cochat P, Koch Nogueira PC, Mahmoud MA, Jamieson NV, Scheinman JI, Rolland MO. Primary hyperoxaluria in infants: medical, ethical, and economic issues. J Pediatr. 1999;135:746–50.
14. Coulthard MG, Sharp J. Haemodialysing infants: theoretical limitations, and single versus double lumen lines. Pediatr Nephrol. 2001;16:332–4.
15. Beanes SR, Kling KM, Fonkalsrud EW, Torres M, Salusky IB, Quinones-Baldrich WJ, Atkinson JB. Surgical aspects of dialysis in newborns and infants weighing less than ten kilograms. J Pediatr Surg. 2000;35:1543–8.
16. Goldstein SL, Macierowski CT, Jabs K. Hemodialysis catheter survival and complications in children and adolescents. Pediatr Nephrol. 1997;11:74–7.
17. Bourquelot P. Vascular access in children: the importance of microsurgery for creation of autologous arteriovenous fistulae. Eur J Vasc Endovasc Surg. 2006; 32:696–700.
18. Bagolan P, Spagnoli A, Ciprandi G, Picca S, Leozappa G, Nahom A, Trucchi A, Rizzoni G, Fabbrini G. A 10 year experience of brescia-cimino arteriovenous fistula in children: technical evolution and refinements. J Vasc Surg. 1998;27:640–4.
19. Bourquelot P, Gagnadoux MF. Vascular access for hemodialysis in children. Pediatr Nephrol. 1997;11:659–60.
20. Bourquelot P, Tawakol JB, Gaudric J, Natario A, Franco G, Turmel-Rodrigues L, Van Laere O, Raynaud A. Lipectomy as a new approach to secondary procedure superficialization of direct autogenous forearm radial-cephalic arteriovenous accesses for hemodialysis. J Vasc Surg. 2009;50:369–74, e361.
21. Fischbach M, Terzic J, Menouer S, Provot E, Bergere V. Hemodialysis in children: principles and practice. Semin Nephrol. 2001;21:470–9.
22. Goldstein SL, Sorof JM, Brewer ED. Evaluation and prediction of urea rebound and equilibrated Kt/V in the pediatric hemodialysis population. Am J Kidney Dis. 1999;34:49–54.
23. Goldstein SL, Sorof JM, Brewer ED. Natural logarithmic estimates of Kt/V in the pediatric hemodialysis population. Am J Kidney Dis. 1999;33: 518–22.
24. Katz A, Bock GH, Mauer M. Improved growth velocity with intensive dialysis. Consequence or coincidence? Pediatr Nephrol. 2000;14:710–2.
25. Bunchman TE, Maxvold NJ, Kershaw DB, Sedman AB, Custer JR. Continuous venovenous hemodiafiltration in infants and children. Am J Kidney Dis. 1995;25:17–21.
26. Andre JL, Deschenes G, Boudailliez B, Broux F, Fischbach M, Gagnadoux MF, Horen B, Lahoche-Manucci A, Macher MA, Roussel B, Tsimaratos M, Loirat C. Darbepoetin, effective treatment of anaemia in paediatric patients with chronic renal failure. Pediatr Nephrol. 2007;22:708–14.
27. Lorton F, Veinberg F, Ielsch D, Deschenes G, Bensman A, Ulinski T. Procalcitonin serum levels in children

undergoing chronic haemodialysis. Pediatr Nephrol. 2007;22:430–5.
28. Brem AS, Lambert C, Hill C, Kitsen J, Shemin DG. Clinical morbidity in pediatric dialysis patients: data from the network 1 clinical indicators project. Pediatr Nephrol. 2001;16:854–7.
29. Fischbach M, Dheu C, Seuge L, Orfanos N. Hemodialysis and nutritional status in children: malnutrition and cachexia. J Ren Nutr. 2009;19:91–4.
30. Mehls O, Tonshoff B, Haffner D, Wuhl E, Schaefer F. The use of recombinant human growth hormone in short children with chronic renal failure. J Pediatr Endocrinol. 1994;7:107–13.
31. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22:1689–702.
32. Srivaths PR, Wong C, Goldstein SL. Nutrition aspects in children receiving maintenance hemodialysis: impact on outcome. Pediatr Nephrol. 2009;24:951–7.

Intensified Hemodialysis in Children

20

Dominik Müller and Denis Geary

Keywords
Intensified hemodialysis • Children • Pediatric dialysis • End-stage renal disease

Intensified Programs: Rationale

Renal transplantation is considered as the therapy of choice in childhood and adolescent end-stage renal disease (ESRD). Survival after renal transplantation is significantly superior to hemodialysis and the younger the children, the more pronounced this discrepancy becomes. However, the availability of organs limits transplantation and the time on the waiting list may take several years because of national or international transplantation policies and laws and individual factors like age, body weight, and alloimmunization. Therefore, dialysis programs should not only aim to bridge the time to transplantation simply to guarantee survival. Instead, they must be optimized in order to maximally correct the disadvantages of ESRD including improvement of psychosocial well-being [1].

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Currently, conventional or maintenance dialysis programs performed three times for 4–5 h per week guarantee short-term survival for most patients. Despite delivering a minimum Kt/V urea of 1.2, they are not able to ameliorate sufficiently the consequences of ESRD, neither in adults nor in children. Electrolyte disturbances, fluid overload, and hypertension persist in these patients. Medium- and long-term problems like secondary hyperparathyroidism, phosphate control, and cardiovascular disorders also contribute significantly to morbidity and mortality. Several studies have confirmed that ESRD in young adults is associated with a tremendously high morbidity and mortality when compared to the normal population. Furthermore, they show that the age of the patients is relevant, and there is a linear negative correlation between age at ESRD and morbidity and mortality. Additionally, and especially in children, malnutrition and poor growth are major complications in ESRD.

Two major studies have been conducted in the adult population to determine whether increasing the delivered dialysis dosage per session or per week is sufficient to ameliorate the negative consequences of ESRD in terms of improving morbidity and/or mortality. The HEMO study group demonstrated that increasing the delivered dosage

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of thrice-weekly dialysis (from an eKt/V of 1.36 in the standard group to 1.53 in the intensified group) did not improve morbidity or mortality [2]. Neither did the use of high-flux filters improve outcome. Interestingly, similar results have been obtained in patients on peritoneal dialysis. Here, the ADEMEX (Adequacy of Peritoneal Dialysis in Mexico) study demonstrated that also in this population, increasing Kt/V did not improve outcome in terms of morbidity and mortality [3].

These trials challenged current concepts of dialysis adequacy, and specifically the value of Kt/V as the major marker of morbidity and mortality but opened on the other hand new avenues for alternative concepts. Considering the pediatric aspects, such concepts that vary basically the duration and timing of dialysis may provide several advantages, like improved growth and nutrition but also social rehabilitation. Education is only possible during a certain time of life. If this narrow frame is missed, e.g., by spending three daytime dialysis sessions per week in an in-center dialysis unit, accompanied by intra- and interdialytic problems, this time is lost for education and social contacts. Such patients face the fact that they will probably be recipients of social welfare rather than givers for their entire life. Whereas increased frequency of HD, particularly if performed in hospital, increases social isolation, this is at least partially negated by the improved well-being experienced by these patients.

History

In 1966, prompted by a need to reduce the costs associated with the large numbers of staff required for in-center HD and to reduce time at the hospital for patients who at that time received 8–12 h dialysis, two or three times weekly, Eschbach et al. initiated home HD [4]. They described eight adult patients who underwent 20–30 h of nocturnal HD (NHD) weekly. This treatment regimen minimized restrictions on the patients' daily lives, and allowed liberalization of dietary salt and protein intake. In 1969, De Palma and colleagues in Los Angeles described seven home HD patients who were switched from conventional in-center HD to a 5 day per week regimen of 4–5 h each at home [5]. They described increased appetite and improved blood pressure control. Unreliable equipment and excessive cost resulted in discontinuation of this program. These innovations occurred around the time when the use of HD for maintenance therapy was first reported in children [5]. Since these reports in the 1960s, hemodialysis in North America has been predominantly prescribed for 3–4 h on a thrice weekly basis.

Since 1968 in Tassin in France, more than 800 patients have been treated in-center for 8 h thrice weekly [6]. This treatment has demonstrated a two- to threefold lower mortality for patients on HD compared with those on conventional HD in the Unites States, but has nonetheless not widely been adopted, presumably because of the associated increased staffing costs and inconvenience to patients and staff. In Italy, in the early 1980s, a number of programs were developed for provision of home HD five to seven times weekly, each session lasting 3–4 h. Once again, compared with conventional thrice-weekly HD, these patients reported greatly improved overall well-being, reduced intradialytic symptoms, and improved blood pressure control [7].

In North America, the reintroduction of intensified HD for adults was pioneered by Uldall, in Toronto, who introduced the concept of home slow NHD [8]. The impetus for this initiative was to reduce the impact of the increasing population of adult in-center dialysis patients. Five patients were initially described who underwent 8 h of dialysis on five to seven nights weekly with a dialysate flow of 100 mL/min. Vascular access was provided by the recently designed internal jugular central venous line. This treatment overcame the social inconvenience of frequent hospital visits. Remote monitoring of the treatments was provided to overcome the fears of staff and patients that major intradialytic complications might occur and be undetected. This program has been sustained for more than 15 years, and its success has led to the introduction of frequent or prolonged HD for adults in multiple centers globally.

Individual clinicians have for many years provided intensive HD for children in special circumstances, specifically for infants requiring intensive nutrition, and for specific diseases such as primary hyperoxaluria. However, these treatments

have usually been for relatively short periods of time, as a bridge to transplantation, and have not been studied comprehensively as a maintenance treatment. The feasibility and practicality of frequent or prolonged dialysis as maintenance treatments for older children were more slowly realized. Concerns existed, and are still expressed, that school attendance and social development would be adversely affected by a requirement for increased hours attached to a dialysis machine – though there is good evidence that barely half of children on conventional thrice-weekly HD in North America do attend school regularly [9]. Also, the fears of severe complications, and the requirement for a responsible care provider were greatly magnified for children compared with adults. Despite these concerns, in 1999, Tom et al. showed that HD prescribed for 5 h thrice weekly, provided solute removal that greatly exceeded recommendations at that time, and was associated with better growth than previously reported with shorter dialysis treatments [10]. This clearly suggested that increased dialysis delivery might improve well-being for children, and provided an impetus to explore "intensified" HD for children.

This challenge was accepted by a number of nephrologists in Europe and North America who initiated a variety of programs to provide more frequent and or prolonged hemodialysis for children both in-center and in their homes [10–17].

Definition

Intensified programs broaden the spectrum of hemodialys is prescriptions. Today, they do not substitute for conventional programs. Thus, intensified programs can be considered as an alternative and superior option to conventional programs for appropriately selected patients.

Intensified programs basically differ from conventional programs by increased duration and/or frequency of the dialysis so that an increase dosage is delivered. Thus, they can be grouped according to their duration (hours per session), frequency (three times per week to six or even seven times per week), their location (in-center or at home), and daytime (day or nocturnal). Furthermore, intensified programs can be classified according to the blood and the dialysate flow (slow) when compared to conventional HD programs. The latter is currently only applicable to daily nocturnal programs as have been reported in adult patients from Canada. All three major concepts of intensified programs have been demonstrated to be feasible in children and adolescents (Table 20.1).

Patient Selection Criteria

Theoretically, all children will benefit from intensified HD and the primary basis for acceptance is the expressed wish of the patients and/or the care givers. Whereas it is possible to dialyze a patient too rapidly, it is difficult to imagine a circumstance where a patient is overdialyzed. A urea clearance of 10 mL/min equates to approximately 14 L/day, which in turn approximates 100 L/week. For a patient who is dialyzed three times/week therefore, a clearance of ≈30 L/session is required; if divided by the distribution volume of urea (total body water, v) for a 70 kg adult therefore, the Kt/V urea equivalent of a urea clearance of 10 mL/min is 0.75. Therefore, if a Kt/V of 1.5 is obtained thrice weekly, which represents excellent dialysis according to current recommendations from both European and American experts, this still only equates to a urea clearance of 20 mL/min for the week – which is still low enough to permit many of the complications of ESRD to

Table 20.1 Dialysis programs: modalities of different intensified programs when compared to conventional hemodialysis

HD program	Sessions per week	Duration (h)	Modality	References
Conventional	3	3–5	In-center	
Short daily	5–6	2–3	In-center	Fischbach et al. [13]
	6	2–3	Home	Goldstein et al. [12]
Nocturnal daily	5–6	8	Home	Geary et al. [16]
Nocturnal intermittent	3	8	In-center	Müller et al. [17]

Table 20.2 Criteria for patient selection in intensified hemodialysis regimens

Selection criteria
• Patient size
• Facility and staff experience
• Vascular access
• Underlying disease and comorbidities
• Psychosocial support/availability of a treatment supervisor
• Geographic location
• Persistent noncompliance
• Anticipated duration of dialysis

manifest. Certainly, it is difficult to argue against doubling that total weekly clearance to approximate 40 mL/min, which at best continues the patient in the equivalent state to chronic kidney disease (CKD) stage 3. This roughly estimates the status of children who receive twice the standard amount of weekly HD. However, achievement of a Kt/V of approximately nine on a thrice-weekly schedule is impractical, will invariably expose the child to the risk of disequilibrium during each procedure, and because the treatment is so discontinuous, will not provide the physiological equivalence of a natural renal urea clearance of 40 mL/min. Therefore, the selection of children for intensified HD does not need to consider an argument that excessive HD might be provided.

We have not included an economic argument for or against the introduction of intensive HD for the following reasons:

(a) Costs will vary according to the type of intensive HD introduced, e.g., home versus in-center.
(b) The overwhelming evidence of vastly increased mortality for children treated for ESRD according to current recommendations, when compared with the normal population, must outweigh cost considerations.
(c) Evidence that neither pediatric nephrologists or dialysis nurses rank either governmental or hospital costs highly when considering the introduction of dialysis for infants with renal failure.

The selection criteria of children for intensified HD should include the factors outlined in Table 20.2 and are discussed in detail in the following.

Patient Size

For home HD, minimum patient weight will usually be 20 kg. This somewhat arbitrarily selected weight criterion is chosen for children under consideration for home HD because it corresponds roughly to a patient size and age at which the child will be expected to cooperate during the procedure. Also, smaller children require closer monitoring than is reasonable for a home caregiver to provide. Finally, this weight child has a blood volume which is sufficient to allow a required extracorporeal volume without the need for frequent blood priming of the blood lines and dialyzer. Infants on the other hand are often selected for intensified in-center HD, so that fluid restriction will not be necessary and nutrition will not be compromised.

Facility and Staff Expertise

Children undergoing intensive HD, whether at home or in-center must be under the supervision of staff with appropriate expertise. Ordinarily, the staff involved should include physicians, nurses, social workers, and dietitians with expertise in the management of children with ESRD. However, for a patient being considered for home HD, this does not exclude an adult nephrologist as the physician with primary responsibility for the procedure provided nurses with expertise in pediatric dialysis are closely involved in the day-to-day treatment decisions, and provided a pediatric nephrologist supervises the overall care of the patient.

For small children undergoing in-center frequent or prolonged HD, the primary responsible team should be trained in provision of dialysis for children.

Vascular Access

Provision of intensified hemodialysis, whether at home or in-center, should not be limited by a need for a specific type of vascular access. Either central venous catheters or arteriovenous fistulae

may be used. The former has the advantage that frequent needle pokes are not required, and at least theoretically the risk of needle displacement may be reduced. However, this advantage is offset by the relative permanence of a fistula access for a patient who may have been specifically selected for intensified dialysis because of the likelihood they would require dialysis for a prolonged time. Also, as discussed below (Technical Considerations), with current safeguards, the risk of needle dislodgement, even for home patients, is very small and acceptable. Whereas aneurysmal dilatation of a fistula may occur, and perhaps this risk is increased with frequent needle punctures, the use of only two to three needle puncture sites on a repetitive basis allows a track to form, which should facilitate needle insertion without damaging the vessel wall. Single needle is also feasible in patients, if the fistula allows high blood flow. Adolescents, if willing, can puncture themselves, and it has been demonstrated that this can prolong shunt survival. Thus, as in conventional programs, a fistula is the preferred access.

Underlying Disease and Comorbidity

Children with primary hyperoxaluria require intensive hemodialysis (perhaps supplemented with PD) to maximize oxalate removal and prevent crystal deposition in extra-renal organs, while awaiting renal or combined renal–liver transplantation.

Intensified HD may also be required, at least on a temporary basis, for children with ESRD undergoing chemotherapy for a primary renal or other neoplasm.

Finally, the increasing population of children with nonrenal, solid organ transplants, who have developed ESRD, may have impaired cardiac or hepatic function, which may necessitate intensified dialysis. It should be emphasized that intensified HD is especially suited to very ill patients because of the superior detoxification and the relatively slow removal of water.

Psychosocial Support/Care Provider

For children on home HD, a consistent, reliable person must be available to assist the patient. The requirements for these assistants will vary, but all must be capable of recognizing and responding to potential complications related to the dialysis procedure, and terminate the procedure safely if required. The assistant is usually, but not invariably a parent. For most patients, except a few older teenagers, the assistant must know how to set up the dialysis machine and administer the treatment. The psychosocial burden that is imposed on the assistant is enormous, and burnout can be anticipated. Selection of patients for intensified home HD must include a thorough evaluation of potential assistants, and input from a social worker who is familiar with the process is mandatory. Nursing input is also essential, to assist with the psychosocial evaluation of the patient and assistant, and even more important to determine if the patient and assistant are both capable of learning and performing the dialysis procedure safely at home.

For in-center intensified HD, the need for psychosocial support is clearly less than for home-based treatment. On the other hand, the expense for families associated with frequent prolonged visits to the hospital should not be underestimated (missed work, travel and parking, childcare for other children, etc.). When nocturnal dialysis is considered, coordination with psychologists, social workers, and dietitians should ensure one comprehensive appointment per month during daytime in the outpatient clinic.

Geographic Location

For in-center intensified HD, frequent and prolonged hospital visits mandate that the family lives close to the hospital. Thus, such programs are especially feasible in metropolitan areas. We believe that traveling more than 1 h to or from the dialysis center is not acceptable since it counteracts the benefits of intensified programs on the quality of life.

On the other hand, for patients located a long distance from the hospital, particularly if they cannot tolerate PD, some form of home HD is recommended. The effort that is expended by hospital staff and also families to accommodate home HD, and the teaching that is required to learn the procedure, will be most beneficial if practiced in a way that optimizes dialysis care for the child, i.e., either frequent daily sessions, or prolonged overnight dialysis.

Persistent Noncompliance

Patients who do not adhere to fluid and other dietary restrictions, as well as medications are particularly suited to, and will benefit the most from intensive HD. For children undergoing intensive HD in the hospital, there is an assurance of increased observation by medical staff, the ability to ensure that medications are given if provided post each procedure, opportunities for ongoing education of the patient and family about the complications that occur with poorly treated renal failure, and the opportunity to reduce the need for the restrictions with which the patient cannot adhere.

For children undergoing home HD, nonadherence to dialysis can be a problem if remote monitoring of dialysis is not possible. However, if dialyzed frequently for either short or nocturnal sessions, children require much less medications and no fluid or dietary restrictions, so that the need for compliance is greatly reduced.

Anticipated Duration of Dialysis

For children undergoing dialysis at home, there is an expectation that the patient will remain on HD for at least 1 year. Training, which takes about 6 weeks, purchase of equipment for home use, and renovations to the patient's home make it economically and socially unrealistic to start home HD for a shorter period. For children requiring intensive HD in a hospital dialysis unit, there is no limitation on the anticipated duration of dialysis. If the perceived benefits outweigh the patient inconvenience, or if the patient meets some of the other criteria discussed above, increased dialysis should be prescribed.

Technical and Staff Requirements for Intensified Hemodialysis

The technical and staffing requirement for intensified HD will vary depending on whether the dialysis is provided in-center or at home, and also on the selected dialysis modality (standard HD, slow HD as provided by Nx Stage method or hemodiafiltration).

If hemodialysis or hemodiafiltration is provided in-center, the equipment needs are similar to those used for standard thrice-weekly HD/HDF, although the dialysis machine must be capable of dialysis flows as low as 100 mL/min for some patients on long overnight HD.

For intensive hemodiafiltration, clearly a machine must be selected, which is capable of providing predilution and replacement fluid infusions, in addition to the regular dialysis component. The patients treated by Fischbach using this methodology have used a Fresenius 4,008 machine with high-flux polysulfone dialyzers. Dialysate, blood, and predilution/replacement fluid volumes have been chosen to provide a Kt/V of at least 1.5 per session. Each treatment session lasts 3 h and is undertaken five to six times weekly. The machine provides online clearance monitoring which displays Kt/V values. The disadvantage of hemodiafiltration as compared with hemodialysis is the need for ultrapure dialysis water, which (although optimal for all dialysis patients) is not available in many dialysis units.

The Nx Stage machine uses sterile dialysate provided in bags. This system is particularly suited for home dialysis because it requires little modification of home plumbing, and provides pyrogen-free dialysis fluid in a compact machine. The cartridge including dialyzer and lines has an extracorporeal volume of 210 mL, which has precluded its use in children weighing less than 35 kg. In the reported pediatric experience with this home dialysis system, the authors used the 4.5 or 5 L bags of dialysate, which clearly limits

the amount of dialysate that is deliverable and either reduces the efficiency or duration of dialysis that is achievable. A more recent innovation with this system uses a concentrate bag which can deliver 60 L of mixed dialysate in a 7 h period. Again this limits the dialysate flow rate to a maximum of less than 150 mL/min for a dialysis lasting 7 h so that the actual delivered dose of dialysis is less than is possible with prolonged HD using conventional dialysis machines. Finally, the Nx Stage system uses lactate-based fluid, which may be a concern for some patients.

Provision of conventional HD in the home requires sufficient space to store a machine, and supplies similar to children on peritoneal dialysis. If NHD is prescribed, the bedroom must be of sufficient size to accommodate a dialysis machine. Also required are an activated carbon water purification unit and a reverse osmosis machine; finally, if the local water is particularly hard, a water softening unit may be needed.

Conventional HD machines are used at home, though a dialysate flow as low as 100 mL/min should be possible for some children on NHD. Real-time monitoring of dialysis-related data is usually recommended for children on NHD, and the machine should have a port to connect with a central monitoring site via a personal computer.

Home HD requires that the water supply continue uninterrupted when other family members are bathing, and drainage must be sufficient to accept the flow of effluent, which might be as great as 30 L/h. The home electrical supply must be sufficient to ensure sufficient power supply for the dialysis machine and water treatment unit. Flooring may be damaged by dialysate or water leakage from the dialysis or water treatment machines, so that waterproof flooring is preferred; alternatively, pans should be placed beneath the machines to collect leaked fluid.

A theoretical "ideal" home hemodialysis machine has been described by Drs. Kjellstrand [18], and the technical components are outlined in Table 20.3. This ideal machine contains some components of the different machines described above, and includes other attainable and valuable innovations. This machine will permit both short and long dialysis sessions, and also incorporate diafiltration to facilitate removal of large-molecular-weight toxins. Patient convenience and adherence will be enhanced if some such hybrid form of dialysis is possible. This machine will eliminate the current approximately 30–45 min that are spent on set up and tear down of the dialysis equipment and dialysis will be provided via a cartridge including lines and dialyzer, which is heat sterilized and reusable on multiple occasions. Dialysate from concentrate will be prepared to a standard that surpasses the current standards for ultrapure dialysate, thereby avoiding endotoxins, plasticizers, bacterial fragments which can contaminate current fluids. The machine will also be capable of rapidly infusing a bolus of this same sterile dialysate to the patient in the event of a hypotensive event. The machine will permit single needle dialysis, thereby reducing by half the number of needle pokes and reducing the potential for damage to a fistula. Finally, the dialyzer and lines will be coated with an anticoagulant or citrate will be added to the dialysate to reduce clotting, which will eliminate the need for systemic anticoagulation in many patients. Although a theoretical machine like that described would certainly improve HD for children, both in-center and at home, for the moment patients must rely on machines which are overly complicated or too simplistic to perform all the desirable functions.

Table 20.3 Technical requirements of the ideal home hemodialysis machine

• Dialyzer and blood tubing sets are parts of the machine and replaced monthly or twice a year
• Incorporates "push-pull" hemodiafiltration
• Makes all fluids needed for dialysis
• Is capable of intravenous infusion
• Can be used with single needle technique
• Has an interactive graphic screen
• Heat sanitizes itself

The obvious benefit of in-center intensive HD is that supervision is by trained staff, and the responsibility for care does not fall upon a family member. This removes a major obstacle to the use of intensified HD in children. However, there is a substantial cost involved in provision of intensive HD in-center, because of the increased

requirement for highly trained dialysis nurses. By contrast, savings from reduced medication needs, including EPO, offsets these costs. Finally, since these patients are less often hospitalized for ESRD or dialysis-related complications, these programs are cost effective when compared to conventional programs. During thrice-weekly nocturnal dialysis, machines, tubing, and dialyzer do not differ from the ones used in the conventional form. Also blood and dialysate flow are comparable and dialysate bags with increased bicarbonate concentration are available from industry. Routine checks of ACT, Electrolytes, and blood pressure can be reduced to a minimum (3 × per night).

Advantages of Intensified Dialysis Programs

Impact of Intensive HD on Cardiovascular Disease

Parekh et al. analyzed the United States Renal Data System, and reported 1,380 deaths among patients aged less than 30 years who had started ESRD therapy in childhood [19]. The cardiac mortality rate was 1,000 times higher than the general population. This study focused attention on the need to define the factors contributing to cardiovascular disease in the pediatric dialysis population. Groothoff et al. reviewed deaths in children treated for ESRD in The Netherlands, and found that cardiovascular disease was a major contributor to mortality, and that the time since starting dialysis and long-standing hypertension greatly increased the risk of death [20].

A number of studies have been conducted in young adults who had initiated therapy for ESRD in childhood, and a number of features of cardiovascular disease were consistently documented.

Although the pathogenesis of cardiovascular disease in children on maintenance hemodialysis is often multifactorial, three common associated features are most often implicated:

(a) Hypertension and fluid overload
(b) Vascular calcification
(c) Chronic inflammation

Each of these issues is discussed in detail elsewhere in this book.

Of the variety of risk factors for development of cardiovascular disease in dialysis patients, some have been evaluated in patients receiving intensified HD. Jean and colleagues reviewed vascular calcification in adults receiving long (8 h) HD thrice weekly and reported that a plain radiological score confirmed the presence of vascular calcification in 83% of patients in spite of a long and intensive dialysis strategy [21].

In adults receiving NHD, Yuen et al. found similarly that cardiac calcification, evaluated by CT scans of the coronary arteries, was present in a large proportion of their adult patients [22]. Although there was only mild progression of this calcification over 16 months in these 38 patients, there was nonetheless no overall improvement.

The persistence of vascular calcification in adults on intensified HD [23, 24] suggests that cardiovascular mortality should not to be improved in this population when compared with conventional HD patients. However, somewhat surprisingly, this may not be true. When 32 patients were studied for 1 year pre, and for 2 years post starting NHD (×5–6/night), and also compared with 42 other patients on conventional HD, conversion to NHD was associated with a decrease in dialysis and cardiovascular-related hospital admissions [25].

Although there are no long-term data documenting the effects of intensified HD on the cardiovascular system in children, there are nonetheless some encouraging preliminary data. Four patients treated with the Nx Stage system for a period of 16 weeks exhibited reduction of blood pressure based both on casual readings and also on 24 h ambulatory monitoring, and none required antihypertensive medications [12]. Somewhat variable effects on blood pressure were observed in patients treated with NHD with some patients who had reached their estimated dry weight still requiring some antihypertensive medications; interestingly a phenomenon of persistent hypotension was observed in two anephric children, such that they required midodrine to maintain BP during dialysis [14]. Persisting hypotension in anephric patients on NHD has

previously been described in adults. Perhaps the most impressive reports of blood pressure control are the larger experiences with daily hemodiafiltration reported by Fischbach et al., and the experience with in-center NHD from Muller et al. Fischbach reported that mean arterial BP fell from 99 ± 18 to 88 ± 12 mmHg in 15 children followed over a period ranging from 11 to 39 months; by the end of their study, only two patients required treatment with one antihypertensive drug [15]. Similarly, Hoppe et al. reported that in children treated with thrice-weekly in-center NHD Mean arterial pressure (MAP) decreased during NHD from a median of 102 mmHg (range: 71–123) to 93 mmHg (range: 60–142). Three patients, lacking a diurnal–nocturnal rhythm in the ambulant blood pressure monitoring (24 h) before NHD, showed lowering of nocturnal MAP by >20% under NHD [17].

Although direct effects of intensified HD on vessel calcification have not been reported, the ability to control phosphate levels and thereby Ca × PO_4 product, both of which are recognized risk factors for vascular calcification, suggests that intensified HD should reduce this risk.

Because the exact causes of the chronic inflammatory state in children on HD are unknown, it is difficult to predict whether intensified HD will impact this factor. There is also very little, and inconclusive information on this subject from studies of the children who have undergone intensified HD. No consistent effect on inflammation has been described in the children treated with short daily HD or either home or in-center NHD. In the children treated with daily hemodiafiltration, a mean CRP <4 mg/dL has been reported in the absence of nonrenal causes for inflammation. Whether this reflects intensification of the dialysis process, or is a direct result of the additional hemofiltration component to this method of renal replacement is unknown.

Impact on Phosphate, Calcium, Parathyroid Hormone Levels

Compared with children on conventional thrice-weekly HD, patients prescribed all forms of intensified HD have reduced need for dietary restriction of phosphate or use of phosphate-binding agents, Furthermore, children undergoing NHD × 5–6/week have no restrictions whatever, and actually require phosphate supplementation. This is provided in the dialysate by addition of approximately 1 mmol/L (3 mg/dL) to the acid bath.

Control of plasma calcium values is similarly easier to achieve with all forms of intensified HD, in association with normalization of the phosphate values. However, for children receiving NHD × 5–6/week, if significant ultrafiltration is required, calcium supplementation may be necessary to prevent chronic negative calcium balance. This supplementation can be administered by increasing the dialysate calcium from a standard value of 1.25 mmol/L (2.5 mEq/L) to as high as 1.75 mmol/L (3.5 mEq/L), or alternatively by oral supplementation, though the latter method negates one of the benefits of NHD – reduction of supplementary medications.

Not surprisingly, since calcium and phosphate levels can be maintained in the normal range without medications, as shown by Hothi et al., PTH values are easily maintained in the normal (or sometimes lower) range in children on NHD [26]. This raises a concern that these patients may be at risk to develop low turnover or adynamic bone disease, particularly if they are also prescribed Vitamin D analogues. However, it is equally unclear if these children, who have plasma urea values which are persistently in the normal range, should be considered at risk of adynamic bone disease, since they are very different to the usual population of children on dialysis who are uremic. Because our normal surrogate markers of renal bone disease such as phosphate, calcium, and PTH may be maintained in the normal range by manipulation of the dialysis prescription, it is important to measure 25OH Vit D3 levels to ensure they are normal, and preserve the effects of Vitamin D, which are unrelated to calcium and phosphate metabolism.

Fluid and Diet Control

For children, particularly adolescents, adherence to fluid and dietary restrictions is particularly difficult. Similarly, dietary restrictions whether

prescribed by the medical staff or self-induced by persistent anorexia associated with uremia, are major impediments to achievement of normal weight gain and growth for all children with renal failure. Conventional hemodialysis is frequently accompanied by some or all of these problems. Not surprisingly, all forms of intensified HD have been associated with a reduced requirement for restriction of both fluid and dietary intake. Reporting children receiving short daily HD with the Nx Stage system, Goldstein et al. have documented improvement in normalized protein catabolic rate (nPCR) without significant weight change over a 16 week period. Their patients continued to require phosphate binders to maintain normal plasma phosphate levels.

Patients treated with NHD or HDF five to six times weekly also have improved and unrestricted dietary intake and no restrictions of fluid. They do not require any phosphate binders or potassium binding resins, to maintain normal plasma values of these electrolytes. Rather, patients on NHD × 6/week almost always require supplemental phosphate in their dialysate to prevent phosphate deficiency. Interestingly, we have observed that switching to a form of hybrid dialysis, with NHD provided four times weekly and one in-center 3 h dialysis (for parental respite) is no longer sufficient for these children to avoid the need for phosphate binders.

For children treated with daily hemodiafiltration, a mean dietary protein intake, estimated from 3 day food records, of 2.5 gm/kg day was documented. This high protein intake (which was greater than the calculated values for nPCR) did not produce hyperphosphatemia and provided pre-dialysis urea values approximately twice normal. This high protein intake was associated with improvement of the body mass index (BMI) from the 48th to the 65th percentile.

It is clear that irrespective of the precise method chosen to intensify HD, as compared with conventional thrice-weekly HD, dietary and fluid restrictions are markedly reduced or eliminated, thereby permitting a much more palatable diet which can only lead to less adherence problems than is usually seen in this population, and is a major component of the improved quality of life reported by these patients.

Growth

Optimization of growth is a fundamental requirement for all children with ESRD. For children on conventional thrice-weekly HD, attainment of normal growth is a major challenge, and often only attainable with daily Growth Hormone injections. Tom et al. first demonstrated that with provision of intensive nutrition, and increased duration of HD to 5 h/session as compared with the more common 3–4 h/session, were able to maintain normal or achieve sustained catch-up growth. Their results pointed out the possibilities that might be attainable if dialysis were even further intensified.

Most reports of intensified HD in children have been for a duration that is insufficient to measure growth accurately. Our own experience with a small number of children on NHD for a longer period included only adolescents with little growth potential, so that meaningful evaluation of growth was not valid.

Reporting on 15 children with a mean age of 8 years, who despite receiving GH the preceding year had remained growth retarded, Fischbach et al. have clearly documented catch-up growth [15] (Fig. 20.1). These children were treated with online HDF for 3 h, 6 days weekly. Growth velocity increased from 3.8 ± 1.1 to 14.3 ± 3.8 cm/year over a 1 year period, changing their height standard deviation scores (HSDS) from −1.5 to +0.2 SDS. Whether this growth was a nonspecific result of the increased frequency and intensity of dialysis, or whether the convectional component of the HDF procedure, with improved removal of middle molecules was a critical factor to achieve these results is not known. Similarly, it is not known if the use of ultrapure water, which is required for HDF might have reduced the chronic inflammatory response, thereby resulting in improved growth. However, it is very gratifying to observe that intensified renal replacement therapy can have such a profound effect to improve growth.

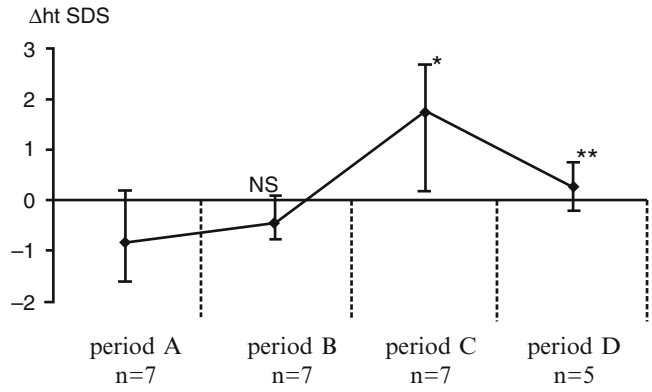

Fig. 20.1 Growth in children on daily hemodialfiltration – Median (± range) of normalized height standard score changes (Δ height SDS/year) in the prepubertal group of children (n=7) between the considered periods of treatment: Period A conventional dialysis without rhGH, Period B conventional dialysis under rhGH therapy, Period C intensified-daily dialysis, Period D transplanted up to last follow-up, *p<0.01, Period C versus Period A and Period C versus Period B, **p<0.05 Period D versus Period C, Period D versus Period A and Period D versus Period B. *NS* not statistically different, Period B versus Period A, *n* number of patients (Reprinted with permission from Ref. [13])

Medications

Antihypertensive Drugs

One of the main advantages of all intensified programs is the relatively little interdialytic weight gain. As a consequence, the demand for antihypertensive medication is dramatically reduced, and in 50% of all cases it can be withdrawn completely. Most of the remaining patients can be put on a single therapy, preferentially an ACE Inhibitor or a Calcium Channel Blocker.

Phosphate Binders

Normally, patients on intensified programs do not require or have greatly reduced need for phosphate-binding agents; nor have they to follow special diets. On three times weekly regimens, like in-center nocturnal dialysis, they are able to choose either withdrawal of medication or dietary restrictions. On daily nocturnal programs, even supplementation of phosphate may be necessary.

Erythropoietin

It appears that Epo dosage can be reduced on average, but only discontinued in some cases [27]. The reason remains unclear. This effect has been reported for different erythropoietic stimulating agents (ESAs). Likewise, reduction of iron supplementation has not been demonstrated convincingly; however, considering the clear nutritional benefit, it can be anticipated that there is also a positive effect on iron status and iron availability.

Special Aspects

Sleep Disturbances

In adults, sleep apnea is overrepresented in dialysis patients. It is associated with morbidity and mortality, and significant improvement after switching patients to intensified programs has been demonstrated [28]. It has been demonstrated that sleep disorders are frequent in patients on daytime dialysis and that nocturnal programs do not adversely impact this condition, nor do they increase daytime sleepiness [29].

Recovery from Dialysis

Recovery from Dialysis plays an important role in conventional dialysis when large volumes have to be removed within a limited time frame. Hypotension and disequilibrium symptoms are frequently encountered. For intensified programs, it has been demonstrated that such symptoms can be avoided [30].

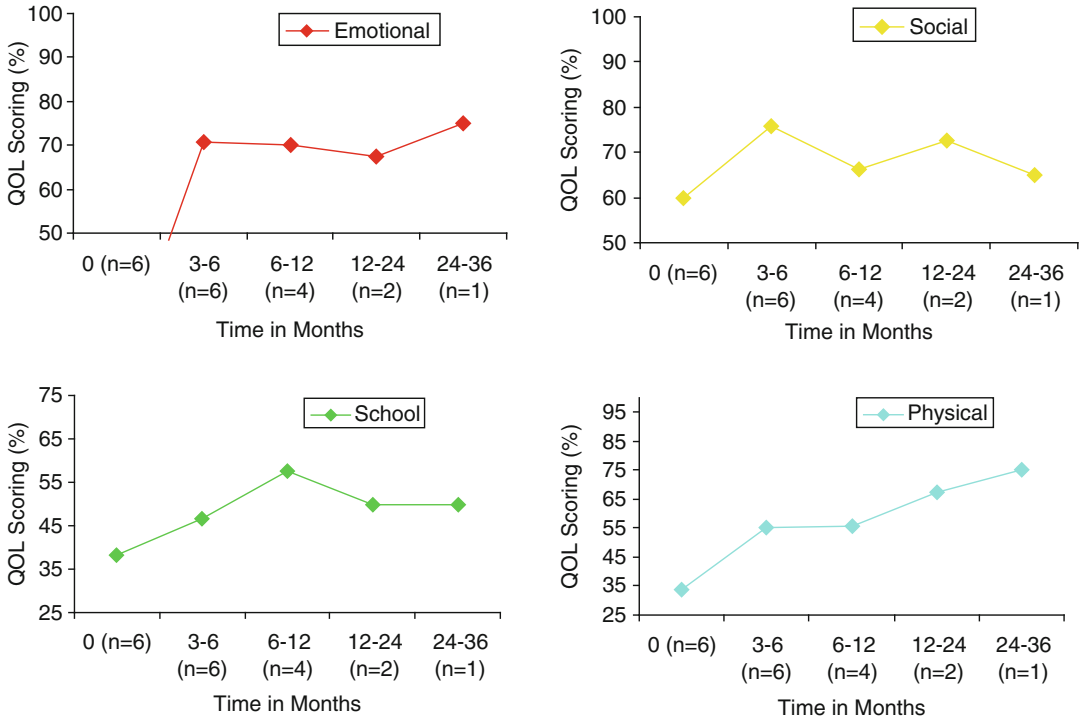

Fig. 20.2 Home nocturnal hemodialysis in children. Mean quality-of-life scores

Stem Cell Precursors

A study conducted by Chan et al. has demonstrated that intensified dialysis programs, and specifically daily nocturnal home hemodialysis has led to an increased presence of stem cells, when compared to conventional hemodialysis Although interesting, functional meaning of this finding remains to be addressed by future studies.

Quality of Life

The effect of intensified HD will be impacted in a number of ways. An adverse impact may result from the increased time that the dialysis takes, particularly if this involves frequent hospital visits. Similarly, frequent in-center dialysis sessions may have a substantial financial cost for the family because of transport and parking costs, potential loss of time at work, and potentially increased costs for child care for siblings of the patient. For children on NHD at home, social life will similarly be negatively impacted by the need to be connected to a machine six nights each week. On the other hand, the general feeling of improved well-being that almost all these children express, and the free diet and fluid intake that is permitted, increase their potential to socialize. Similarly, for children treated at home, who experience improved well-being and improved energy, their ability to contribute meaningfully at school is greatly increased.

The impact of NHD on quality of life for a small number of children is illustrated in Fig. 20.2. These evaluations were performed using the Peds QL instrument developed by Varni et al. [23]. This test provides a numeric score for four domains tested including, physical, emotional, social, and school. As illustrated, the mean score for physical, emotional, school all improved impressively, while the social score showed initial improvement, which was not sustained in the two children treated beyond 1 year.

Cost and Reimbursement

The cost of increased dialysis time and/or frequency is influenced by two conflicting factors. For patients who are dialyzed more frequently,

there are significant additional expenses related to increased use of disposables, e.g., dialyzers and lines. Also, for children dialyzed in-center either for longer periods or more frequently, there are increased costs related to a need for more nurses and the permanent presence of a trained pediatric nephrologist to supervise the session. These costs are not covered, despite advocacy from several sides, by any national health insurance system. Therefore, programs are mainly covered by staff motivation and the use of surplus or saved funds from other facilities to support the intensified programs. This is a paradox, since the savings of medication and the reduced hospitalization of these patients clearly makes such programs highly cost effective.

For patients dialyzed at home, there is a relatively small cost (usually less than $1,500) for home renovations to ensure appropriate storage, plumbing, and electrical supply. Also, for home dialysis, a dedicated machine must be purchased or leased, which is the major reason to insist that children must anticipate remaining on dialysis for at least 1 year before being trained for home HD. For estimating costs of home HD, we amortized the cost of an individual machine over 5 years, assuming that if the patient stopped home HD sooner, the machine would be returned to the dialysis unit for use by other children. Another cost related to home HD is the training time (about 6 weeks), which requires a dedicated nurse for approximately 3 days weekly. On the other hand, substantial savings result for children treated at home because of the reduced need for nursing care to supervise the procedure several days each week. These savings are much greater for children than adults on home HD because of the much higher nurse/patient ratio in pediatric dialysis units. Overall, despite the increased use of disposables, the nursing time required for training the patient and home supervisor, and the need for a dedicated machine at home, because of the substantial savings on nursing time, the overall cost annually has been estimated to be reduced by 25% [24]. These savings are increased if the patient remains on home HD beyond 1 year.

Relative Efficacy of Different Intensified Hemodialysis Modalities

The different techniques for intensified HD in children have not been directly compared, and comparisons with patients receiving conventional HD ×3–4 weekly have also not been controlled. As a result, it is difficult to document alterations in well-being between the different modalities. Clearly, there is a strong selection bias, which might affect which children are chosen for intensified HD, although this may for some patients be a negative bias since there is at least strong anecdotal evidence that some of the children chosen for intensified HD are preferentially those who are faring poorly on conventional treatment. On the other hand, those children on home HD may have a social advantage, since by definition they have home support available to assist with the treatment, and a home with sufficient space to accommodate the equipment.

The relative merits and disadvantages of the different modalities of intensive dialysis are outlined in Table 20.4.

Among adults, in uncontrolled observational studies, mortality appears greatly reduced with intensified HD modalities; results from the NIH sponsored controlled clinical trials are not available.

Outcomes

The long-term outcomes for children receiving intensified HD as compared with conventional thrice-weekly HD are unknown. Nonetheless, it is extremely likely that the multiple short-term benefits of intensive HD, which are outlined above, and illustrated in Table 20.4, will translate also into long-term benefit.

Summary

Intensified programs are superior to conventional HD programs. Irrespective of their modality, they deliver increased Kt/V and dramatically reduce

Table 20.4 Comparative features of the different intensified HD modalities

HD program	Weekly Kt/V_{urea}	BP control	Quality of life	Growth	School attendance	Phosphate binders/ diet restriction	Cost
Short daily[a,b]	9.1–10.5[a]	Improved[a]	No data[a]	Improved[a]	In-center school[a]	None 11/12[a]	Increased nursing[a]
	1.9–3.0[b]	Improved[b]	No change[b]	No data[b]	No data[b]	Little change[b]	No data[b]
Nocturnal daily[c]	>10	Nephric variable, anephric hypotensive	Improved 3/4	No data	Improved 3/4	None	Reduced (25%)
Nocturnal intermittent[d]	3.6–9.7	Improved	Improved	No data	Improved	None	No data

[a]Refs. [13, 15]
[b]Ref. [12]
[c]Ref. [14]
[d]Ref. [17]

many negative consequences of ESRD including social deprivation. If the funding issue can be solved, such programs will certainly provide a long-sought option for children and adolescents on or off the transplantation list.

References

1. Pauly RP, Gill JS, Rose CL, Asad RA, Chery A, Pierratos A, et al. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. Nephrol Dial Transplant. 2009;24: 2915–9.
2. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane Flux in maintenance Hemodialysis. N Engl J Med. 2002;347(25):2010–9.
3. 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.
4. Eschbach JW, Wilson WE, Wakefield AW, Babb AL, Scribner BH. Unattended overnight home hemodialysis. Trans Am Soc Artif Intern Organs 1966;12: 346–56.
5. Fine RN, DePalma JR, Liebermann E, Donnell GN, Gordon A, Maxwell MH. Extended hemodialysis in children with chronic renal failure. J Pediatr. 1968; 73(5):706–13.
6. Laurent G, Charra B. The results of an 8 h thrice weekly haemodialysis schedule. Nephrol Dial Transplant. 1998;13(suppl_6):125–31.
7. Buoncristiani U, Quintaliani G, Cozzari M, Giombini L, Ragaiolo M. Daily dialysis: long-term clinical metabolic results. Kidney Int Suppl. 1988;24: S137–40.
8. Uldall R, Ouwendyk M, Francoeur R, Wallace L, Sit W, Vas S. Pierratos A. Slow nocturnal home hemodialysis at the Wellesley hospital. Adv Renal Replace Ther. 1996;3(2):133–6.
9. (NAPRTACS) NAPRTaCS. Annual report. 2008.
10. 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;134:464–71.
11. Müller D, Zimmering M, Chan C, McFarlane P, Pierratos A, Querfeld U. Intensified hemodialysis regimens: neglected treatment options for children and adolescents. Pediatr Nephrol. 2008;23(10): 1729–36.
12. Goldstein S, Silverstein D, Leung J, Feig D, Soletsky B, Knight C, et al. Frequent hemodialysis with NxStage™ system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008; 23(1):129–35.
13. Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J. In-center daily on-line hemodiafiltration: a 4-year experience in children. Clin Nephrol. 2008;69(4):279–84.
14. 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.
15. 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;28(3):867–73.
16. Geary DF, Piva E, Gajaria M, Tyrrel J, Picone G, Harvey E. Development of a nocturnal home hemodialysis (NHHD) program for children. Semin Dial. 2004;17(2):115–7.
17. Hoppe A, Von Puttkamer C, Linke U, Kahler C, Booß M, Braunauer-Kohlberg R, Hofmann K, Joachimasky P, Hirte I, Schley S, Utsch B, Thumfart J, Briese S, Gellermann J, Zimmering, Querfeld U, Müller D. A hopital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr, 2011;158(1):95–9.
18. Kjellstrand C, Kjellstrand P. The ideal home hemodialysis machine. Hemodial Int. 2008;12(s1):S33–9.
19. 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.
20. Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, Van De Kar NJ, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. Kidney Int. 2002;61(2):621–9.
21. Jean G, Bresson E, Terrat JC, Vanel T, Hurot JM, Lorriaux C, et al. Peripheral vascular calcification in long-haemodialysis patients: associated factors and survival consequences. Nephrol Dial Transplant. 2009;24(3):948–55.
22. 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.
23. Varni JW, Limbers CA, Burwinkle TM, Bryant WP, Wilson DP. The ePedsQL in type 1 and type 2 diabetes: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Internet administration. Diabetes Care. 2008;31(4):672–7.
24. 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.
25. Bergman A, Fenton SS, Richardson RM, Chan CT. Reduction in cardiovascular related hospitalization with nocturnal home hemodialysis. Clin Nephrol. 2008;69(1):33–9.
26. 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.
27. Chan CT, Liu PP, Arab S, Jamal N, Messner HA. Nocturnal hemodialysis improves erythropoietin responsiveness and growth of hematopoietic stem cells. J Am Soc Nephrol. 2009;20(3):665–71.

28. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344(2): 102–7.
29. Hanly PJ, Gabor JY, Chan C, Pierratos A. Daytime sleepiness in patients with CRF: impact of nocturnal hemodialysis. Am J Kidney Dis. 2003; 41(2): 403–10.
30. Chan CT, Li SH, Verma S. Nocturnal hemodialysis is associated with restoration of impaired endothelial progenitor cell biology in end-stage renal disease. Am J Physiol Renal Physiol. 2005;289(4):F679–84.

Common Complications of Haemodialysis

21

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Keywords
Hemodialysis • Complications • Children • Air Embolism and Microbubbles • Blood and Dialyser • Membrane Reactions • Dialysis Disequilibrium Syndrome (DDS)

Introduction

Haemodialysis (HD) is a life sustaining treatment that is considered a standard of care for children with end stage renal disease (ESRD). Like most medical treatments it is potentially associated with adverse effects. Acute and/or technical problems can arise during individual HD sessions, and for those on maintenance HD, chronic complications can develop over time. This chapter, while not all inclusive, will review some of the more common acute and chronic complications associated with HD.

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Acute Adverse Problems

Dialysis Disequilibrium

Dialysis Disequilibrium Syndrome (DDS) was initially defined in 1962 [1] and refers to HD-induced acute interstitial cerebral oedema. Three causal mechanisms have been postulated:

Reverse urea effect: During HD the efficient clearance of urea from plasma creates a significant blood–brain urea and osmotic gradient. This was first described in rats that underwent rapid HD, with a 53% reduction in the plasma urea content but only a 13% reduction in brain urea content [2]. Aquaporins (AQP4 and AQP9) and urea transporters UT-B1 are mainly expressed in the brain and most likely facilitate equilibration of water and urea throughout the brain parenchyma. Uremic rats have a marked reduction in UT-B1 in brain parenchyma and an increase in AQP4 and AQP9. In combination these findings provide the basis for the reverse urea hypothesis

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[3, 4]. Low UT-B1 expression delays the movement of urea out of the brain. Rapid clearance of plasma urea by HD thus creates an osmotic driving force favouring movement of water into the brain through the abundant aquaporin channels with resultant brain oedema.

Organic osmolytes (idiogenic osmoles): Animal studies have shown that HD results in an acute urea gradient of 12 mmol/kg of H_2O between the cerebral cortex and plasma [5]. However it has been estimated that at least 35–45 mOsm/kg of H_2O gradient is required for the significant change in brain water content during HD. These results raise the possibility of an additional component in the pathophysiology of DDS, namely, the generation of other osmotically active substances (organic osmolytes) in the brain which are yet to be defined.

Cerebrospinal fluid (CSF) pH and brain intracellular pH: During dialysis, the rapid correction of metabolic acidosis causes secondary hypoventilation with a rise in plasma carbon dioxide (CO_2). Plasma CO_2 rapidly diffuses into the CSF but plasma bicarbonate is slower to cross the blood–brain barrier [1, 6] and thus a paradoxical CSF academia occurs. The increased source of brain H+ ion concentration is postulated to arise from brain organic acid production resulting in a 12% increase in brain water content.

The true incidence of DDS is unknown as it is essentially a diagnosis of exclusion. Nonetheless diffusion-weighted MRI is a tool which may be helpful in facilitating the diagnosis. The risk of DDS is highest in patients with very high plasma urea concentrations and aggressive urea removal. It is more common in children, in patients with a history of neurological disease, with malignant hypertension, and in patients with conditions such as hyponatremia and severe metabolic acidosis that predispose to cerebral oedema [7]. Symptoms include nausea, vomiting, headache, blurred vision, muscular twitching, disorientation, hypertension, tremors, seizures, and coma, and less commonly reports of muscular cramps, anorexia, restlessness, dizziness, papilledema, and leukoencephalopathy with central pontine and extrapontine myelinosis [8]. Symptoms normally occur at the end of dialysis or just after dialysis. In milder cases DDS is self-limiting, but recovery can take several days. Rarely DDS can be fatal.

Management

The treatment strategies for managing DDS are primarily preventative. In children starting chronic dialysis or patients with acute kidney injury it is important to begin with slow, gentle HD to allow for the gradual reduction in plasma uremic toxin levels over a series of dialysis treatments. This can be achieved by using smaller, less efficient dialysers; reducing the dialysis time (2 h) and decreasing the blood flow (2–3 mL/kg/min) and dialysate flow rate (maintaining the 2:1 dialysate:blood flow rate ratio). If the patient is grossly fluid overloaded, a period of sequential HD with an initial period of UF alone followed by conventional dialysis provides an opportunity to remove excess water with near iso-osmolar clearance. Once a steady state is achieved the dialysis prescription can be modified to improve the dialysis dose and dialysis adequacy. For those patients with extremely high starting plasma urea levels additional measures may be required to lessen the risk of DDS further as described below.

There are a number of children on maintenance HD who suffer from recurrent episodes of dialysis disequilibrium. Strategies need to be initiated to reduce the severity or frequency of DDS without compromising dialysis adequacy. The most evidence-based manoeuvre is higher dialysate sodium concentrations or reverse sodium profiling. The dialysate sodium is increased in a linear or stepwise manner from 135–137 mmol/L to 142–148 mmol/L over the course of the dialysis session. The rationale for sodium profiling in this context is the transfer of sodium as dialysis progresses to counterbalance the rapid decline in plasma osmolarity from urea purification. The concern with using this option repeatedly is that the chronic sodium load may stimulate thirst causing increased interdialytic weight gain and hypertension. An alternative osmotic agent that can be delivered to patients during dialysis is intravenous mannitol. In a

Table 21.1 Dialysis disequilibrium

Risk factors	Signs and symptoms	Preventative measures
High pre-dialysis urea Aggressive urea removal Neurological disease Malignant hypertension	Nausea, vomiting Headache Blurred vision Muscle twitching, cramps	Gradual reduction of urea during initiation of dialysis Reduced dialysis time (2 h) Slow blood flow (2–3 mL/kg/min) Decreased dialysate flow Use of smaller surface area, less efficient dialyzers
Hyponatremia	Altered sensorium including disorientation	Sequential dialysis for large UF requirements
Severe metabolic acidosis	Tremors, restlessness	Sodium ramping Reverse sodium profiling
Diabetics with poor glycaemic control	Seizures Coma Hypertension Papilledema	Intradialytic mannitol Prophylactic phenytoin Change in dialysis regimen to Short-daily dialysis Nocturnal HD Haemodiafiltration Peritoneal dialysis

cohort of children prone to intradialytic symptoms and or hypotension, 1 g/kg of mannitol administered weekly during the first hour of dialysis for the first dialysis session of the week or 0.5 g/kg twice weekly halved the odds of intradialytic symptoms [9]. Mannitol is an osmotically active solute which unlike sodium does not leak into the interstitium and thus produces a more sustained oncotic effect. In addition it rapidly lowers intracranial hypertension within minutes of administration, with a maximal effect at 20–40 min. The ability to clear mannitol is reduced in renal failure. Therefore no more than twice weekly dosing is recommended as mannitol accumulation can cause a rebound rise in intracranial pressure, especially in the face of acidosis. Other adverse effects include nausea, vomiting, lower limb oedema, thrombophlebitis, headaches, and chest pain. In patients prone to seizures, prophylactic phenytoin is effective at reducing neurological excitability and the risk of seizures, but it has no effect on the underlying cerebral oedema. Finally in extremely resistant cases, switching dialysis modality to short-daily HD, peritoneal dialysis or haemodiafiltration (HDF) [10] may reduce or eliminate the risk of dialysis disequilibrium (Table 21.1).

Blood and Dialyser Membrane Reactions

Exposure of the blood to foreign materials in the extracorporeal circuit can be associated with a number of adverse reactions. In 1988, Daugirdas and Ing suggested that first-use dialyser reactions be classified into Type A, a hypersensitivity reaction characterized by anaphylactic signs and symptoms, and Type B, a non-specific type of reaction typified by chest and back pain [11]. Ascertaining the true incidence of these reactions is hampered by the lack of a uniform definition. A survey published in 1985 estimated an incidence of 3–7 reactions per 1,000 patients per year for Type A and 3–5 reactions per 1,000 patients per year for type B reactions [12]. Reactions occur more commonly with hollow fibre dialysers than with the older flat plate dialysers. The causes of many of these adverse reactions have been elucidated over time through careful clinical observation and epidemiological investigation [13].

Allergic reactions: Anaphylactic reactions are severe and potentially fatal reactions to a component of the dialysis circuit, and are usually mediated by antigen-antibody complex formation.

These severe reactions occur early in the dialysis treatment and typically manifest within minutes of dialyzed blood returning to the patient. As with any severe allergy, symptoms can include wheezing, shortness of breath, flushing, headache, urticaria, and hypotension and in very severe allergies, can manifest as hypoxia, cardiovascular collapse, and death.

Patients may react to multiple components of the dialysis circuit. These include the membrane itself; sterilizing agents, particularly ethylene oxide (ETO); the anticoagulant, heparin; the potting compounds; and reuse agents if applicable. As well, certain medications may be associated with adverse reactions to specific membranes [14, 15].

Ethylene oxide: ETO is a bactericidal gas used as a sterilizing agent in dialysers. Sensitivity to ETO has been recognised since the 1970s [16]. Symptoms range from full blown anaphylactic reactions shortly after initiation of dialysis, mediated by anti-ETO antibodies, to non-specific symptoms including fever, malaise, and myalgias [17]. In a population of 70 adults on dialysis, IgE specific anti-ETO antibodies were detected in 21% overall [18]. The group with a history of hypersensitivity reactions on dialysis had a 55% incidence of antibodies and a high rate of positivity on allergen skin testing, compared to only 6% with antibodies in the control group without allergic symptoms. Measures to reduce the incidence of ETO reactions include careful flushing of the circuit, reuse of dialysers (though this is rare in paediatrics), and avoidance of ETO altogether. Alternate methods of dialyser sterilization not associated with allergic reactions include steam sterilization, gamma irradiation, and e-beam.

Heparin: Anticoagulation to prevent clotting of the extracorporeal circuit is required in most patients on HD. Unfractionated heparin is the most commonly used anticoagulant world-wide as it is effective, inexpensive, readily available, has a relatively short half-life even in HD patients, and if necessary can be reversed with protamine. Anaphylactic reactions to heparin are rare but have been described [19], including recurrent anaphylaxis in a HD patient [20]. More common, but still relatively rare, is heparin-induced thrombocytopenia (HIT), an immune mediated disease, which manifests as thrombocytopenia and increased risk of thrombotic events [21]. HIT is associated with the development of antibodies to a platelet factor 4/heparin antigen complex. It is estimated that 8% of patients treated with heparin develop antibodies, but that only 1–5% will develop HIT. A diagnosis of exclusion, HIT should be suspected when other causes of thrombocytopenia are eliminated, and confirmed with antibody and functional testing. Patients with a true heparin allergy or HIT should not be exposed to either unfractionated heparin or low-molecular-weight heparin, due to cross-reactivity [21]. Alternate anticoagulants such as danaparoid, hirudin, or argatroban can be used.

AN69 membranes: In the early 1990s a flurry of reports documented anaphylactic reactions in patients undergoing HD with an AN69 membrane while receiving ACE inhibitors [22]. Affected patients were subsequently found to have very high bradykinin (BK) levels suggesting BK as the mediator of the allergic symptoms [23]. Compared to other membranes, AN69 membranes were associated with higher BK generation rates; concomitant use of ACE inhibitors blocked degradation of the BK, producing severe symptoms. More recent investigations suggest that the propensity to anaphylactic reactions when exposed to AN69 membranes may be genetically determined and related to plasma levels of aminopeptidase activity [24]. In vitro studies with AN69 membranes show that the generation of BK is pH dependent and can be ameliorated by rinsing the blood and dialysate compartment with an alkaline solution [25]. However, with the availability of alternate biocompatible membranes, avoidance of AN69 membranes for patients on ACE inhibitors seems prudent.

First-use reactions: So-called first-use reactions are adverse events which occur during dialysis with a new dialyser. They may be caused by ETO, as well as concomitant use of ACE inhibitors and AN69 membranes as outlined above.

The biocompatibility of a dialyser is defined by the extent to which it activates a number of biological systems including the complement, coagulation, and Kallikrein systems. Older cellulose based dialyzers were shown to activate complement leading to profound transient neutropenia in the first hour of dialysis, thought to be due to complement induced pulmonary sequestration associated with respiratory symptoms, back pain, hypoxia, or general malaise [26]. Thrombocytopenia was also described [27]. Synthetic membranes such as polyacrylonitrile and polymethylmethacrylate (PMMA) were more biocompatible. Research to improve the biocompatibility of dialysers without impairing their performance is ongoing and includes such manoeuvres as surface coating with antioxidants. Many outbreaks of adverse events, including scleritis and iritis, acute loss of vision and hearing, and death have been linked to contaminants left in the dialyser during the manufacturing process, or to degradation of dialyser components with aging [28]. Perfluorohydrocarbon contamination caused death in a number of patients. In late 2007 and early 2008, heparin contaminated with oversulphated chondroitin sulphate was epidemiologically linked to an outbreak of allergic reactions in multiple HD units in the USA [29]. It was first described in a paediatric facility. Patients typically presented within minutes of starting dialysis, with symptoms of hypotension, nausea, shortness of breath, and facial oedema, with some having lesser symptoms including vomiting, tingling and flushing, sweating, and urticaria. The identified contaminant was subsequently found capable of activating the complement system, the presumed mechanism of the symptoms.

Reuse agents: Few, if any, paediatric centres practice dialyser reuse. Reuse is associated with a reduction in the incidence of 'first-use' reactions, but may be associated with allergic reactions to residual sterilizing agents, such as formaldehyde. Inadequate sterilization of dialysers may cause pyrogen reactions or frank infection, manifest by fever, chills, and rigors [28].

Other causes: Microcontamination from back leak across the dialyser is a potential cause of fever, chills, and malaise. This is more common with the use of high-flux dialysers, despite using dialysis water which meets industry standards. Recurrent severe allergic reactions in an adult presumed to be caused by microcontamination were alleviated by using a highly absorptive AN69 membrane and a saline infusion pre-dialyser to maintain fluid movement from the blood into the dialysate compartment, thus preventing backflow [30].

Treatment of a suspected or proven anaphylactic reaction includes immediate cessation of dialysis without the return of the blood prime to prevent further antigen exposure. Supportive measures include intravenous antihistamines and steroids and epinephrine for life-threatening reactions. Patients with bronchospasm may require supplemental oxygen and inhaled bronchodilator. Every attempt must be made to identify the allergen, with stepwise removal of potential offending agents [30].

Physicians caring for dialysis patients must maintain a heightened awareness of the potential for adverse reactions during dialysis, and must be vigilant for clustering of unusual reactions which might herald a contaminant or problem with the dialyser manufacturing process (Table 21.2).

Air Embolism and Microbubbles

Air embolism is an infrequent, but potentially fatal complication of HD treatments. Estimates of clinical air embolism of one event per 2,000 dialysis treatments are quoted in the older dialysis literature albeit in the era before modern air detectors [31]. With the standard safety features on the current dialysis machines, the incidence is likely lower than this, though nonclinically significant air leaks may occur with a greater frequency. No paediatric specific data appears to exist.

In dialysis patients, air embolism is a recognised complication of central venous line (CVL) insertion [32]. It can also occur during accidental disconnection of the CVL and during connection and disconnection of the dialysis circuit. With

Table 21.2 Important dialyser reactions

Potential allergens	Timing/manifestations/comments
Sterilizing agent – ethylene oxide	Shortly after initiation of dialysis Anaphylaxis Non-specific malaise, fever
Anticoagulant – heparin	Allergic reaction – rare Heparin-induced thrombocytopenia (HIT)
Dialyser membrane especially AN69 membrane	Minutes after blood-membrane contact Hypotension, anaphylaxis Risk factors Blood prime, metabolic acidosis, patients on ACE inhibitors
Cellulose dialysers	First hour of dialysis Neutropenia
Microcontamination from back leak	Fevers, chills, malaise Risk factors High-flux membranes, water quality

arteriovenous fistulae (AVF) or grafts, air can enter the circuit if the arterial needle becomes dislodged. Air may also be introduced into the dialysis circuit though loose connectors, defects in the tubing or central line, during infusions into the dialysis circuit and if the fluid level in the venous drip chamber becomes too low or on some machines, if it becomes tilted.

Venous embolism: The clinical manifestation of venous embolism can vary from clinically insignificant to complete cardiovascular collapse and death, and the severity of symptoms relates to the volume of air introduced, the rate of air delivery, and the position of the patient during the event. Children are reported to have greater haemodynamic instability from air embolism than adults, likely relating to their smaller cardiac volumes.

Patients may present with hypotension, cyanosis, and tachypnoea, and may also exhibit nausea, vomiting, altered level of consciousness, seizures, or neurological deficit. A large air embolism produces a mechanical right ventricular outflow tract obstruction, resulting in elevated right ventricular and pulmonary pressures. This may be associated with a loud churning murmur best heard along the left sternal border. The blood air interface promotes activation of the clotting cascade and release of vasoactive substances which can result in pulmonary vasoconstriction, bronchospasm, and pulmonary oedema. Treatment is aimed at restoring flow within the circulation and correcting hypoxia. There is some controversy about how best to position the patient, but common practice suggests positioning them left side down in the Trendelenburg position in an attempt to force air into the right ventricular apex, thus allowing flow into the pulmonary circulation. If the patient is dialysed through a central line, attempts should then be made to aspirate the air.

Arterial embolism: As a consequence of right to left shunting, a venous air embolism may subsequently result in a 'paradoxical' arterial embolism [33]. This most commonly occurs through a patent foramen ovale, which occurs in 15–40% of the population [34] or within the pulmonary circulation. Even small amounts of air in the arterial system can have potentially devastating consequences, especially in the brain.

Hyperbaric oxygen therapy (HBOT) is an established therapy for arterial gas emboli of multiple aetiologies. It has also been successful in treating paradoxical arterial emboli in a HD patient [35]. An important potential sequelae of the air-tissue interface is thromboembolism [36] and thus the routine use of heparin as an anticoagulant during HD may reduce the severity of symptoms that arise both from the arterial air emboli and thromboemboli. Experimental animal work in a cardiopulmonary bypass circuit has

shown an infusion of perfluorocarbon to be protective of neurological consequences following air embolism [37]; however, a greater understanding of the risks and benefits of such treatment is necessary before application to humans [38]. Other therapies which change the air-tissue interface such as surfactant are also being explored.

Microbubbles: Microbubbles are invisible to the naked eye and are too small to be detected by the standard air detectors on current HD machines. In vivo and in vitro studies show that Microbubbles occur throughout most dialysis sessions in adults [39–41]. While not documented in paediatric patients, it is reasonable to presume they occur in children as well. Microbubbles originate within the extracorporeal circuit, and are thought to be due in part to residual air in the tubing and dialyser following priming. This is supported by a lower incidence of microbubble detection with pre-filled versus dry dialysers [41, 42]. Microbubbles are also formed de novo as a result of turbulent flow in the circuit lines or access, especially at the venous drip chamber. Higher blood flow rates are associated with more microbubble formation [40, 43], and a lower likelihood the bubbles will rise to the surface of the fluid stream for subsequent removal in the venous drip chamber. Other potential sources of microbubbles include air entry during connection and disconnection, air leaks in the circuit or degassing of blood. Microbubble elimination from the circulation is dependent on size and bubble configuration, and varies from seconds to weeks, with longer dissolution times for bubbles of larger size and non-spherical configuration.

Microbubbles are thought to result in tissue injury through a variety of mechanisms. They lodge in the microcirculation obstructing blood flow, inducing tissue ischaemia and damaging vascular endothelium, with resultant activation of the inflammatory cascade and coagulation pathway. As blood returns to the patient's venous circulation during HD, microbubbles are delivered to the pulmonary circulation and may be associated with acute and chronic respiratory symptoms. It is speculated that recurrent microbubble emboli may be responsible in part for the high incidence of pulmonary hypertension in adults on chronic HD through AVF [44, 45]. Whether the incidence of pulmonary hypertension is also high in patients dialysed with CVL is unknown. In the presence of right to left shunts, microbubbles may be carried to the systemic circulation and brain, potentially contributing to the neurological consequences of chronic uremia.

Although the sequelae of microbubbles remain to be fully elucidated, there is sufficient evidence to support the use of treatment strategies to reduce microbubble formation and/or enhance their removal from the extracorporeal circuit. Microbubble formation can be reduced by maintaining higher fluid levels in the venous air trap [46], by appropriate priming of dialysers to remove air, or by the use of pre-filled dialysers [42], and wherever possible, by employing lower flow rates within the circuit [43]. Conventional bubble filters which are based on mechanical obstructing filtering devices are associated with high resistance to flow and activation of the coagulation and complement cascades and are not suitable for HD circuits. Newer methods of removing microbubbles, such as acoustical bubble traps, are under development [47].

Modern dialysis machines are equipped with many safety features including air detectors, which stop the blood pump when significant air is detected, to prevent infusion of air into the patient should a system breach occur. However, all the modern technology available is no substitute for vigilance to prevent potentially catastrophic complications of HD. Although many patients prefer to sleep while on dialysis and may hibernate under blankets, 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 an absolute standard of nursing care.

Miscellaneous Problems

Blood leaks: Separation of the blood and dialysate compartments is essential for both the safety and efficacy of HD. Blood leaks occur when there is

a disruption in dialyser hollow fibre integrity allowing passage of blood from the blood compartment into the dialysate compartment. During the manufacturing process, tests for fibre integrity are standard. However, fibre disruption may occur during manufacturing, from dialyser 'misadventure' during shipping, storing, and handling, or if the fibres rupture if they are subjected to an excessive transmembrane pressure. Blood leaks are suspected by the presence of red stained dialysate in the absence of haemolysis. Modern dialysis equipment is equipped with optical sensors to detect the presence of blood in the dialysate compartment. If a blood leak is detected, the dialysis procedure must be terminated immediately and dialysis restarted, if indicated, with a freshly primed circuit.

Haemolysis: Haemolysis is a rare but potentially life-threatening complication of HD. It may manifest as non-specific malaise, weakness, nausea, and abdominal pain, or may cause arrhythmias and cardiac arrest. The presentation may relate both to the aetiology of the haemolysis and the haemolysis itself. Haemolysis is diagnosed by the finding of a fall in plasma haemoglobin, pink plasma with elevated free plasma haemoglobin, elevated LDH and low haptoglobin, elevated plasma bilirubin, and in dialysis patients a rise in potassium.

A variety of causes of haemolysis during HD have been described. Haemolysis and death were described in the 1970s following inadvertent heating of the dialysate to above 47°C [48, 49]. Dialysate temperatures of 40°C have been tolerated without haemolysis [50]. Several episodes of haemolysis were observed in adults during continuous haemodialysis therapy in the critical care unit when they were inadvertently dialysed against distilled water following improper reconstitution of Normocarb™ dialysate [51]. Other reported causes of haemolysis, to name a few, include kinking of the tubing during dialysis [52], manufacturing defects in dialysis tubing [53], contamination of the dialysate or tubing with substances such as copper or chlorites, red cell trauma from the blood pump, and mechanical red cell trauma due to a mismatch between blood flows and access size [53] [54].

Blood volume monitoring may provide a clue to haemolysis. During several of the reported episodes of haemolysis it was noted in retrospect that affected patients had a rising blood volume, due to release of water from lysed cells, and a falling haematocrit [53]. However, in vitro studies using the CritLine™ suggest that the change in haematocrit during haemolysis is small and this device is not sufficiently sensitive to pick up haemolysis in vivo [55].

If haemolysis is identified during a HD session, treatment should be terminated immediately. Supportive measures including packed red cell transfusion if needed should be initiated. The dialysis circuit should be saved if possible to determine the aetiology of the haemolysis if not readily apparent.

Acute Haemodynamic Changes

Acute haemodynamic changes during dialysis are the most common complication of treatment. They contribute to acute and chronic patient morbidity, may affect the duration and efficacy of individual treatment sessions, and increase the need for patient monitoring, and intervention by nursing and medical staff. The following section reviews the pathophysiology and treatment of intradialytic hypotension and paradoxical hypertension.

Intradialytic Hypotension

During conventional 4 h HD treatments the prevalence of intradialytic hypotension in children ranges between 20% and 30% [56]. The pathophysiology is complex, multifactorial and still not entirely understood. The uremic milieu impairs compensatory responses to haemodynamic stress with ineffective pressor response and venoconstriction; excessive nitric oxide generation; reduced plasma refilling; suboptimal metabolic stress response with a deficiency in endogenous arginine vasopressin, L-carnitine and steroids; inadequate ventricular refilling and myocardial contractile reserve and impaired resting baroreflex sensitivity [57–61]. In addition inappropriate activation of the simpatico-inhibitory,

Bezold–Jarisch reflex can result in sudden hypotension combined with bradycardia. There are also a number of HD-specific factors that influence the central blood pressure. 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 dialyser 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 most likely to cause hypotension due to its plasma calcium chelating effect.

The introduction of noninvasive blood volume monitors has made it possible to measure the relative changes in the blood volume (RBV) real time during individual dialysis treatments. Initially there was a hope that this would allow prediction of adverse intradialytic events. In adults Kim showed that if RBV fell below a given threshold, arterial hypotension appeared [62]. Larger observational studies failed to corroborate this idea of a critical level of RBV reduction but found that irregularity of the RBV course, gradient of the RBV curve and switching from an exponential to a linear RBV reduction were the most powerful predictors of intradialytic hypotension [57, 63, 64]. Results in children were not too dissimilar. The RBV at the point of decompensation showed large intra-patient and inter-patient variability and differed in polyuric patients, such that treatment failure occurred at higher RBV thresholds compared with oliguric patients. Changes in heart rate and a steeper gradient of the RBV curve in the first hour were predictive of haemodynamic decompensation [56], not the final RBV measurement.

Consequences

Acutely, intradialytic hypotension requires immediate action to stop or reduce the severity of symptoms that may precede or follow the drop in blood pressure (BP). These include a temporary suspension of ultrafiltration (UF), a 5 mL/kg isotonic fluid bolus and in resistant cases, premature discontinuation of the dialysis treatment. Such measures although necessary have an adverse impact on dialysis outcomes by reducing UF goals and adequacy of solute removal. Of greater concern, however, is the evidence linking repeated episodes of intradialytic hypotension with a more devastating effect on morbidity and mortality. Several observational studies in adult patients with essential hypertension have described a 'J' shaped curve between BP and mortality [65]. The same trend has been described in adult dialysis patients, with a suggestion that hypertension is associated with morbidity but mortality is associated with hypotension [66]. Zager et al. reported a fourfold increase in the relative risk of cardiac-related death in adult patients with pre-dialysis systolic BP less than 110 mmHg compared with a systolic BP between 140 and 149 mmHg, and a 2.8-fold increase in relative risk for a cardiac-related death with post-dialysis systolic BP less than 110 mmHg compared with systolic BP 140–149 mmHg [67].

Frequent intradialytic hypotensive episodes have been implicated in accelerating the decline in residual renal function and precipitating serious vascular complications. There is growing evidence from isotopic, electrocardiographic, biochemical, and echocardiographic studies implicating HD as a source of recurrent ischaemic injury. Silent intradialytic ST depression [68, 69] associated with acute changes in serum cardiac troponin levels both in adults [70, 71] and children [72] have been demonstrated. Using single photon emission computed tomography (PET) McIntyre et al. demonstrated an acute reduction in global and segmental myocardial blood flow in adults during dialysis with matched reductions in segmental contractile function, even in patients without angiographically proven epicardial coronary artery disease [73]. A direct correlation was seen between the degree of myocardial dysfunction and intradialytic BP changes and UF volume [74]. Such transient myocardial ischaemia with resultant reversible regional left ventricular dysfunction is known as myocardial stunning [75]. In the model of coronary heart disease repeated stunning is progressive and leads to myocardial hibernation, defined as ischaemic, non-infarcted myocardium that exists in a state of contractile dysfunction [76]. In dialysis patients

myocardial stunning also appears to be progressive. In a 12 month follow-up of adult HD patients the presence of acute HD-induced regional myocardial dysfunction negatively influenced survival, increased the likelihood of cardiac arrhythmias [77], and resulted in regional fixed systolic dysfunction and a reduction in global systolic function [74, 78] with resultant congestive heart failure. Records from the US Renal Data System have shown that HD-associated de novo and recurrent congestive heart failure is highly relevant as it is associated with a 2-year mortality as high as 51% [79]. Of greater concern, perhaps, has been the demonstration of dialysis induced acute regional myocardial dysfunction in 12 children aged 2–17 years. This was associated with varying degrees of compensatory hyperkinesis in unaffected segments and thus the global LV function was maintained throughout HD. In children intradialytic systolic BP reduction was significantly associated with mean segmental shortening fraction but no correlation was seen with actual intradialytic systolic BP or dialysis vintage [80].

Management

It is generally accepted that haemodynamic stability during dialysis is improved by withholding antihypertensive medications on dialysis days, avoiding food during dialysis, using bicarbonate buffers, and treating intradialytic hypocalcaemia. However, these measures alone may be insufficient in preventing intradialytic hypotension and thus other strategies are necessary.

During HD, dialysate sodium generates a crystalloid osmotic pressure and thus influences fluid shifts between the different body compartments. Manipulation of the dialysate sodium, through sodium profiling, utilizes a sodium concentration that falls in a step, linear or exponential fashion. The higher dialysate sodium at the start allows a diffusive sodium influx to counterbalance the rapid decline in plasma osmolarity due to clearance of urea and other small molecular weight solutes thus promoting plasma refilling. The low dialysate sodium at the end aids diffusive clearance of the sodium load thus minimizing the adverse effects of hypertonicity. Compared with a constant dialysate sodium bath, profiling has been shown to increase stability of intradialytic blood volume, and reduce both intradialytic cramps and interdialytic fatigue in adults and children [81]. In a direct comparison of a linear and step sodium ramp from 148 to 138 mmol/L a step ramp decreased the odds of intradialytic hypotension or premature discontinuation of treatment by 27% [82] in children. Despite the benefits, the risk of chronic sodium loading with sodium profiling is real and as of yet not clearly defined in children.

The plasma refilling capacity increases proportionately with interstitial volume expansion. Decreasing stepwise or linear profiles starting with high UF rates at the time of maximal tissue hydration, and progressively reducing the rate in line with decreasing interstitial hydration provides the rationale for UF profiles. However in patients with a high UF requirement, high UF rates can be counterproductive. Saran et al. found that a UF rate greater than 10 mL/kg/h increased the odds of intradialytic hypotension and heightened the risk of mortality [83]. UF profiles (decreasing step, decreasing linear and alternating high/low UF rate) have been shown to be no better than a constant UF rate in preventing intradialytic symptoms or hypotensive episodes in children [82]. Programming large UF goals into profiles can result in UF rates which are both greater than an equivalent constant UF rate for part of the treatment, and also exceed the body's capacity to compensate, offering very limited reserve for variations in refilling capacity and thus at best only achieving minor gains in dialysis quality. Techniques focusing on UF rates alone without consideration of refilling rates are in reality destined to fail. In comparison automated relative blood volume (RBV) biofeedback techniques or more simply, RBV driven algorithms that adjust UF rates according to RBV changes are proving to be superior in achieving equivalent or higher UF volumes with reduced cardiovascular instability [56, 84]. In a cohort of children on conventional 4 h dialysis against decreasing sodium profiles safe UF rates against RBV thresholds were identified as: greater than 88% at the end of the first hour, greater than 84%

Table 21.3 Intradialytic hypotension

Consequences	Moderators
Intradialytic symptoms	Withhold antihypertensive medications on dialysis days
Suspension of UF with resultant chronic hypervolemia	Avoid food intake during dialysis
Premature discontinuation of treatment and inadequate dialysis	Dialysate Bicarbonate buffer Higher dialysate calcium Sodium profiling
Accelerated decline in residual renal function Mesenteric ischaemia	UF profiling
Cerebrovascular Transient ischaemic attacks Stroke	Periods of isolated UF Cooled dialysate
Cardiovascular Regional LV dysfunction Ischaemic cardiomyopathy progressing to heart failure Increased risk of arrhythmias	Pre-dialysis or Intradialytic midodrine Biofeedback dialysis RBV driven UF algorithms Alternative dialysis regimens Short-daily dialysis Haemodiafiltration Prolonged/nocturnal HD

at the end of the second hour, and greater than 82% at the end of the third hour, measuring RBV with the Fresenius™ blood volume monitor.

Alternative strategies for stabilising intradialytic BP include sequential dialysis, a method traditionally used in patients with large UF goals. In an analysis of children prone to intradialytic hypotension, isolated UF halved the odds of intradialytic symptoms and improved the UF potential, but produced no benefit in decreasing the number of intradialytic episodes of hypotension [9]. Finally midodrine is a specific a-1 adrenergic agonist that mediates constriction of both arterial and venous capacitance vessels and thus prevents venous pooling while supporting central BP. Oral administration achieves peak levels at 1 h with a half-life of 3 h extending to 9–10 h in dialysis patients. It is renally cleared and due to low protein binding capacity it is effectively removed by HD. Minor adverse reactions such as scalp paraesthesia, heartburn, flushing, headache, weakness and neck soreness have been described. Adult nephrologists have the greatest experience with midodrine and report variable success [85]. In contrast paediatric data is very limited. One regimen that reports successful management of declining BP in children utilizes administration of 2.5 mg of oral midodrine in the event of a declining BP, with a further 2.5 mg dose if the BP fails to improve within 30 min. A cutoff of 7.5 mg total dose is applied for a 3 h treatment and no midodrine is given in the final 30 min irrespective of BP. Prescribed in this manner Hothi et al. observed a 10–15 mmHg increase in the systolic BP within 30 min of administering midodrine in the absence of adverse effects in the intradialytic or interdialytic period [9].

Finally, the supportive measures for managing haemodynamic instability in high risk patients have a ceiling effect and in resistant cases treatment has to be escalated by switching patients to alternative dialysis programmes. Extrapolating from predominantly adult data cooled dialysate, HDF, short-daily HD and home nocturnal HD can all potentially be of benefit (Table 21.3).

Intradialytic or Paradoxical Hypertension

Hypertension is the most common complication of chronic kidney disease (CKD) in children, and in HD patients is most often due to salt and volume overload, which responds to UF during HD. Intradialytic or paradoxical hypertension is a less well characterized but nonetheless important

complication of HD. Estimates of its frequency are hampered by the lack of a standardized definition in the literature. Suggested definitions include: hypertension in the second or third hour of dialysis despite significant UF; an increase in mean arterial pressure (MAP) of more than 15 mmHg during or immediately after dialysis; and an increase in blood pressure that is resistant to fluid removal. Estimates of the incidence in adults range from 5% to 15% with no paediatric-specific numbers currently being available [86].

The pathogenesis of intradialytic hypertension is complex, with multiple proposed contributory mechanisms. It may occur early in dialysis, secondary to intravascular volume expansion due to mobilization of extracellular fluid accumulated in the interdialytic period in response to osmotic agents such as sodium and mannitol, or an increase in oncotic pressure when concentrated albumin solutions are used for hypoalbuminemic patients. In these instances, hypertension is frequently transient and improves with UF.

Sustained hypertension is often due to failure to achieve an appropriate dry weight [87]. However, many patients manifest intradialytic hypertension that is refractory to appropriate fluid removal. One theory is that excessive UF leads to activation of the renin-angiotensin system, resulting in angiotensin II mediated vasoconstriction and hypertension. In support of this theory is the lower incidence of hypertension in anephric HD patients and studies showing amelioration of hypertension in non-anephric patients treated with angiotensin converting enzyme (ACE) inhibitors [88, 89]. Likewise, severe paradoxical hypertension has also been described in two adults on HD treated with the ACE inhibitor ramipril for bilateral renal artery stenosis [94], presumably secondary to activation of the renin-angiotensin system as a result of drug induced hypotension in the setting of fixed afferent obstruction.

Sympathetic nervous system over activity is well documented in patients with CKD and occurs through a variety of mechanisms including enhancement of sympathetic activity by angiotensin II, afferent renal nerve stimulation caused by renal injury, impairment of brain nitric oxide synthesis, and increased production of catecholamines [89, 91–94]. Recent studies have shown enhanced production of the vasoconstrictor endothelin I during dialysis in hypertensive patients and in particular those exhibiting paradoxical hypertension [95, 96]. It is likely that an imbalance caused by reduced nitric oxide production and enhanced endothelin I production contributes to the increased peripheral vascular resistance seen in patients prone to paradoxical hypertension [98].

Pearl et al. suggested a role for a new pressor protein (NPP) in the production of severe hypertension in three anephric children, despite optimal dry weight in two [99]. NPP is a 30-kiloDalton extrarenal enzyme related to the coagulation factor β-FXIIa that exhibits cardiotonic and pressor activity in rats. Serum of these three patients produced characteristic pressor responses, suggesting in vivo activation of this protein as a contributory factor in their hypertension. The patients' hypertension responded to α and β-blockade with labetalol. Further studies are required to ascertain the significance of these findings in HD patients.

Iatrogenic changes in electrolytes may also contribute to hypertension. Sodium ramping may result in chronic sodium gain and subsequent hypervolemia and hypertension [100]. Hypokalemia is a known risk factor for hypertension. Dolson et al. studied the effect of potassium removal during dialysis on BP in adults. They demonstrated significant rebound hypertension at 1 h post dialysis in patients dialyzed against lower potassium baths [101] presumed to be due to increased peripheral 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 intradialytic hypertension. Within each class of drugs, some are removed by dialysis while others are not. The beta-blockers atenolol, nadolol, and metoprolol are removed by dialysis. The ACE inhibitors captopril, enalapril, lisinopril, and ramipril are also removed, as are the vasodilators minoxidil, nitroprusside, and diazoxide.

Methyldopa is removed, while calcium channel blockers are generally not removed by dialysis.

Management

Treatment of paradoxical hypertension should start first with ensuring a correct dry weight has been ascertained and achieved. BP control measures must include salt and fluid restriction, and where feasible, augmentation of urine output with loop diuretics. Noninvasive monitoring of haematocrit and relative blood volume should be employed to optimize fluid removal [82, 56, 84, 102]. Increased frequency of dialysis and/or intensive UF may be required to ascertain the true dry weight [87, 103, 104]. Nocturnal dialysis is associated with better BP control with fewer antihypertensives in children.

If hypertension persists despite an appropriate dry weight and avoidance of excessive interdialytic weight gain, blockade of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers has been shown to improve BP control and reduce sympathetic tone in HD patients. A frequent first choice for pharmacological therapy of hypertension in children is a calcium channel blocker due to convenient dosing forms and a low side effect profile. However, calcium channel blockers do not modify sympathetic nervous system activity and available data suggests that if ACE inhibition or ARB therapy produces insufficient BP control, addition of an adrenergic receptor blocker, either a beta-blocker or alpha-blocker (or possibly a centrally acting antihypertensive such as methyldopa) is physiologically logical. Attention should be paid to the timing of BP medications to ensure they do not contribute to intradialytic hypotension. Similarly, if drug removal by HD is contributing to suboptimal BP control, consideration should be given to switching to an agent that is not significantly removed by dialysis.

The dialysis prescription should be examined to ensure there is no iatrogenic contribution to paradoxical hypertension. Specifically, the dialysate potassium content should be modified to avoid acute hypokalemia and net dialysate sodium load lowered when possible. While higher calcium baths have not been shown clinically to be associated with significant hypertension, a lower calcium bath should be considered in patients with rebound hypertension.

Finally, the incidence of hypertension in dialysis patients has increased in the post-erythropoietin (EPO) era. This may relate to increased viscosity, increased peripheral vascular resistance, or a direct effect of EPO on endothelin one production. While there are no published studies showing a direct relationship between haemoglobin and hypertension, effort should be made to avoid excessive haemoglobin values in patients with intradialytic hypertension.

Chronic Complications

Cardiovascular Disease

Overall mortality in children with ESRD is 30 times higher than in the general population and the risk of cardiac death is more than 700-fold greater [105]. The incidence of cardiovascular events ranges from 24.3% in the 0–4 year age group to 36.9% in 15–19 year olds [106]. Manifestations of cardiovascular disease (CVD) range from arrhythmias (19.6%), and valvular heart disease (11.7%), to cardiomyopathy (9.6%), and acute cardiac death (2.8%).

Classical risk factors for CVD are common in children. Hypertension occurs in 50–75% of dialysis dependent children; dyslipidemia occurs in 70–90% and the incidence of obesity and glucose intolerance is rising. There is an exhaustive and expanding list of additional uremia-specific risk factors that are prevalent in children on HD. Examples include anaemia (50–70%), hyperphosphatemia and hyperparathyroidism (60%), raised CRP (75%) indicative of chronic inflammation, oxidative stress with raised asymmetric dimethylarginine (ADMA) levels, hyperhomocysteinemia (90%) [33], hypervolemia, activated renin-angiotensin-aldosterone pathway, abnormal adipokines leptin and adiponectin with resultant insulin resistance, and aberrant sympathetic activity [107].

Manifestations of Cardiovascular Disease

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) develops early in CKD and progresses as renal function deteriorates such that at the initiation of dialysis 69–82% of children show evidence of LVH [108] and during maintenance dialysis 40–75% of children have LVH [109]. The factors that contribute to the risk of cardiac hypertrophy include chronic hypervolemia, hyperdynamic circulation secondary to arteriovenous fistulae or anaemia, increasing arterial stiffness and elevated parathyroid hormone (PTH) levels [110]. Somewhat surprisingly, both adult data and now paediatric data from the ESCAPE trial have failed to demonstrate any relationship between office BP or ambulatory BP monitoring and left ventricular mass [111]. Cardiac hypertrophy in combination with continued mechanical stress triggers pathways that result in myocardial remodelling characterized by decreased capillary density and reduced coronary flow reserve. At times of haemodynamic stress or increased demand the reduced ischaemic threshold predisposes to subendocardial perfusion defects with a resultant tendency to arrhythmias, ischaemic myocardial fibrosis with eventual myocyte death, and myocardial dysfunction. In children with kidney disease there is evidence of LV diastolic dysfunction [112] that is progressively worse in dialysis patients compared with CKD or post transplant patients. In addition conventional HD induces regional LV systolic dysfunction that is significantly associated with intradialytic blood pressure reduction [80]. It is unclear whether the poor myocardial contractile reserve is responsible for the drop in BP or vice versa, regardless the two are most likely self-perpetuating. Of greater significance, this evidence presents a direct link between HD and uremic myocardial dysfunction. In contrast, generally global LV systolic function in paediatric dialysis patients is on the whole preserved.

Endothelial Dysfunction

Endothelial dysfunction starts early in renal failure and progresses during dialysis and is thought to be the initiating step in atherosclerosis and arteriosclerosis. HD is thought to be pro-inflammatory as a consequence of an immune mediated response to bioincompatible membranes, blood contact with non-sterile dialysate solution and/or 'back-leaking' of dialysate across the membrane. In addition large fluid shifts during UF change blood viscosity and laminar shear stress and alter endothelial cell dynamics [113]. Intradialytic hypotension and resultant ischaemia has the potential to cause hypoxic apoptosis of the vascular endothelium. Finally, reduced clearance of the endothelial nitric oxide synthase inhibitor ADMA with resultant decreased bioavailability of endothelial nitric oxide, activation of angiotensin II, hyperhomocysteinemia, and hyperlipidemia are all postulated mechanisms for endothelial dysfunction. Not only is uremia an independent factor associated with endothelial dysfunction but it is also associated with reduced haematopoiesis and capacity for repair. In adults, endothelial progenitor cells are reduced with pronounced functional impairment [114, 115] and HD depletes this source further. However, the pool of smooth muscle cell progenitor cells is preserved and with it the potential for adverse remodelling [116]. Little is known about circulating endothelial progenitor cells in children. In contrast there is clear clinical evidence of endothelial dysfunction. Loss of flow-mediated dilatation (FMD) and increased aortic pulse wave velocity has been demonstrated in children on dialysis [117, 118]. In adults impaired FMD has been shown to be predictive of CVD morbidity and mortality. Encouragingly the risk of endothelial injury in dialysis patients may be amenable to treatment. In adults both HDF and home nocturnal HD have been shown to lower dialysis related endothelial dysfunction compared with conventional HD [119, 120].

Atherosclerosis, Arteriosclerosis, and Calcification

Calcification of the cardiovascular system is accelerated in dialysis patients. It is highly prevalent in children as well as adults and thus warrants equitable attention both from adult and paediatric nephrologists. Studies of young adults

who developed ESRD during childhood found a high prevalence of abnormal carotid intima-media thickness (cIMT), diminished arterial wall compliance, and coronary artery calcification [121, 122]. These results were mirrored in a study of children on dialysis [123]. All vascular measures positively correlated with serum phosphorus levels, while cIMT and cardiac calcification scores also correlated with intact PTH levels and dosage of vitamin D. Patients with mean intact PTH levels less than twice the upper limit of normal had vascular measures that were comparable to age-matched controls, but levels in excess of this resulted in stiffer vessels and increased cIMT and cardiac calcification scores. The relationship with 1,25 dihydroxy vitamin D levels showed a U-shaped distribution, patients with both low and high 1,25 dihydroxy vitamin D had significantly greater cIMT and calcification scores than those with normal levels. Calcification was most frequently observed in patients with the lowest 1,25 dihydroxy vitamin D and the highest high-sensitivity C-reactive protein [124]. Litwin et al. reported vascular abnormalities in children with CKD but again found the most marked changes in the dialysis patients. The degree of arteriopathy correlated with conventional CVD risk factors such as hypertension and dyslipidemia in pre-dialysis CKD and with hyperphosphatemia, hyperparathyroidism, and treatment with calcium-containing phosphate binders in dialysis patients [125].

The consequences of myocardial and vascular calcification are widespread, and the risk factors are iatrogenic or akin to the most challenging aspects of renal care, hyperphosphatemia, and hyperparathyroidism. Managing these risks requires a multidisciplinary approach with patient education, dieticians, pharmacists, and occasionally psychologists to address adherence issues, but even then the outcomes remain inadequate. Looking specifically at the dialysis prescription, phosphate clearance can be improved by increasing the dialysis time or employing convective clearance. Switching patients to short-daily HD, HDF, and especially home nocturnal HD can result in dramatic improvements in phosphate clearance with normalisation of PTH levels to the extent that patients on home nocturnal HD develop abnormally low phosphate levels and require oral supplementation or dialysis against a phosphate containing bath [103, 126]. The question that arises thereafter is what level of vitamin D supplementation is required in patients with normal or even low PTH levels. Vitamin D has several important systemic musculoskeletal, cardiovascular, and immunological effects. However inappropriate use in renal failure can induce adynamic bone disease and hypercalcemia. Pending the evidence to guide us it would be prudent to treat documented vitamin D deficiency, with careful monitoring for any adverse effects.

Sudden Cardiac Death

Sudden cardiac death is a common phenomenon in dialysis patients; the most vulnerable patients are infants aged 0–4 years, with a 5–10-fold increase risk of cardiac arrest compared to other age groups [127]. It is also temporally related to the HD procedure. Cardiac arrests are 50% higher for HD patients 3 months after dialysis initiation. The risk remains higher in HD compared with peritoneal dialysis for up to 2 years on maintenance dialysis, but then the trend reverses and at 3 years of maintenance dialysis the risk is higher among peritoneal dialysis patients. The risk of sudden death in adults is also 1.7 times higher in the 12 h period starting with the dialysis procedure and 3 times higher in the 12 h before HD at the end of the weekend interval [128].

The precise aetiology of sudden cardiac death remains elusive but there is a distinct possibility that specific dialysis and uremic factors are responsible for this heightened vulnerability. Myocardial interstitial fibrosis, left ventricular hypertrophy, endothelial dysfunction, cardiac and vascular calcification, microvascular disease with decreased perfusion reserve, and diminished ischaemia tolerance are all prevalent in dialysis patients. This, in combination with dialysis related acute fluid shifts, acid/base disturbances and rapid electrolyte shifts and autonomic imbalance with abnormal sympathetic activity, place patients at risk of sudden death. Clinically the only modifiable risk factor that has been identified and found to be of benefit is manipulation of

the dialysate potassium. Patients who suffered a cardiac arrest at the time of dialysis were twice as likely to be dialysed against a 0 or 1.0 mEq/l potassium dialysate compared to controls, despite no difference in pre-dialysis potassium levels [129]. Kovesdy et al. found that a serum potassium between 4.6 and 5.3 mEq/l was associated with the best survival but levels below 4.0 mEq/l or higher than 5.6 mEq/l were associated with increased mortality [130].

Sleep Disorders

Disorders of sleep are common in both peritoneal dialysis and HD patients and are associated with morbidity. Sleep disturbance is thought to contribute to the lack of well-being, cardiovascular disease, hypertension, and increased mortality seen in patients on conventional HD [131]. Manifestations include disorders of the initiation and maintenance of sleep, sleep apnoea, and restless leg syndrome/periodic limb movement disorder.

Sleep apnoea (SA) is defined as cessation of air flow accompanied by a fall in oxygen saturation. In the general population symptoms of SA include snoring, witnessed apnoeas, daytime somnolence, general malaise and fatigue, difficulty initiating sleep, frequent nocturnal awakenings, and morning headaches. In contrast, in patients with ESRD, snoring, witnessed apnoeas, unrefreshing sleep, and morning headaches are described less frequently [132]. This suggests a different clinical phenotype of SA in ESRD, and the need for a high index of suspicion for diagnosis. The gold standard for the diagnosis of SA is polysomnography (PSG). This test is time consuming, inconvenient for patients and expensive to perform, and suffers from significant variability. Ambulatory PSG has gained popularity but lacks the ability to diagnose periodic leg movements and rapid eye movement sleep behaviour disorder, which are important in the CKD population [133].

SA is reported to occur in more than 50% of patients on HD. In a community-based sample of HD patients there was a fourfold increase in severe SA in the HD patients compared to matched controls [134]. Using home PSG, patients on conventional HD demonstrated significantly less sleep time, more frequent arousals, and greater apnoea frequency than the general population. Obstructive SA is reported to be most common in patients on conventional HD [135], but central or mixed sleep apnoeas may coexist, and relative frequencies vary over studies. Unanimously, the literature reports poor overall sleep quality in ESRD [136, 137].

There are multiple postulated explanations for the SA of dialysis. Compensation for chronic metabolic acidosis may contribute to hypocapnia and reduced respiratory drive. Upper airway oedema, elevated leptin levels, and elevated levels of pro-inflammatory cytokines especially interleukin 1α have all been implicated. Other potentially contributory factors include anaemia, accumulation of endorphins, and dialysis membrane induced complement activation. Increased ventilatory sensitivity to hypercapnia has been described in patients on dialysis [138]. This is hypothesized to destabilize the chemoreflex control of respiration during sleep, potentially contributing to both central and obstructive SA. HD patients with severe hyperparathyroidism unresponsive to conventional therapy have poor sleep quality with a high rate of insomnia, compared to matched controls, though the mechanism is unknown [139]. Finally sleep disordered breathing in dialysis patients has been associated with insulin resistance, elevation in levels of the vasoconstrictor endothelin-1, and suppression of vasodilatory nitric oxide production, all of which likely contribute to the hypertension commonly seen with obstructive SA.

Options to reduce the morbidity of SA include use of continuous positive airway pressure (CPAP), change in dialysis modality, and transplantation. While the use of CPAP is well described in the general population, there is little published on its use in patients on HD. CPAP is reported to improve the frequency of apnoeas and sleep quality in a small group of patients with ESRD [140]. Nocturnal oxygen therapy has successfully lowered the episodes of hypopnoea and central apnoeas in patients on peritoneal dialysis,

but the effect on patients on conventional HD is unknown [141]. In HD patients excess intradialytic weight gain is a reported modifiable risk factor for SA [142]. NHD has been shown to markedly reduce the frequency of apnoeas and hypopnoeas [143], and reduce pharyngeal oedema, with resultant improvement in SA in some but not all patients [144]. This is thought to be secondary to superior volume and uremia control, improved cardiac function, and normalisation of increased sympathetic tone. In spite of this, overall sleep quality remains suboptimal [145]. Transplantation offers the greatest gain and improvement in sleep quality [146, 147].

Restless leg syndrome (RLS) occurs in 60–80% of patients with CKD, compared to 10% in the general population. The criteria for diagnosing RLS include an almost irresistible urge to move the legs that is accompanied by a noxious sensation. It is aggravated by inactivity; relieved by movement; and is worse during the evening and night [148]. The sensations are variably described as crawling, prickling, creeping, and itching. On dialysis, RLS may cause premature discontinuation of the dialysis treatment. Reported risk factors include female gender, length of time on dialysis, obesity, under-dialysis, hyperphosphatemia, and iron deficiency. While the aetiology remains to be elucidated, investigations suggest the involvement of endogenous opioid and dopaminergic pathways. Iron deficiency in the substantia nigra has recently been reported in RLS, suggesting iron supplementation as a potential treatment for RLS [149]. Treatment of RLS includes dopamine agonists given at bedtime, and gabapentin or opioids for more severe symptoms.

Periodic Limb Movement Disorder (PLMD) frequently coexists with RLS [150] and is a disorder that can only be diagnosed with PSG. It is characterized by rhythmic, repetitive, highly stereotyped movements that occur both during sleep and while awake. The movement consists of triple flexion, with flexion of the leg, dorsiflexion of the ankle, and extension of the great toe. Movements last for approximately 2 s and occur every 20–40 s with variable duration. It is associated with significant sleep disruption, with frequent nocturnal awakening, non-refreshing sleep, and daytime hypersomnia. In 48 adults on dialysis, studied with a 2 day PSG recording, the frequency of RLS was 58.3% and of PLMD was 70.8% [150]. The coexistence of both RLS and PLMD was associated with both subjective and objective evidence of poor sleep quality, and lower quality of life. There was no correlation between iron studies and the presence of RLS; however, correction of anaemia with erythropoietin lowered the frequency of RLS [151].

There is relatively little published on sleep disorders in children on dialysis, but there is no doubt clinically that it exists. Available studies show that sleep disorders are common and start early during CKD. In a questionnaire study of 49 children with CKD stages 2–4, including those with a renal transplant, 37% had a sleep disorder [152] with 29% reporting RLS. An interview of 21 children on HD and PD highlighted sleep disorders in 86% [153]. Sleep disordered breathing, primarily snoring, occurred in 46% of children, RLS or periodic leg movements occurred in 29%, and excessive daytime sleepiness was documented in 60%. Finally Applebee assessed 26 children age 6–18 with varying degrees of CKD using a questionnaire based on consensus criteria for diagnosing RLS [148]. Thirty-five per cent of participants met the criteria for RLS compared to only 2% of the general paediatric population [154]. Of interest, in children without CKD, RLS was associated with attention deficit/hyperactivity disorder. This raises the possibility that sleep disorders in uremic children may potentially contribute to associated behavioural and cognitive disturbances.

All available studies show an incidence of sleep disorders greater than that seen in healthy children. Unfortunately these studies are all based on questionnaire, and not on objective studies. Furthermore paediatric specific data on treatment does not currently exist.

Dialysis Related Amyloidosis

Dialysis related amyloidosis (DRA) or β-2 microglobulin amyloidosis is a disabling acquired form of amyloidosis associated with high serum levels

of β-2 microglobulin, seen primarily in patients on long-term dialysis and characterized clinically by osteoarticular lesions and to a lesser extent, systemic manifestations.

β-2 microglobulin is an 11,815 Da molecular weight protein which is the light chain component of the major histocompatibility complex (MHC) and is present on all cells that express MHC. When released into the circulation it is in its monomeric form, and is filtered by the glomerulus, then reabsorbed and catabolised in the proximal tubule. Plasma β-2 microglobulin levels rise if the glomerular filtration rate falls. If the plasma levels remain persistently high, β-2 microglobulin will eventually deposit in tissue, most commonly periarticular tissue and bone. In ESRD β-2 microglobulin is removed by HD. Clearance is determined by the dialyzer pore size, time on dialysis, and UF volume. Thus with the older, low-flux cellulosic dialyzers, clearance was poor. In recent times with the wide spread use of high-flux dialysers, and a move to longer or more frequent dialysis regimens and HDF, the incidence of DRA is thought to be declining but it has not been completely eliminated [155]. Tissue deposition precedes manifestation of clinical symptoms. The prevalence of amyloid deposits relative to time on HD is reported to be 33% at 2–4 years, 50% at 4–7 years, 90% at 7–13 years, and 100% at more than 13 years [156]. Similar findings have been documented in patients on PD [157], although clinical DRA is more common in HD patients compared to PD patients [158].

Reported risk factors for the development of DRA are prolonged time on HD, elevated age at start of HD, use of bioincompatible membranes, dialysis with low-flux membranes, and lower purity of dialysate. Additionally, genetic risk factors have also been identified [159]. Elevated serum β-2 microglobulin levels alone are not sufficient to explain amyloid deposition, and it is most likely that multiple factors specific to the uremic milieu predispose to the development of DRA [160]. The toxicity of amyloid deposits is thought to occur both from disruption of normal tissues, and also from a direct cellular toxicity.

The definitive diagnosis of amyloidosis is histological, with characteristic findings of positive staining with Congo red dye and birefringence under polarized light in affected tissues, combined with immunostaining to confirm the presence of β-2 microglobulin. DRA is divided into two forms, osteoarticular and visceral or systemic.

Osteoarticular DRA: Carpal tunnel syndrome due to entrapment of the median nerve at the wrist is the most common manifestation of osteoarticular DRA. It is frequently bilateral and tends to progress in severity over time. Patients present with pain which is usually worse on dialysis and at night, and numbness and paraesthesias in the distribution of the median nerve. Over time, atrophy of the thenar muscles occurs, reducing hand strength. Amyloid deposition can also occur in the rotator cuff causing shoulder pain and limitation of movement, and in the hips, knees, and long bones. Spondyloarthropathy most commonly affects the cervical spine. Destruction of paraspinal ligaments or intervertebral discs may result in spinal cord impingement and spinal stenosis. Subchondral bone cysts can develop in the carpal bones, femoral head, humerus, acetabulum, and spine causing pain and soft tissue swelling as they grow and are often the site of pathological fractures. Tenosynovitis may result in ‘trigger finger’ with pain and snapping of the tendon on digit re-extension. Clinically, osteoarticular DRA is diagnosed by a combination of the symptom complex and radiological findings. Serum matrix metalloproteinase three (MMP-3) levels, a marker for joint destruction in rheumatoid arthritis, are elevated in HD patients and correlate with plasma β-2 microglobulin levels and dialysis vintage [161]. MMP-3 levels may therefore be a useful diagnostic marker for DRA joint destruction.

Visceral DRA: The incidence of visceral amyloid increases with increasing time on dialysis. Visceral amyloid affects the gastrointestinal (GI) system, heart, genitourinary (GU) system, and lungs. GI manifestations include macroglossia, malabsorption, pseudo-obstruction, and potentially life-threatening intestinal bleeding. Cardiac

involvement may manifest as myocardial and pericardial inflammation, valvular disease, or arrhythmias. GU symptoms include renal and bladder calculi and bladder deposits, which may cause obstruction. Pulmonary hypertension and pulmonary haemorrhage can occur. Skin involvement is less common, but may manifest as hyperpigmentation and lichenoid lesions, as well as pedunculated masses [162]. β-2 microglobulin deposition in extra-articular sites affects primarily vessel walls and is now thought to be an important risk factor for uremic cardiovascular disease [155].

Management

In the absence of a cure, prevention remains the best approach to DRA. Patients on HD with residual renal function have lower β-2 microglobulin levels [163]. All high performance, biocompatible membranes provide far greater β-2 microglobulin clearance than the older cellulosic membranes, with no one membrane showing superiority. Compared with conventional thrice weekly or short-daily dialysis, β-2 microglobulin clearance is higher with long daily or nocturnal dialysis, or HDF [155, 157, 159, 164–166]. What remains unclear is the plasma β-2 microglobulin saturation threshold or the concentration that predisposes to tissue deposition. In addition there is uncertainty as to whether more intensive dialysis regimens such as nocturnal HD will prevent DRA. There is, however, certainty in the fact that more aggressive β-2 microglobulin removal arrests symptoms in many patients with DRA. A newer, adjunct therapy, not yet in widespread use, includes addition of a β-2 microglobulin adsorption column (Lixelle) in series with a high-flux dialyser. In a 2-year study of 22 adults, treatment with the Lixelle column significantly increased β-2 microglobulin removal and provided improvement in clinical symptoms as well as cessation of new bone cyst formation [167]. Newer treatments on the horizon may use nanobiotechnology such as magnetically assisted HD for targeted removal of β-2 microglobulin, though these treatments are not yet in clinical use [168].

DRA has not been described in paediatric patients; however based on adult data, children on long-term dialysis are at risk. Very high levels of β-2 microglobulin have been documented in paediatric patients dialysed with cellulosic membranes [163] and in those receiving on-line haemodiafiltration with a polysulphone membrane [179]. Following the conversion of 5 children from 3 to 6 days per week of on-line haemodiafiltration, Fischbach demonstrated a small but statistically significant drop in β-2 microglobulin levels at 6 months of treatment with no further improvement at 12 months [169], and levels remained approximately 10 times normal. Preliminary experience with nocturnal HD in four children failed to show a reduction in β-2 microglobulin levels [103]. While this preliminary data is discouraging, results in larger numbers of patients are required to draw a meaningful conclusion. Therapy should thus be directed at early transplantation, which is known to halt the progression of DRA, and dialysis modalities associated with optimal β-2 microglobulin removal, to try and lessen at least one of the long-term morbidities of HD.

Residual Renal Function

In patients who commence dialysis the assumption that dialysis and renal clearances are equivalent and therefore additive is incorrect. Residual renal function (RRF) has a survival advantage. A large incident HD population Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study showed that for each 1-unit increase in renal Kt/V_{urea} a 66% decrease in relative risk of death was observed [170]. Shemin et al. reported that the presence of RRF, even at a low level, was protective against mortality when compared with those without RRF [171]. RRF also plays an important role in achieving dialysis adequacy, in maintaining fluid balance, in small and middle molecule clearance, in supporting nutrition and growth, and in anaemia control. Patients with RRF greater or equal to 1 mL/min had a significantly lower mean creatinine, UF requirement, serum potassium, and uric acid levels, significantly lower erythropoietin requirements and erythropoietin resistance indices [172], better plasma phosphate control, improved β-2

microglobulin and p-cresol clearance, and higher quality of life [163, 173]. RRF also appears to be anti-inflammatory with an inverse relationship between renal function and pro-inflammatory mediators [174]. In a study of adolescents and young adults on chronic HD treatment, nPCR was higher in patients with RRF and renal clearance positively influenced nutrition independently of HD efficiency and recombinant growth hormone treatment [175].

The counterargument for prioritising efforts to preserve RRF is the concern that in proteinuric patients, maintaining a high urine output has the potential to worsen hypoalbuminemia, malnutrition, and clotting derangements. Secondly, prioritising the preservation of RRF at the expense of volume control has the potential to cause chronic hypervolemia with worsening hypertension. Although true, this last statement is only partially correct, as both volume and salt are symbiotic, and equally important in managing volume status in children on dialysis. Controlling salt intake is often a neglected component of management.

Strategies to Preserve RRF

Peritoneal dialysis appears to be superior to conventional HD in preserving RRF. This effect is less pronounced in children owing to the high prevalence of renal hypo/dysplasia accompanied by preserved and often excessive water and salt excretion and such RRF may last years after initiating HD. Nonetheless every endeavour should be made to protect RRF in all dialysis patients. Important general measures include avoidance of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs or aminoglycosides and where possible contrast for radiological investigations. In the event of unavoidable need to administer contrast agents, nephrotoxicity can be minimized by ensuring patients are adequately hydrated prior to the investigation or by prescribing prophylactic acetylcysteine and ensuring that the subsequent dialysis session is timed immediately after the investigation. In PD patients, calcium channel blockers and angiotensin converting enzyme inhibitors appear to lower the rate of RRF loss but not in HD patients [174]. In CKD and PD patients diuretics are used to drive urine output. On this basis, diuretic use was investigated in 16,420 HD patients from the Dialysis Outcomes and Practice Patterns (DOPPS) Study. Diuretics lowered interdialytic weight gain and the odds of hyperkalemia, and significantly reduced the risk of cardiac-specific mortality by 14% with a nonsignificant reduction in all cause mortality. Patients with RRF who received diuretics had almost twice the odds of retaining RRF following 1 year of maintenance dialysis compared with those not on diuretics [177].

In HD patients the dialysis prescription and intradialytic events also have the potential to influence the RRF. McKane et al. demonstrated a comparable decline in RRF to continuous ambulatory peritoneal dialysis using high-flux, biocompatible membranes such as polysulphone, and ultrapure water for HD [178]. Overzealous UF resulting in intradialytic hypotension is a recognised factor for precipitating a decline in the RRF, therefore strategies that improve cardiovascular stability such as bicarbonate buffered fluids, cooling, sequential dialysis, and volumetric UF control may be of benefit. Finally the most effective and perhaps extreme measure for preserving RRF is switching dialysis modality to PD, short-daily HD, or home nocturnal HD.

Preservation of RRF is important in children on HD but it needs to be taken within the context of the global health needs of each individual child. It is in truth a strategy for optimising renal replacement therapy and not an absolute requirement (Table 21.4).

Table 21.4 Strategies to preserve RRF

Switch to peritoneal dialysis
Avoid nephrotoxic agents *NSAIDs, radiological contrast agents, aminoglycosides*
Maintenance diuretic therapy
Manipulate the HD prescription High-flux, biocompatible membranes Strategies to avoid hypotension (*cooling, sequential dialysis, UF and sodium profiling*)
Employ alternate dialysis regimens (*Short-daily HD, home nocturnal HD*)

Quality of Life

Children on dialysis are on dietary and fluid restrictions, face disruptions to home and school life, and some require multiple surgeries and hospitalization. This almost definitely has the potential to have an adverse effect on physical and emotional well-being. Eijsermans et al. assessed ten chronic HD patients, aged 7–16 years and found abnormal gross motor functioning in 5/8 children, 1 child showed fine motor problems, and 7/10 reduced exercise tolerance, of which six children were physically inactive. There was no significant difference between the self-assessed physical and mental health of children on dialysis and the general population. Social contacts with parents and peers was however good and the occurrence of positive and negative moods was normal compared with healthy controls [179]. In contrast children with renal failure reported more psychiatric disturbance than normal controls and children below 17 years were found to be more vulnerable than young adults. Psychological problems were reported in almost 60% of children starting dialysis but this fell to 21% 1 year later [180]. Lower self-esteem was linked to early-onset renal disease and to educational and social dysfunction.

Renal failure in childhood arising from congenital urological disease is commonly associated with urinary incontinence, a factor thought to be negatively associated with self-esteem and emotional well-being. However Dodson et al. found no difference in Health Related Quality Of Life (HRQOL) scores between adolescents with urological versus medical renal disease. The congenital urological disease group scored better in the sub-domain 'Limitations of Activity', and both renal groups were less likely than the general population to be involved in risk taking behaviours (individual risks, threats to achievement, peer influences) [181].

Receiving a kidney transplant is perceived to be a positive influence on quality of life by health professionals; however, the data from children and their parents is less clear cut. Children and adolescents on dialysis demonstrated lower activity levels, home safety, and an increase in physical discomfort compared with children with CKD, transplant recipients and healthy controls [182, 183]. They were less likely to have a special friend, had a lower self-esteem and higher depression scores than transplant recipients [184]. Height gain was an important confounder in both groups, such that shorter patients reported lower self-esteem and lower satisfaction with health [183].

A comparison between patients' and care givers' perceptions of the physical, emotional, social, and school impact of childhood kidney disease is discrepant. Caregivers scored their children lower in almost all categories than their child's self-reports [185, 186]. Both children receiving HD and their parents reported a greater fatigue and physical impact of their kidney disease (About My Kidney Disease Scale) than children with a transplant and their parents. There was a significant negative correlation between number of medications a patient was on and their physical subscale score [185]. Parents scored transplants recipients higher than those on dialysis on all domains except the 'Perceived Physical Appearance Scale'. In contrast Goldstein et al. found paediatric renal transplant recipients self-reported HRQOL scores were comparable to dialysis patients across the ESRD Module Scales, with the exception of the Family and Peer Interaction Scale, in which transplant patients self-reported significantly higher HRQOL than dialysis patients [185]. McKenna et al. found transplant recipients scored the lowest compared to dialysis and CKD patients. Despite their increased hospitalization time and number of medications, the dialysis patients had higher scores in emotional and school subscales than the transplanted children [186]. It has been postulated that transplant patient's fears about kidney rejection are responsible for their HRQOL scores. In comparison dialysis patients have relative stability and they experience a 'response shift', namely, that their internal standards change as they adapt to their diagnosis and medical surroundings, and this yields higher self-reported HRQOL as living with their illness becomes routine.

There are no consistent HRQOL differences between peritoneal dialysis and HD. Goldstein reported similar HRQOL scores for HD and peritoneal dialysis patients [187]. Tsai et al. found

parents of children on peritoneal dialysis exhibited significantly more symptoms of depression and lower quality of life than parents of healthy children [188]. Similarly Geary et al. reported a substantial workload and emotional burden of home therapies; nonetheless home HD improved the quality of life, in particular school attendance in three of four children [103]. In reality the absolute burden of home-based therapies on care givers still remains to be determined.

Following patients with childhood ESRD to adulthood highlights a physical, vocational, and psychosocial disadvantage compared with the general population. A Europe-wide study by the EDTA reported an increased unemployment rate ranging from 25% to 65%, depending on whether the patients suffered from additional handicaps, like hearing, sight, or motor deficits [189, 190]. Rosenkranz et al. followed 283 patients treated for early childhood CKD that were transferred to an adult unit at 16–20 years. The average period for renal disease was 19 years and the cumulative dialysis time was 5 years (range 0–22 years). Fifty-eight per cent achieved a high school certificate, 87% vocational graduation, and 67% of all patients were in paid employment with 72% fully or partly earning their own living. While 49% lived alone or together with a partner, 46% still lived in their parents' homes and 5% had other accommodation. Four patients (all fathers) had one or two children [191]. In renal patients the mean body height SDS score was – 1.56 and 36% of the patients expressed dissatisfaction with their own body height. Once again a significant positive correlation was seen between self-reported quality of life and satisfaction with height. In 4/8 categories (mobility, vision and hearing, being free of fear, independence of assistance) patients achieved similar scores to healthy controls but consistently reported concerns with health issues, being free of fear, being free of pain, physical health, and ability to relax/inner balance. Compared to the general population, the satisfaction with their job/income was much lower, and their desire for a family life and children was high and yet to be fulfilled. Neither the length of renal disease or dialysis time correlated with patients' general satisfaction and outcomes were similar between dialysis and transplanted patients [191].

As we begin to recognise the full impact of renal disease on physical, social, and psychological well-being, as paediatric nephrologists we must place an equal priority on all aspects of our patients' health combined with a renewed emphasis on transition and preparing children for adulthood.

Dialysis Dose and Prognosis

USRDS Registry between 1978 and 1999 reporting on the outcomes of patients who developed ESRD during adolescence showed that the overall 10-year survival rate was 79.9% during the study period [192] and the 2.2% annual mortality rate was 30-times greater than the general population. Of the patients on renal replacement therapy HD patients fared worse than transplant patients. Currently the expected lifespan of a child on dialysis is 40–60 years lower than that expected in the general population, while that of a paediatric transplant recipient is 20–30 years lower [193].

The outcome of HD patients is not only a consequence of their method of renal replacement therapy but reflects the combined effects from a number of factors related to the dialysis prescription and dose. In the HEMO study comparing high-dose HD (urea-reduction ratio of 75.2%, single-pool Kt/V of 1.71 and equilibrated Kt/V of 1.53) against standard dose HD (urea-reduction ratio of 66%, single-pool Kt/V of 1.32, and equilibrated Kt/V of 1.16) the relative risk of death was not significantly different between the two groups. Likewise the relative risk of death in the high-flux group compared with the low-flux group was no different [194]. On a secondary analysis stratifying patients according to their dialysis vintage, in the subgroup that had been on dialysis for >3.7 years, high-flux dialysis was associated with 37% reduction in mortality and 20% reduction in cardiac deaths compared with low-flux dialysis [195]. Furthermore high-dose dialysis was found to be beneficial in women compared with the low dose group. Wolfe et al. corroborated these findings, reporting an association with body mass index

(BMI), dialysis dose, and mortality. The lowest BMI group had a 42% higher mortality risk than the highest BMI. The RR of mortality was 17%, 17%, and 19% lower per 5% higher URR category among groups with small, medium, and large BMI, respectively [196]. These results suggest a survival advantage in increasing HD dose in women and low BMI patients.

Dialysis dose can be altered by increasing the dialysis time and/or frequency. The DOPPS review of 22,000 HD patients from seven countries found that for every 30 min longer on HD the relative risk of mortality was reduced by 7%. A higher Kt/V was a significant and independent predictor of lower mortality on HD and a synergistic survival advantage existed between Kt/V and treatment time. A more pronounced mortality risk reduction was seen combining a higher Kt/V with a longer treatment time [83]. An ANZDATA analysis of 4,193 patients found that the optimal dialysis dose for survival was a Kt/V greater or equal to 1.3 and a dialysis session greater than or equal to 4.5 h. A duration less than 3.5 h was associated with a higher mortality risk [197]. Mortality in HD patients also appears to be temporally related to the dialysis day. In a comparison of dialysis days, sudden cardiac death was more prevalent on 'Bloody Mondays', 12 h before HD at the end of the weekend interval and in the 12 h period starting with the dialysis procedure [128].

Translating this to the clinical environment, converting patients from conventional dialysis regimens to quotidian dialysis regimens has been met with positive results. Patients switching to short-daily HD report a cumulative survival of 33% at 6 years and reduced hospitalization [198]. A systematic review of short-daily HD concluded that it was more effective than conventional dialysis. Patients on daily HD seem to exhibit fewer vascular access problems, better control of hypertension and reduced antihypertensive medication burden, better quality of life, lower incidence of ventricular hypertrophy, lower consumption of recombinant erythropoietin due to the better control of anaemia, and a reduction in the use of phosphate binders as a consequence of the improved phosphorous clearance [199]. In a comparison of HDF and low-flux, high-efficiency HD, HDF patients had a significant 35% lower mortality risk than those receiving low-flux HD [10]. Even though the dialysis dose as measured by Kt/V was higher in HD patients the survival advantage appeared to be related to the improved β-2 microglobulin clearance, improved nutrition, and a reduction in the frequency of intradialytic acute hypotension episodes [200]. These results mirror findings in children on in-centre daily HDF [126].

Finally home nocturnal HD has been receiving a lot of interest as preliminary data demonstrates its superiority over all other quotidian dialysis regimens. Nocturnal HD is associated with a significant reduction in the risk for mortality or major morbid events when compared to conventional HD [201]. In fact during a matched cohort study comparing survival between nocturnal HD and deceased and living donor kidney transplantation, the proportion of deaths amongst the three was 14.7%, 14.3%, and 8.5%, respectively, and there was no difference in the adjusted survival between nocturnal HD and deceased donor renal transplantation [202]. This is both relevant and important because for the first time, we may be able to bridge the gap between dialysis and transplantation.

Despite these remarkable results scepticism surrounds the quotidian dialysis literature, with many arguing a selection bias and recruitment of 'healthier', independent adults. Data in children is limited, however, Geary et al. reported the outcomes of children on home nocturnal HD, including two patients that had exhausted all other treatment options. Both of these patients survived and the group outcomes showed improved BP control and reduced antihypertensive medication burden, improved growth and nutrition, greater control of renal bone disease with normalisation of plasma phosphate and parathyroid hormone levels, liberalisation of diet and fluid restrictions, and discontinuation of all phosphate binders [103]. Quotidian dialysis or convection based therapies are producing results we never anticipated in dialysis patients and even though data is scarce in children, the projected and demonstrable benefits are hard to ignore.

Conclusion

Haemodialysis is a necessary evil for many patients with ESRD, and one that is fraught with complications, with outcomes that are inferior to transplantation. However, individualization of HD prescriptions will benefit our patients and intensified dialysis regimens, though demanding on the care givers, hold the promise of improved long-term outcomes.

References

1. Pauli HG, Vorburger C, Reubi F. Chronic derangements of cerebrospinal fluid acid-base components in man. J Appl Physiol. 1962;17:993–8.
2. Silver SM, DeSimone Jr 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.
3. Manley GT, Fujimura M, Ma T, et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. Nat Med. 2000;6(2):159–63.
4. 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.
5. Fenstermacher JD, Johnson JA. Filtration and reflection coefficients of the rabbit blood-brain barrier. Am J Physiol. 1966;211(2):341–6.
6. Arieff AI, Guisado R, Massry SG, Lazarowitz VC. Central nervous system pH in uremia and the effects of hemodialysis. J Clin Invest. 1976;58(2):306–11.
7. Arieff AI. Dialysis disequilibrium syndrome: current concepts on pathogenesis and prevention. Kidney Int. 1994;45(3):629–35.
8. Chang CH, Hsu KT, Lee CH, et al. Leukoencephalopathy associated with dialysis disequilibrium syndrome. Ren Fail. 2007;29(5):631–4.
9. 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.
10. Bunchman TE, Hackbarth RM, Maxvold NJ, Winters JW, Barletta GM. Prevention of dialysis disequilibrium by use of CVVH. Int J Artif Organs. 2007;30(5): 441–4.
11. Daugirdas JT, Ing TS. First-use reactions during hemodialysis: a definition of subtypes. Kidney Int Suppl. 1988;24:S37–43.
12. Villarroel F, Ciarkowski AA. A survey on hypersensitivity reactions in hemodialysis. Artif Organs. 1985;9(3):231–8.
13. Levin NW, Zasuwa G. Relationship between dialyser type and signs and symptoms. Nephrol Dial Transplant. 1993;8(Suppl 2):30–9.
14. Ebo DG, Bosmans JL, Couttenye MM, Stevens WJ. Haemodialysis-associated anaphylactic and anaphylactoid reactions. Allergy. 2006;61(2):211–20.
15. Tielemans C, Gastaldello K, Goldman M, Vanherweghem JL. Acute haemodialysis membrane-associated reactions. Nephrol Dial Transplant. 1996;11(Suppl 2):112–5.
16. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. Br Med J (Clin Res Ed). 1986; 292(6530):1221–2.
17. Rockel A, Klinke B, Hertel J, et al. Allergy to dialysis materials. Nephrol Dial Transplant. 1989;4(7): 646–52.
18. Purello DF, Savica V, Gangemi S, et al. Ethylene oxide allergy in dialysis patients. Nephrol Dial Transplant. 1997;12(7):1461–3.
19. Bircher AJ, Harr T, Hohenstein L, Tsakiris DA. Hypersensitivity reactions to anticoagulant drugs: diagnosis and management options. Allergy. 2006;61(12):1432–40.
20. Berkun Y, Haviv YS, Schwartz LB, Shalit M. Heparin-induced recurrent anaphylaxis. Clin Exp Allergy. 2004;34(12):1916–8.
21. Franchini M. Heparin-induced thrombocytopenia: an update. Thromb J. 2005;3:14.
22. 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.
23. 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.
24. Molinaro G, Duan QL, Chagnon M, et al. Kinin-dependent hypersensitivity reactions in hemodialysis: metabolic and genetic factors. Kidney Int. 2006;70(10):1823–31.
25. Coppo R, Amore A, Cirina P, et al. Bradykinin and nitric oxide generation by dialysis membranes can be blunted by alkaline rinsing solutions. Kidney Int. 2000;58(2):881–8.
26. Hakim RM, Lowrie EG. Hemodialysis-associated neutropenia and hypoxemia: the effect of dialyzer membrane materials. Nephron. 1982;32(1):32–9.
27. Hakim RM, Schafer AI. Hemodialysis-associated platelet activation and thrombocytopenia. Am J Med. 1985;78(4):575–80.
28. Twardowski ZJ. Dialyzer reuse – part II: advantages and disadvantages. Semin Dial. 2006;19(3): 217–26.
29. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. N Engl J Med. 2008;359(25):2674–84.
30. Yang RC, Lindsay RM. Dialyzer reactions in a patient switching from peritoneal dialysis to hemodialysis. Hemodial Int. 2005;9(2):120–6.

31. Ward MK, Shadforth M, Hill AV, Kerr DN. Air embolism during haemodialysis. Br Med J. 1971;3(5766):74–8.
32. Morello FP, Donaldson JS, Saker MC, Norman JT. Air embolism during tunneled central catheter placement performed without general anesthesia in children: a potentially serious complication. J Vasc Interv Radiol. 1999;10(6):781–4.
33. Yu AS, Levy E. Paradoxical cerebral air embolism from a hemodialysis catheter. Am J Kidney Dis. 1997;29(3):453–5.
34. Foster PP, Boriek AM, Butler BD, Gernhardt ML, Bove AA. Patent foramen ovale and paradoxical systemic embolism: a bibliographic review. Aviat Space Environ Med. 2003;74(6 Pt 2):B1–64.
35. Dunbar EM, Fox R, Watson B, Akrill P. Successful late treatment of venous air embolism with hyperbaric oxygen. Postgrad Med J. 1990;66(776):469–70.
36. Leslie-Mazwi TM, Avery LL, Sims JR. Intra-arterial air thrombogenesis after cerebral air embolism complicating lower extremity sclerotherapy. Neurocrit Care. 2009;11(2):247–50.
37. Cochran RP, Kunzelman KS, Vocelka CR, et al. Perfluorocarbon emulsion in the cardiopulmonary bypass prime reduces neurologic injury. Ann Thorac Surg. 1997;63(5):1326–32.
38. Spiess BD. Perfluorocarbon emulsions as a promising technology: a review of tissue and vascular gas dynamics. J Appl Physiol. 2009;106(4):1444–52.
39. Barak M, Nakhoul F, Katz Y. Pathophysiology and clinical implications of microbubbles during hemodialysis. Semin Dial. 2008;21(3):232–8.
40. 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.
41. Stegmayr C, Jonsson P, Forsberg U, Stegmayr B. Hemodialysis dialyzers contribute to contamination of air microemboli that bypass the alarm system in the air trap. Int J Artif Organs. 2008;31(4):317–22.
42. Droste DW, Beyna T, Frye B, Schulte V, Ringelstein EB, Schaefer RM. Reduction of circulating microemboli in the subclavian vein of patients undergoing haemodialysis using pre-filled instead of dry dialysers. Nephrol Dial Transplant. 2003;18(11):2377–81.
43. Stegmayr CJ, Jonsson P, Forsberg U, Stegmayr BG. Development of air micro bubbles in the venous outlet line: an in vitro analysis of various air traps used for hemodialysis. Artif Organs. 2007;31(6):483–8.
44. Abassi Z, Nakhoul F, Khankin E, Reisner SA, Yigla M. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Curr Opin Nephrol Hypertens. 2006;15(4):353–60.
45. Yigla M, Abassi Z, Reisner SA, Nakhoul F. Pulmonary hypertension in hemodialysis patients: an unrecognized threat. Semin Dial. 2006;19(5):353–7.
46. 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.
47. Palanchon P, Birmele B, Tranquart F. Acoustical bubble trapper applied to hemodialysis. Ultrasound Med Biol. 2008;34(4):681–4.
48. Berkes SL, Kahn SI, Chazan JA, Garella S. Prolonged hemolysis from overheated dialysate. Ann Intern Med. 1975;83(3):363–4.
49. Fortner RW, Nowakowski A, Carter CB, King Jr LH, Knepshield JH. Death due to overheated dialysate during dialysis. Ann Intern Med. 1970;73(3):443–4.
50. Jepson R, Alonso E. Overheated dialysate: a case study and review. Nephrol Nurs J. 2009;36(5): 551–3.
51. 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.
52. Abtahi M, Uzan M, Souid M. Hemolysis-induced acute pancreatitis secondary to kinked hemodialysis blood lines. Hemodial Int. 2007;11(1):38–41.
53. Harman E, Dutka P. Hemolysis: a hidden danger. Nephrol Nurs J. 2007;34(2):219–20. 223.
54. Tantalo F, Holtzer C. Investigation of possible causes of massive hemolysis occurring at Toronto western hospital. 1985. CANNT J. 2008;18(3):32–4.
55. 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.
56. Hothi DK, Harvey E, Goia CM, Geary D. Blood-volume monitoring in paediatric haemodialysis. Pediatr Nephrol. 2008;23(5):813–20.
57. Andrulli S, Colzani S, Mascia F, et al. The role of blood volume reduction in the genesis of intradialytic hypotension. Am J Kidney Dis. 2002;40(6): 1244–54.
58. Chesterton LJ, Selby NM, Burton JO, Fialova J, Chan C, McIntyre CW. Categorization of the hemodynamic response to hemodialysis: the importance of baroreflex sensitivity. Hemodial Int. 2009;14(1):18–28.
59. Ligtenberg G, Barnas MG, Koomans HA. Intradialytic hypotension: new insights into the mechanism of vasovagal syncope. Nephrol Dial Transplant. 1998;13(11):2745–7.
60. Mangoni AA, Hewitson CL, Woodman RJ, Whiting MJ, Teer-Carr B, Barbara JA, Barbara JA. Symmetric dimethylarginine is an independent predictor of intradialytic hypotension. Am J Hypertens. 2008;21(8):955–9.
61. Thompson AM, Oliver JA. Endogenous and exogenous vasopressin during hemodialysis. Semin Dial. 2009;22(5):472–5.
62. Kim KE, Neff M, Cohen B, et al. Blood volume changes and hypotension during hemodialysis. Trans Am Soc Artif Intern Organs. 1970;16:508–14.
63. Beige J, Sone J, Sharma AM, et al. Computational analysis of blood volume curves and risk of intradialytic morbid events in hemodialysis. Kidney Int. 2000;58(4):1805–9.

64. Mitra S, Chamney P, Greenwood R, Farrington K. Linear decay of relative blood volume during ultrafiltration predicts hemodynamic instability. Am J Kidney Dis. 2002;40(3):556–65.
65. Port S, Garfinkel A, Boyle N. There is a non-linear relationship between mortality and blood pressure. Eur Heart J. 2000;21(20):1635–8.
66. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int. 1996;49(5):1379–85.
67. Zager PG, Nikolic J, Brown RH, et al. "U" curve association of blood pressure and mortality in hemodialysis patients. Medical directors of dialysis clinic, Inc. Kidney Int. 1998;54(2):561–9.
68. Conlon PJ, Krucoff MW, Minda S, Schumm D, Schwab SJ. Incidence and long-term significance of transient ST segment deviation in hemodialysis patients. Clin Nephrol. 1998;49(4):236–9.
69. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. J Am Soc Nephrol. 2000;11(5):912–6.
70. Tarakcioglu M, Erbagci A, Cekmen M, et al. Acute effect of haemodialysis on serum markers of myocardial damage. Int J Clin Pract. 2002;56(5): 328–32.
71. Wayand D, Baum H, Schatzle G, Scharf J, Neumeier D. Cardiac troponin T and I in end-stage renal failure. Clin Chem. 2000;46(9):1345–50.
72. Lipshultz SE, Somers MJ, Lipsitz SR, Colan SD, Jabs K, Rifai N. Serum cardiac troponin and subclinical cardiac status in pediatric chronic renal failure. Pediatrics. 2003;112(1 Pt 1):79–86.
73. McIntyre CW, Burton JO, Selby NM, 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.
74. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4(5):914–20.
75. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation. 1982;66(6):1146–9.
76. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. N Engl J Med. 1998;339(3):173–81.
77. Burton JO, Korsheed S, Grundy BJ, McIntyre CW. Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmias. Ren Fail. 2008;30(7):701–9.
78. 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.
79. Bethesda. US RDS. Annual data report: Atlas of chronic kidney disease and end-stage renal disease in the US 2007.
80. 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.
81. 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.
82. Hothi DK, Harvey E, Goia CM, Geary DF. Evaluating methods for improving ultrafiltration in pediatric hemodialysis. Pediatr Nephrol. 2008;23(4):631–8.
83. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int. 2006;69(7):1222–8.
84. Jain SR, Smith L, Brewer ED, Goldstein SL. Noninvasive intravascular monitoring in the pediatric hemodialysis population. Pediatr Nephrol. 2001; 16(1):15–8.
85. Prakash S, Garg AX, Heidenheim AP, House AA. Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. Nephrol Dial Transplant. 2004;19(10):2553–8.
86. Chen J, Gul A, Sarnak MJ. Management of intradialytic hypertension: the ongoing challenge. Semin Dial. 2006;19(2):141–5.
87. Cirit M, Akcicek F, Terzioglu E, et al. 'Paradoxical' Rise in blood pressure during ultrafiltration in dialysis patients. Nephrol Dial Transplant. 1995;10(8): 1417–20.
88. Blankestijn PJ, Ligtenberg G, Klein IH, Koomans HA. Sympathetic overactivity in renal failure controlled by ACE inhibition: clinical significance. Nephrol Dial Transplant. 2000;15(6):755–8.
89. Klein IH, Ligtenberg G, Oey PL, Koomans HA, Blankestijn PJ. Enalapril and losartan reduce sympathetic hyperactivity in patients with chronic renal failure. J Am Soc Nephrol. 2003;14(2):425–30.
90. Cronin EM, Leavey SF, Walker JF. Severe paradoxical hypertension with angiotensin-converting enzyme inhibitors: an unusual feature of renal artery stenosis. Hypertension. 2009;54(3):e17–8.
91. Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease. Nephrol Dial Transplant. 2004;19(6): 1354–7.
92. Hansen J, Victor RG. Direct measurement of sympathetic activity: new insights into disordered blood pressure regulation in chronic renal failure. Curr Opin Nephrol Hypertens. 1994;3(6):636–43.
93. Koomans HA, Blankestijn PJ, Joles JA. Sympathetic hyperactivity in chronic renal failure: a wake-up call. J Am Soc Nephrol. 2004;15(3):524–37.
94. Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. Kidney Int. 2004;65(5):1568–76.
95. El-Shafey EM, El-Nagar GF, Selim MF, El-Sorogy HA, Sabry AA. Is there a role for endothelin-1 in the hemodynamic changes during hemodialysis? Clin Exp Nephrol. 2008;12(5):370–5.

96. Raj DS, Vincent B, Simpson K, et al. Hemodynamic changes during hemodialysis: role of nitric oxide and endothelin. Kidney Int. 2002;61(2):697–704.
97. Surdacki A, Sulowicz W, Wieczorek-Surdacka E, Herman ZS. Effect of a hemodialysis session on plasma levels of endothelin-1 in hypertensive and normotensive subjects with end-stage renal failure. Nephron. 1999;81(1):31–6.
98. Chou KJ, Lee PT, Chen CL, et al. Physiological changes during hemodialysis in patients with intradialysis hypertension. Kidney Int. 2006;69(10):1833–8.
99. Pearl RJ, Papageorgiou PC, Goldman M, et al. Possible role of new pressor protein in hypertensive anephric hemodialysis patients. Pediatr Nephrol. 2003;18(10):1025–31.
100. Sang GL, Kovithavongs C, Ulan R, Kjellstrand CM. Sodium ramping in hemodialysis: a study of beneficial and adverse effects. Am J Kidney Dis. 1997; 29(5):669–77.
101. Dolson GM, Ellis KJ, Bernardo MV, Prakash R, Adrogue HJ. Acute decreases in serum potassium augment blood pressure. Am J Kidney Dis. 1995;26(2):321–6.
102. Michael M, Brewer ED, Goldstein SL. Blood volume monitoring to achieve target weight in pediatric hemodialysis patients. Pediatr Nephrol. 2004;19(4): 432–7.
103. Geary DF, Piva E, Tyrrell J, et al. Home nocturnal hemodialysis in children. J Pediatr. 2005;147(3): 383–7.
104. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14(3):297–303.
105. 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.
106. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62(2):648–53.
107. Mitsnefes MM. Cardiovascular complications of pediatric chronic kidney disease. Pediatr Nephrol. 2008;23(1):27–39.
108. 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.
109. 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.
110. Mitsnefes MM, Kimball TR, Kartal J, et al. Progression of left ventricular hypertrophy in children with early chronic kidney disease: two-year follow-up study. J Pediatr. 2006;149(5):671–5.
111. Colan SD, Sanders SP, Ingelfinger JR, Harmon W. Left ventricular mechanics and contractile state in children and young adults with end-stage renal disease: effect of dialysis and renal transplantation. J Am Coll Cardiol. 1987;10(5):1085–94.
112. 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.
113. Boulanger CM, Amabile N, Guerin AP, et al. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease. Hypertension. 2007;49(4):902–8.
114. Choi JH, Kim KL, Huh W, et al. Decreased number and impaired angiogenic function of endothelial progenitor cells in patients with chronic renal failure. Arterioscler Thromb Vasc Biol. 2004;24(7):1246–52.
115. Herbrig K, Pistrosch F, Oelschlaegel U, et al. Increased total number but impaired migratory activity and adhesion of endothelial progenitor cells in patients on long-term hemodialysis. Am J Kidney Dis. 2004;44(5):840–9.
116. Westerweel PE, Hoefer IE, Blankestijn PJ, et al. End-stage renal disease causes an imbalance between endothelial and smooth muscle progenitor cells. Am J Physiol Renal Physiol. 2007;292(4):F1132–40.
117. Kari JA, Donald AE, Vallance DT, et al. Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int. 1997;52(2): 468–72.
118. Lilien MR, Koomans HA, Schroder CH. Hemodialysis acutely impairs endothelial function in children. Pediatr Nephrol. 2005;20(2):200–4.
119. Chan CT, Li SH, Verma S. Nocturnal hemodialysis is associated with restoration of impaired endothelial progenitor cell biology in end-stage renal disease. Am J Physiol Renal Physiol. 2005;289(4):F679–84.
120. Ramirez R, Carracedo J, Merino A, et al. Microinflammation induces endothelial damage in hemodialysis patients: the role of convective transport. Kidney Int. 2007;72(1):108–13.
121. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol. 2001;12(10):2131–8.
122. 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(1):100–5.
123. Shroff RC, Donald AE, Hiorns MP, et al. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol. 2007;18(11):2996–3003.
124. Shroff R, Egerton M, Bridel M, 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.
125. 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(5):1494–500.
126. Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J. In-center daily on-line hemodiafiltration: a 4 year experience in children. Clin Nephrol. 2008;69(4): 279–84.

127. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial. 2008;21(4):300–7.
128. Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. Kidney Int. 2006; 69(12):2268–73.
129. Karnik JA, Young BS, Lew NL, et al. Cardiac arrest and sudden death in dialysis units. Kidney Int. 2001;60(1):350–7.
130. Kovesdy CP, Regidor DL, Mehrotra R, et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(5):999–1007.
131. Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the dialysis outcomes and practice patterns study (DOPPS). Nephrol Dial Transplant. 2008;23(3):998–1004.
132. Beecroft JM, Pierratos A, Hanly PJ. Clinical presentation of obstructive sleep apnea in patients with end-stage renal disease. J Clin Sleep Med. 2009;5(2): 115–21.
133. Unruh ML. Sleep apnea and dialysis therapies: things that go bump in the night? Hemodial Int. 2007;11(4):369–78.
134. Unruh ML, Sanders MH, Redline S, et al. Sleep apnea in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the sleep heart health study. J Am Soc Nephrol. 2006;17(12):3503–9.
135. Tada T, Kusano KF, Ogawa A, et al. The predictors of central and obstructive sleep apnoea in haemodialysis patients. Nephrol Dial Transplant. 2007;22(4): 1190–7.
136. Beecroft JM, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Decreased chemosensitivity and improvement of sleep apnea by nocturnal hemodialysis. Sleep Med. 2009;10(1):47–54.
137. Gul A, Aoun N, Trayner Jr EM. Why do patients sleep on dialysis? Semin Dial. 2006;19(2):152–7.
138. Beecroft J, Duffin J, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Enhanced chemo-responsiveness in patients with sleep apnoea and end-stage renal disease. Eur Respir J. 2006;28(1):151–8.
139. De Santo RM, Esposito MG, Cesare CM, et al. High prevalence of sleep disorders in hemodialyzed patients requiring parathyroidectomy. J Ren Nutr. 2008;18(1):52–5.
140. Pressman MR, Benz RL, Schleifer CR, Peterson DD. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. Kidney Int. 1993;43(5): 1134–9.
141. Kumagai T, Ishibashi Y, Kawarazaki H, et al. Effects of nocturnal oxygen therapy on sleep apnea syndrome in peritoneal dialysis patients. Clin Nephrol. 2008;70(4):332–9.
142. Argekar P, Griffin V, Litaker D, Rahman M. Sleep apnea in hemodialysis patients: risk factors and effect on survival. Hemodial Int. 2007;11(4): 435–41.
143. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med. 2001;344(2):102–7.
144. Beecroft JM, Hoffstein V, Pierratos A, Chan CT, McFarlane P, Hanly PJ. Nocturnal haemodialysis increases pharyngeal size in patients with sleep apnoea and end-stage renal disease. Nephrol Dial Transplant. 2008;23(2):673–9.
145. Chan CT, Hanly P, Gabor J, Picton P, Pierratos A, Floras JS. Impact of nocturnal hemodialysis on the variability of heart rate and duration of hypoxemia during sleep. Kidney Int. 2004;65(2):661–5.
146. Auckley DH, Schmidt-Nowara W, Brown LK. Reversal of sleep apnea hypopnea syndrome in end-stage renal disease after kidney transplantation. Am J Kidney Dis. 1999;34(4):739–44.
147. Langevin B, Fouque D, Leger P, Robert D. Sleep apnea syndrome and end-stage renal disease. Cure after renal transplantation. Chest. 1993;103(5): 1330–5.
148. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the national institutes of health. Sleep Med. 2003;4(2):101–19.
149. Snyder AM, Wang X, Patton SM, et al. Mitochondrial ferritin in the substantia nigra in restless legs syndrome. J Neuropathol Exp Neurol. 2009;68(11): 1193–9.
150. Rijsman RM, de Weerd AW, Stam CJ, Kerkhof GA, Rosman JB. Periodic limb movement disorder and restless legs syndrome in dialysis patients. Nephrology (Carlton). 2004;9(6):353–61.
151. Benz RL, Pressman MR, Hovick ET, Peterson DD. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (the SLEEPO study). Am J Kidney Dis. 1999;34(6):1089–95.
152. Sinha R, Davis ID, Matsuda-Abedini M. Sleep disturbances in children and adolescents with non-dialysis-dependent chronic kidney disease. Arch Pediatr Adolesc Med. 2009;163(9):850–5.
153. Davis ID, Baron J, O'riordan MA, Rosen CL. Sleep disturbances in pediatric dialysis patients. Pediatr Nephrol. 2005;20(1):69–75.
154. 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.
155. Dember LM, Jaber BL. Dialysis-related amyloidosis: late finding or hidden epidemic? Semin Dial. 2006;19(2):105–9.
156. Jadoul M, Garbar C, Noel H, et al. Histological prevalence of beta 2-microglobulin amyloidosis in hemodialysis: a prospective post-mortem study. Kidney Int. 1997;51(6):1928–32.
157. Jadoul M, Garbar C, Vanholder R, et al. Prevalence of histological beta2-microglobulin amyloidosis in

CAPD patients compared with hemodialysis patients. Kidney Int. 1998;54(3):956–9.
158. Lameire N, Vanholder R, De SR. Uremic toxins and peritoneal dialysis. Kidney Int Suppl. 2001;78: S292–7.
159. Saito A, Gejyo F. Current clinical aspects of dialysis-related amyloidosis in chronic dialysis patients. Ther Apher Dial. 2006;10(4):316–20.
160. Drueke TB, Massy ZA. Beta2-Microglobulin. Semin Dial. 2009;22(4):378–80.
161. Naganuma T, Sugimura K, Uchida J, et al. Increased levels of serum matrix metalloproteinase-3 in haemodialysis patients with dialysis-related amyloidosis. Nephrology (Carlton). 2008;13(2):104–8.
162. Takayama K, Satoh T, Maruyama R, Yokozeki H. Dialysis-related amyloidosis on the buttocks. Acta Derm Venereol. 2008;88(1):72–3.
163. 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.
164. Rabindranath KS, Strippoli GF, Daly C, Roderick PJ, Wallace S, MacLeod AM. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. Cochrane Database Syst Rev. 2006;18(4):CD006258.
165. Raj DS, Ouwendyk M, Francoeur R, Pierratos A. Beta(2)-microglobulin kinetics in nocturnal haemodialysis. Nephrol Dial Transplant. 2000;15(1):58–64.
166. Schiffl H, D'Agostini B, Held E. Removal of beta 2-microglobulin by hemodialysis and hemofiltration: a 4 year follow up. Biomater Artif Cells Immobilization Biotechnol. 1992;20(5):1223–32.
167. Gejyo F, Kawaguchi Y, Hara S, et al. Arresting dialysis-related amyloidosis: a prospective multicenter controlled trial of direct hemoperfusion with a beta2-microglobulin adsorption column. Artif Organs. 2004;28(4):371–80.
168. Stamopoulos D, Bouziotis P, Benaki D, et al. Nanobiotechnology for the prevention of dialysis-related amyloidosis. Ther Apher Dial. 2009;13(1): 34–41.
169. Fischbach M, Terzic J, Laugel V, et al. Daily on-line haemodiafiltration: a pilot trial in children. Nephrol Dial Transplant. 2004;19(9):2360–7.
170. 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.
171. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis. 2001;38(1): 85–90.
172. Vilar E, Wellsted D, Chandna SM, Greenwood RN, Farrington K. Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose. Nephrol Dial Transplant. 2009;24(8): 2502–10.
173. Morduchowicz G, Winkler J, Zabludowski JR, Boner G. Effects of residual renal function in haemodialysis patients. Int Urol Nephrol. 1994;26(1):125–31.
174. Pecoits-Filho R, Heimburger O, Barany P, et al. Associations between circulating inflammatory markers and residual renal function in CRF patients. Am J Kidney Dis. 2003;41(6):1212–8.
175. 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.
176. Moist LM, Port FK, Orzol SM, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol. 2000;11(3):556–64.
177. Bragg-Gresham JL, Fissell RB, Mason NA, 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.
178. 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.
179. 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(11):1262–6.
180. Gledhill J, Rangel L, Garralda E. Surviving chronic physical illness: Psychosocial outcome in adult life. Arch Dis Child. 2000;83(2):104–10.
181. Dodson JL, Ener-West M, Gerson AC, Kaskel FJ, Furth SL. An assessment of health related quality of life using the child health and illness profile-adolescent edition in adolescents with chronic kidney disease due to underlying urological disorders. J Urol. 2007;178(2):660–5.
182. Gerson AC, Riley A, Fivush BA, et al. Assessing health status and health care utilization in adolescents with chronic kidney disease. J Am Soc Nephrol. 2005;16(5):1427–32.
183. Riano-Galan I, Malaga S, Rajmil L, et al. Quality of life of adolescents with end-stage renal disease and kidney transplant. Pediatr Nephrol. 2009;24(8): 1561–8.
184. Reynolds JM, Garralda ME, Postlethwaite RJ, Goh D. Changes in psychosocial adjustment after renal transplantation. Arch Dis Child. 1991;66(4): 508–13.
185. Goldstein SL, Rosburg NM, Warady BA, 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.
186. 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(7): 1899–905.
187. 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.

188. 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.
189. Ehrich JH, Rizzoni G, Broyer M, et al. Rehabilitation of young adults during renal replacement therapy in Europe. 2. Schooling, employment, and social situation. Nephrol Dial Transplant. 1992;7(7):579–86.
190. Rizzoni G, Ehrich JH, Broyer M, et al. Rehabilitation of young adults during renal replacement therapy in Europe. 1. The presence of disabilities. Nephrol Dial Transplant. 1992;7(7):573–8.
191. 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.
192. 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(7):1020–6.
193. Bethesda. US Renal Data System: USRDS (2003) Annual Report. The National Institute of Diabetes and Digestive and Kidney Diseases; 2003.
194. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25):2010–9.
195. Cheung AK, Levin NW, Greene T, et al. Effects of high-flux hemodialysis on clinical outcomes: Results of the HEMO study. J Am Soc Nephrol. 2003;14(12):3251–63.
196. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA. Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol. 2002;13(4):1061–6.
197. Marshall MR, Byrne BG, Kerr PG, McDonald SP. Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int. 2006;69(7):1229–36.
198. Ting GO, Kjellstrand C, Freitas T, Carrie BJ, Zarghamee S. Long-term study of high-comorbidity ESRD patients converted from conventional to short daily hemodialysis. Am J Kidney Dis. 2003;42(5):1020–35.
199. 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.
200. Santoro A, Mancini E, Bolzani R, et al. The effect of on-line high-flux hemofiltration versus low-flux hemodialysis on mortality in chronic kidney failure: a small randomized controlled trial. Am J Kidney Dis. 2008;52(3):507–18.
201. Johansen KL, Zhang R, Huang Y, et al. Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. Kidney Int. 2009;76(9):984–90.
202. Pauly RP, Asad RA, Hanley JA, et al. Long-term clinical outcomes of nocturnal hemodialysis patients compared with conventional hemodialysis patients post-renal transplantation. Clin Transplant. 2008;23(1):47–55.

Part V

Management of Secondary Complications of Chronic Dialysis

Meeting Nutritional Goals for Children Receiving Maintenance Dialysis

22

KDOQI Clinical Practice Guideline for Nutrition in Children with CKD Work Group

Keywords
Nutritional goals • Children • Weight • Energy • Protein

Introduction

Nutrient imbalances, particularly protein-energy malnutrition, are common in children on maintenance dialysis (MD). Infants and young children are particularly vulnerable to malnutrition because of their low nutritional stores and high nutritional demands for rapid physical and brain growth. Adolescents are also at particular risk because of the high demands of growth during puberty.

Nutrition status is an important determinant of outcome in patients with end-stage renal disease. Markers of nutritional status, particularly serum albumin, correlate with morbidity and mortality in adults. In children, the adverse effects of malnutrition also include growth failure and neurodevelopmental delay. Growth delay and extremes in body mass index (BMI) are associated with an increased risk for morbidity and mortality in children on MD. Children who are chronically malnourished exhibit behavioral changes, including irritability, apathy, decreased social responsiveness, and attention deficits. Stunted children often experience social disadvantages that negatively affect development and quality of life. While several factors contribute to impaired linear growth and development, early and aggressive correction of nutritional imbalances leads to improvements.

Nutritional therapy is therefore a vital element of the care required by children receiving MD. The primary goal is to achieve optimal growth and development through preservation of a good nutritional status and prevention of malnutrition, uremic toxicity, and metabolic abnormalities. A registered dietitian with renal experience should be a central and integral part of the dietary management. Collaborative efforts of the dietitian, nurse, social worker, nephrologist, therapists, parents, and caretakers are essential to meet the nutritional needs of infants and children on MD.

In 2009, the KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update was published, based upon an exhaustive review of the literature and the input of experts in the field. The guideline was developed to assist practitioners in the assessment of nutritional status and the provision of optimal nutrition to children with CKD, including patients on dialysis therapy or those who have a kidney transplant. In view of the fact that this document

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includes the most up to date information on the topic of nutritional management of children on dialysis, we have chosen to duplicate much of the guideline here, letting it serve as this chapter. We appreciate the approval of the National Kidney Foundation for allowing us to do so. As in the guideline, it should be emphasized here that the recommendation statements (all of which are graded based on the strength of the recommendation) and the accompanying rationales are intended to serve as starting points for clinical decision making, and that the clinical judgment of the health-care provider must always be included in the decision-making process and in the application of these recommendations. Whereas the recommendation statements and accompanying tables have been renumbered in this chapter for ease of reading, all reference numbers remain as originally published to facilitate identification of the reference in the complete guideline located in the *American Journal of Kidney Diseases* (53: S1–S124, 2009 (suppl 2)), or online at www.kidney.org/professionals/kdoqi/guidelines_updates/pdf/CPGPedNutr2008.pdf.

Pathogenesis of Malnutrition

Malnutrition in patients on MD is caused by a variety of factors which results in a combination of decreased nutrient intake, increased nutrient losses, and altered nutrient metabolism. Inadequate intake results primarily from anorexia, although other factors may play a role, including gastrointestinal disorders such as nausea, vomiting, and constipation, multiple diet restrictions imposed upon personal or cultural food preferences, financial constraints, behavioral or dysphagia-related feeding problems, and insufficient dialysis. Multiple factors contribute to anorexia, including uremia, dysgeusia, uncorrected anemia, multiple diet restrictions and medications, and feelings of anger, stress, and depression. Comorbid conditions (symptomatic hypertension, other chronic diseases) and sensations of fullness and satiety from dialysate in the peritoneal cavity also contribute to anorexia. Increased losses may result from vomiting, proteinuria, or protein, amino acid, and micronutrient losses across the blood-dialysate barrier. Factors which increase nutrient needs include those associated with increased protein catabolism and negative nitrogen balance (metabolic acidosis, physical activity), recurrent peritonitis, drug–nutrient interactions, catch-up growth, or intercurrent illness or comorbidities (fever, liver disease).

Recommendation 1: Evaluation of Growth and Nutritional Status

1.1: The nutritional status and growth of all children with CKD stages 2–5 and 5D should be evaluated on a periodic basis. (A)

1.2: The following parameters of nutritional status and growth should be considered in combination for evaluation in children with CKD stages 2–5 and 5D. (B)

1. Dietary intake (3-day diet record or three 24-h dietary recalls)
2. Length- or height-for-age percentile or standard deviation score(SDS)
3. Length or height velocity-for-age percentile or SDS
4. Estimated dry weight and weight-for-age percentile or SDS
5. BMI-for-height-age percentile or SDS
6. Head circumference-for-age percentile or SDS (≤3 years old only)
7. Normalized protein catabolic rate (nPCR) in hemodialyzed adolescents with CKD stage 5D

Because of the high prevalence of growth retardation in children with CKD, nutrition has always been a primary focus of pediatric CKD care. Early studies emphasized the importance of adequate energy intake in maintaining normal growth in pediatric CKD. However, no study demonstrated a growth advantage to a caloric intake greater than about 75% of the RDA [2–4], which corresponds approximately to 100% of the EER in children older than 3 months. In children with CKD, the prevalence of undernutrition has been demonstrated to vary widely – from 2% to 65% – depending on the definition used [5]. In the general population, the World Health Organization (WHO) has defined undernutrition as weight-for-age,

height-for-age, and weight-for-height 2 SDs or greater less than the Centers for Disease Control and Prevention (CDC) reference median [6], in recognition of the fact that long-term undernutrition may lead to wasting (low weight-for-height) and/or stunting (low height-for-age). However, this definition may be inappropriate in children with CKD. Whereas stunting can be reasonably attributed solely to long-term undernutrition in otherwise healthy children, the multifactorial cause of stunting in children with CKD makes it a poor choice as a definition of undernutrition in this group. In the CKD population, anthropometric definitions of undernutrition are complicated; consideration must be given to the appropriateness of measures for both age and height of the child.

Body composition has yet to be well characterized in pediatric CKD. Few high-quality studies are available in which measures of body composition were adequately adjusted for height and appropriately compared with a healthy reference population [7–12]. Of these, lean mass deficits were observed in some studies [11], but not others [7]. Fat mass appears to be increased relative to the height in children with CKD [11]. Preliminary evidence in small numbers of children suggests that the use of growth hormone may result in lower fat mass and higher lean mass for height [11].

Interpretation of many prior studies of nutrition and growth in pediatric CKD is difficult because most studies considered infants and older children together as a uniform group. There are reasons to believe that infants younger than 2–3 years behave very differently from older children. First, a much larger proportion of the daily energy requirement is devoted to growth in infants compared with older children. Second, growth is driven primarily by nutrition during infancy, whereas growth hormone and sex hormones have a dominant influence during childhood and adolescence, respectively [13–16]. Inadequate spontaneous calorie intake has been clearly demonstrated in infants with CKD [17–19]; energy intakes for older children usually are normal relative to body size [9]. In studies separating children by age, weight-for-height indices, and BMI-for-age, z scores were low in younger children, but normal in older children [10, 12]. Lean mass deficits were also more likely in younger than older children [7, 8, 10]. Routine calorie and/or protein supplementation have been shown to improve growth in infants with CKD [17–19]. However, there is no clear evidence that routine nutritional supplements have a similar effect in older children. Because of these differences between infants and older children, the present recommendations emphasize the importance of considering the age of the child when planning nutritional monitoring and interventions.

Historically, the main focus of malnutrition in children with CKD has been undernutrition; there is emerging evidence that obesity is beginning to be a problem in the CKD population [20–22].

Dietary Intake

It is suggested that dietary intake be assessed regularly by a skilled registered dietitian by means of a 3-day diet diary. Three 24-h recalls may be preferable in adolescents. Dietary intake data provide useful information about the quantity and quality of nutrients ingested. The two most practical and clinically feasible ways to determine usual daily intake are the prospective 3-day dietary diary and the retrospective 24-h dietary recall. From either of these, daily intake of calories, macronutrients (carbohydrate, protein, and fat), vitamins, and minerals can be estimated. Each of the methods has its own limitations. Dietary diaries have been shown to give unbiased estimates of energy intake in normal-weight children younger than 10 years; however, underreporting is common in adolescents [23, 24]. Twenty-four-hour recalls may be better suited to adolescents. The most important limitation of the 24-h recall method is its poor ability to capture the day-to-day variability in dietary intake. Children may be even more susceptible to this limitation than adults because they tend to have more day-to-day variability [25]. It may be useful to obtain three 24-h recalls to more completely evaluate the food-intake pattern. One weekend day should be included in a 3-day diet diary and as one of three 24-hour recalls. Despite their limitations, dietary recall interviews conducted by a skilled pediatric registered dietitian

or dietary diaries completed by the patient and/or parent as instructed by a registered dietitian provide useful general information about the pattern of food intake. Information about dietary intake allows the treating team to evaluate the adequacy of a patient's intake before significant adverse changes in body composition result.

Poor intake is expected in infants with CKD and should prompt immediate initiation of nutritional supplements if there is any evidence of inadequate weight gain or growth. When spontaneous intake is low in a poorly growing older child, consideration also must be given to the possibility that the poor intake is a result of the poor growth, rather than the cause. Spontaneous calorie intake increased by almost 12% in a study of 33 children with CKD during treatment with rhGH [26].

Length- or Height-for-Age Percentile or SDS

Length (infants <2 years) or height (children >2 years) should be measured regularly, plotted on the length- or height-for-age curves, and the percentile and/or SDS should be calculated. Growth retardation is common in CKD [2, 3, 12, 27, 28]. The impact of CKD on growth depends on both the degree of kidney impairment and age of the child. Normal growth can be divided into three phases: infancy (dominated by nutrition), childhood (dominated by growth hormone), and puberty (dominated by sex hormones) [13]. The infancy phase normally is replaced by the childhood pattern between 6 and 12 months of age. In CKD, onset of the childhood phase frequently is delayed until 2–3 years of age or interrupted by a transient resumption of the infancy pattern [13]. CKD also results in a delay in the onset of pubertal growth, as well as a shorter pubertal growth spurt [29]. Together, these alterations to the normal pattern of growth may lead to severe short stature. The typical CKD growth pattern is characterized by decreased growth velocity during infancy, followed by normal growth velocity during childhood and impaired growth velocity again during adolescence [16]. However, growth velocity also may be low during the childhood phase in children with CKD stages 4 or 5 [3, 30]. Numerous factors may influence growth in CKD, including acidosis [31], disturbances in the growth hormone axis [32], and poor nutritional intake [2]. Nutritional intake has its greatest influence during the infancy phase of growth [16].

Length (infants) should be measured by using a length board, and height (older children), by using a wall-mounted stadiometer, preferably by the same well-trained person at each assessment. Calculating the SDS or plotting the child's height on the normal growth chart to determine the percentile allows comparison with healthy children. In 2000, the CDC published revised North American growth reference charts for infants and children up to 20 years of age [33]. In 2006, the WHO released new growth standards for children from birth to 5 years of age [34]. These growth standards are distinguished from the CDC reference charts in two important ways. First, the children contributing to the WHO Growth Standards were specifically selected to represent children growing under ideal conditions: They had nonsmoking mothers, were from areas of high socioeconomic status, and received regular pediatric health care, including immunizations. A subset of 882 infants, all breastfed for at least 4 months, provided longitudinal data for 24 months. Second, the study population was of broad ethnic diversity; participants were recruited from Brazil, Ghana, India, Norway, Oman, and the United States. Importantly, ethnicity had very little impact on growth, indicating that the growth standards reflect a reasonable expectation for growth regardless of ethnicity; only 3% of the variability in growth within the population could be attributed to the country of origin [34].

Because the WHO Growth Standards represent ideal growth and ideal growth should be the goal for children with CKD, the WHO Growth Standards should be used as the reference for children from birth to 2 years. Differences between the CDC reference curves and the WHO Growth Standards are minimal after 2 years. For this reason and because the switch is made from length to height measurement at 2 years, 2 years appears to be a reasonable age to make the transition from the WHO Growth Standards to the CDC reference curves.

It may be useful to consider the genetic height potential of the child when assessing adequacy of growth. Although the exact contribution of heredity cannot be calculated, an estimate of a child's adult height potential can be made by calculating midparental height adjusted for the sex of the child. Midparental height is calculated as follows:

- Girls: 13 cm is subtracted from the father's height and averaged with the mother's height
- Boys: 13 cm is added to the mother's height and averaged with the father's height

The midparental height is plotted on the growth chart (of the same gender as the child) at 20 years of age. For both girls and boys, 3.5 in. (8.5 cm) on either side of this calculated value (target height) represents the 3rd to 97th percentiles for anticipated adult height [35]. The 5 in. (13 cm) represents the average difference in height of men and women; thus, the child grows, on average, to the midparental height percentile.

Adequate growth is a good indication of adequate nutrition over the long term. However, acute weight loss may be severe and alterations in body composition may be substantial before linear growth is impaired. Growth usually continues at a normal rate in malnourished children until significant wasting occurs [36]. For this reason, additional measures of nutritional status are advised.

Length or Height Velocity-for-Age Percentile or SDS

The growth velocity (change in height per unit of time) can be determined by recording serial height measurements. In children younger than 2 years, the change in length percentile and/or SDS will give an idea of growth velocity (a negative change indicates poor growth; a positive change may represent catch-up growth). Calculation of growth velocity percentile and/or SDS for children younger than 2 years can be done by using data from the 2006 WHO Growth Standards. Height velocity percentile and/or SDS can be calculated for children older than 2 years by using reference data from the Fels Longitudinal Study [37]. It is important to recognize that height velocity cannot be accurately assessed for intervals shorter than 6 months in those older than 2 years. However, more frequent height measurements allow a running look at growth and give a general impression of its adequacy.

Estimated Dry Weight and Weight-for-Age Percentile or SDS

Euvolemic weight should be determined regularly. The weight should be plotted on the weight-for-age curves, and the percentile and/or SDS should be calculated. Weight is an important part of any nutritional assessment. In CKD, it is important to ensure that weight is measured in a euvolemic state. This generally is referred to as "dry weight" because fluid overload is common in those with CKD stage 5. Children with chronic nephrotic syndrome also may have fluid overload, even at milder stages of CKD. Fluid overload will influence not just weight, but also may affect other anthropometric measures, such as arm circumference and skin fold thicknesses [38, 39]. Volume depletion also may be present in some conditions resulting in pediatric CKD (dysplasia, obstructive nephropathy, and cystinosis). It is equally important that the euvolemic weight be considered in these cases. The estimated dry weight can be challenging to ascertain because weight gain is expected in growing children. Five parameters are helpful in the estimation process: weight, presence of edema, blood pressure, certain laboratory values, and dietary interview. The midweek postdialysis weight and the combination of noninvasive blood volume monitoring and the postdialytic vascular compartment refilling rate are used for evaluation purposes in a HD patient [40]. The weight at a monthly visit (minus dialysis fluid in the peritoneal cavity) is used for the child on PD therapy. The estimated dry weight is challenging to evaluate in patients prone to edema and must be done in conjunction with a physical examination. Excess fluid may be visible in the periorbital, pedal, and other regions of the body. Hypertension that resolves with dialysis can be indicative of excess fluid weight. Other responses to dialytic fluid removal, such as

cramping or hypotension, may also give clues about the fluid status of the patient. Decreased serum sodium and albumin levels may be markers of overhydration. Rapid weight gain in the absence of a significant increase in energy intake or decrease in physical activity must be evaluated critically before it is assumed to be dry weight gain.

After the dry weight has been determined, it should be used to calculate the BMI and determine the weight-for-age percentile and/or SDS (or be plotted on the weight-for-age curves). As noted in the section on height, the 2006 WHO Growth Standards should be used as the reference for children up to 2 years; the 2000 CDC growth charts should be used for children older than 2 years. It is important to recognize that the weight-for-age SDS is not particularly useful in isolation – weight-for-age will be low in growth-retarded children. Rather, it should be interpreted in the context of the height-for-age SDS.

BMI-for-Height-Age Percentile or SDS

It is suggested that BMI be determined each time height and weight are measured. BMI should be plotted on the sex-specific BMI-for-age curves, and the percentile and/or SDS should be calculated. BMI is an accepted and easily calculated method of evaluating weight relative to height. However, BMI, calculated as weight (kg) divided by height (m) squared, is not completely independent of either age or height. This is explained in part by age-related changes in body proportions and in part by mathematics: a one-dimensional measure (height) will predict a three-dimensional measure (increasing weight represents body growth in three dimensions) to the third power, not the second power [41]. The solution has been to express BMI relative to age in developing children [42]. In this relation, age functions as a surrogate for both height and maturation. Because height, age, and maturation are highly correlated in healthy children, this approach works reasonably well. Sex-specific BMI-for-age reference data permit calculation of BMI-for-age z scores or percentiles, allowing meaningful and consistent interpretation of BMI in normal children regardless of age. In children with kidney disease, in whom growth retardation and delayed maturation are common, this approach has limitations. Expressing BMI relative to chronological age in a child with growth and/or maturational delay will result in inappropriate underestimation of his or her BMI compared with peers of similar height and developmental age. To avoid this problem, it may preferable to express BMI relative to height-age in children with CKD – i.e., the age at which the child's height would be on the 50th percentile [38, 523]. This approach ensures that children with CKD are compared with the most appropriate reference group: those of similar height and maturation.

Height-age is believed to provide a reasonable surrogate for maturation in most children (i.e., the age at which a child would be at the 50th percentile for height likely is close to the age at which most healthy children would have a similar level of sexual/physical development). Similarly, in children with short stature, expressing BMI relative to height-age will minimize errors that may occur as a result of the correlation between BMI-for-age and height-for-age. However, caution must be used in applying this approach to children outside the pubertal or peripubertal period, for whom the correlation between height-age and maturation is less clear. BMI relative to chronological age may be more logical in some cases, particularly when sexual maturation is complete.

Although the weight-for-height index is a meaningful measure during early and midchildhood, BMI has the advantage of being applicable throughout the lifespan, from infancy to adulthood, and is becoming the standard method of assessing weight relative to height [43]. While BMI-for-age charts are now available from birth onward, clinical experience in using and interpreting BMI before 24 months of age is limited, as are data on its association with current or future morbidity, and for this reason BMI is suggested rather than weight-for-height index after the age of 2 years.

The CDC defines underweight as a BMI-for-age less than the 5th percentile [44]. A BMI-for-age greater than or equal to the 85th percentile is considered overweight, and greater than the 95th percentile, obese [45]. The WHO definitions of underweight differ somewhat from those used by the CDC. A BMI-for-age SDS of −2.0 (BMI-for-age ~ <3rd percentile) recently has been proposed as a cutoff to define underweight or "thinness" in children. This definition is attractive because it corresponds to the cutoff for grade 2 thinness in adults (BMI, 17 kg/m^2) [43]. However, no high-quality studies are available linking BMI less than a certain cutoff to poor outcomes in the general population. Therefore, no evidence-based definitions of undernutrition or "thinness" exist. Furthermore, the applicability of such definitions to the CKD population is unknown. Two large studies of adult HD patients demonstrated an inverse relationship between BMI and mortality risk, with no clear BMI threshold above which the risk stabilized or began to increase; mortality risk continued to decrease even as BMI increased to greater than 30 kg/m^2 [46, 47]. A smaller study of adult HD patients suggested increased mortality risk with BMI less than 17 and BMI greater than 23 kg/m^2 compared with those with BMI between 17.0 and 18.9 kg/m^2 [48]. In children with stage 5 CKD, a U-shaped association was demonstrated between BMI-for-age SDS and mortality risk. Children with a BMI SDS either greater or less than 0.50 had a greater risk of mortality than those with a BMI SDS of 0.5; each 1.0-SD unit difference in BMI SDS was associated with a 6% greater risk of mortality [49]. It is important to recognize that this study only demonstrated an association between BMI and mortality, but could not establish a causal relationship. Furthermore, the additional mortality risk associated with BMI SDS greater or less than 0.5 was small.

Interpretability of BMI may be limited in the CKD population due to fluid overload. Clearly, any excess fluid will artificially increase BMI. Fluid overload representing 10% of the body weight will result in a BMI SDS approximately 0.5–1.0 SD units greater than what it would be at dry weight. Therefore, efforts should be made to use only a true dry weight when calculating BMI.

High-quality reference values for BMI relative to age are now available throughout childhood. The 2000 CDC revised growth charts include sex-specific BMI-for-age curves for children and adolescents between 2 and 20 years of age [33]. These curves, developed using a North American population, provide a contemporary BMI reference that recognizes the dependence of BMI on age and allow calculation of BMI-for-age SDS and percentiles. The 2006 WHO Growth Standards also include BMI standards for children from birth to 5 years of age [34]. Together, the WHO Growth Standards and the CDC growth charts provide reference values for BMI from birth to adulthood. As for length and height measures, BMI should be compared with the WHO Growth Standards up to 2 years of age and with the CDC growth charts thereafter.

Head Circumference-for-Age Percentile or SDS

Head circumference should be measured regularly in children 3 years and younger. Head circumference should be plotted on the head circumference-for-age curves. Poor head growth is well documented in children with CKD [50, 51], with infants at highest risk. Although no studies have specifically related head circumference to nutritional status in CKD, regular measurements of head circumference in conjunction with intermittent developmental assessments are an important part of routine pediatric CKD care. The 2007 WHO Growth Standards should be used as a reference [52].

Normalized Protein Catabolic Rate

PEM may have profound effects on growth and development and may be associated with increased risk of morbidity and mortality. Protein catabolic rate (PCR) has been studied as an objective measure of DPI in stable patients receiving maintenance HD. PCR can be normalized to a patient's weight (nPCR); nPCR initially was studied in the 1980s as a marker of DPI in pediatric HD patients assumed to be in stable nitrogen balance [53]. Calculation of nPCR is based upon

the increase in blood urea nitrogen (BUN) level from the end of one HD treatment to the beginning of the next treatment to calculate the urea generation rate (G; mg/min). nPCR originally was calculated by using formal urea kinetic modeling in association with Kt/V calculations [54]. Recent pediatric data demonstrate that algebraic formulas yield nearly identical nPCR results compared with formal urea kinetic modeling [55]. The algebraic nPCR calculation is as follows:

$$G\left(\text{mg}/\text{min}\right)=\left[\left(C2\times V2\right)-\left(C1\times V1\ \right)\right]/t$$

where C1 is postdialysis BUN (mg/dL), C2 is predialysis BUN (mg/dL), V1 is postdialysis total-body water (dL; V1 = 5.8 dL/kg × postdialysis weight in kg), V2 is predialysis total-body water (dL; V2 = 5.8 dL/kg × predialysis weight in kg), and t is time (minutes) from the end of the dialysis treatment to the beginning of the following treatment.

Then, nPCR is calculated by using the modified Borah equation [56]:

$$\text{nPCR} = 5.43\times \text{estG}/V1 + 0.17$$

where V1 is total-body water (L) postdialysis (0.58 × weight in kg).

Data from adult studies demonstrate that the pre- and postdialysis BUN levels from the same treatment can be used to calculate nPCR; additional blood sampling from the next treatment is not necessary [57]. Recent pediatric data demonstrated increases in nPCR in malnourished children on HD therapy who received IDPN. In these studies, higher nPCR was associated with subsequent weight gain, whereas lower nPCR predicted future weight loss in adolescents [58, 59].

Comparison of nPCR versus serum albumin level in an entire single-center population, irrespective of nutrition status, showed that nPCR less than 1 g/kg/d of protein predicted a sustained weight loss of at least 2% per month for 3 consecutive months in adolescent and young adult–aged patients [60], whereas serum albumin levels could not. In younger pediatric HD patients, neither nPCR nor serum albumin level was effective in predicting weight loss. This potentially could be explained by: (1) better nutritional status in infants and toddlers who are more likely to be tube fed, (2) a greater contribution of unmeasured urine urea clearance, (3) differences in protein catabolism, and/or (4) different growth rates in younger children compared with older children. It is also possible that because nPCR was derived in adult patients receiving HD, nPCR may be a valid measure only for patients of adult age or size.

Although no data exist to guide recommended optimal nPCR measurement frequency in HD patients, the same data needed for Kt/V calculation allow for nPCR calculation without additional blood sampling. Thus, nPCR can be monitored monthly along with Kt/V to follow up trends for a particular patient and provide an objective measure of protein intake [61]. The KDOQI Adult Nutrition Guidelines recommend monthly assessment of nPCR for maintenance HD patients [62]. It is suggested that the nPCR level be targeted to the age-specific protein intake guidelines noted in Recommendation 3.

In a manner similar to the evaluation of nPCR in patients receiving HD, it is recommended that the DPI of adults receiving PD be estimated several times per year by determination of the protein equivalent of nitrogen appearance (PNA) [63]. This is calculated by measuring the urea nitrogen content of urine and dialysate, which represents the total nitrogen appearance (TNA), and multiplying that value by 6.25 (there are ~6.25 g of protein per 1 g of nitrogen) [64]. Although limited data for this subject are available in pediatrics and the assessment is not regularly carried out in pediatric dialysis centers, Mendley and Majkowski [65] defined the relationship between urea nitrogen and TNA in children undergoing PD as follows:

$$\begin{aligned}\text{TNA}\ (\text{g}/\text{d}) = {} & 1.03\ (\text{urea nitrogen appearance}) + \\ & 0.02\ (\text{weight in kg}) + \\ & 0.56\ (\text{for subjects age 0 to 5 years}) \text{ or} \\ & 0.98\ (\text{for subjects age 6 to 15 years})\end{aligned}$$

Patient age was taken into consideration because of its relationship to dialysate protein loss.

Edefonti et al. [66] later reported that incorporating dialysate protein nitrogen and body surface area (BSA) in the formula could improve the prediction of TNA. Their recommended formula is as follows:

Limitations of PNA are that it is valid only when the patient is not anabolic or catabolic, the value changes rapidly when DPI is altered and thus may not reflect usual protein intake, and it should be normalized for patient size, although the best parameter to use has not been determined. In adults, normalization to ideal weight is recommended.

$$\begin{aligned}\text{TNA (g/d)} = {} & 0.03 + 1.138\ \text{urea} - \text{N}_{\text{urine}} + \\ & 0.99\ \text{urea} - \text{N}_{\text{dialysate}} + 1.18\ \text{BSA} + \\ & 0.965\ \text{protein} - \text{N}_{\text{dialysate}}\end{aligned}$$

Frequency of Assessment

1.3: It is suggested that the frequency of monitoring nutritional and growth parameters in all children with CKD stages 2–5 and 5D be based on the child's age and stage of CKD. (C) In general, it is suggested that assessments be performed at least twice as frequently as they would be performed in a healthy child of the same age. (C) Infants and children with polyuria, evidence of growth delay, decreasing or low BMI, comorbidities influencing growth or nutrient intake, or recent acute changes in medical status or dietary intake may warrant more frequent evaluation. (C)

The frequency with which a nutritional evaluation should be conducted depends on both the age of the child and the severity of CKD (Table 22.1). Current recommendations for measurement of growth parameters in healthy infants and children vary slightly by country. In general, two assessments are recommended in the first month, then monthly until 2 months of age, every 2 months until 6 months of age, every 3 months until 18 months of age, every 6 months until 2 years of age, and then yearly thereafter [108, 109].

Given that nutritional intake and growth may be impaired even with mild CKD in infants – and that these improve with nutritional supplementation [17, 18, 110, 111] – it is suggested that growth parameters be monitored at least twice as frequently in infants with moderate CKD as is recommended for healthy infants. More frequent evaluations are required in infants with severe CKD (stages 4–5 and 5D). Early recognition of growth delay in infancy is crucial because growth failure in this critical period is extremely difficult to catch up later [16, 30]. Any evidence of retarded growth in an infant should prompt detailed dietary assessment and intervention.

In older children, the impact of CKD on growth and body fat and lean stores appears to depend to a large degree on the severity of CKD. A "dose–response" relationship between glomerular filtration rate (GFR) and BMI-for-age z score was noted in one study, with lower GFR associated with lower mean BMI-for-age z score [28]. Again, given the risks of growth retardation in children with CKD, assessment of growth parameters is suggested to be performed at a minimum of every 6 months in children with CKD stages 2–3, i.e., at least twice as often as recommended for healthy children. For children with more advanced CKD (stages 4–5 and 5D), more frequent evaluation may be warranted due to the greater risk of abnormalities. Every effort should be made to conduct nutritional status assessments when the child is euvolemic.

These recommendations represent the minimum intervals for assessment. More frequent evaluation may be warranted in children with evidence of growth delay, decreasing or low BMI, any comorbidities potentially influencing growth or nutrient intake, or recent acute changes in medical status or dietary intake. Three-day food records at intervals more frequent than every 3–6 months are not required for infants or children with good appetites, grossly adequate dietary intakes, and adequate weight gain. More frequent records are indicated when there is concern about the adequacy of a child's intake or overconsumption of one or more nutrients.

Table 22.1 Recommended parameters and frequency of nutritional assessment for children with CKD stages 2–5 and 5D

	Minimum interval (mo)									
	Age 0–<1 years			Age 1–3 years			Age >3 years			
Measure	CKD 2–3	CKD 4–5	CKD 5D	CKD 2–3	CKD 4–5	CKD 5D	CKD 2	CKD 3	CKD 4–5	CKD 5D
Dietary intake	0.5–3	0.5–3	0.5–2	1–3	1–3	1–3	6–12	6	3–4	3–4
Height or length-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Height or length velocity-for-age percentile or SDS	0.5–2	0.5–2	0.5–1	1–6	1–3	1–2	6	6	6	6
Estimated dry weight-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.25–1	1–3	1–2	0.5–1	3–6	3–6	1–3	1–3
BMI-for-height-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1	3–6	3–6	1–3	1–3
Head circumference-for-age percentile or SDS	0.5–1.5	0.5–1.5	0.5–1	1–3	1–2	1–2	N/A	N/A	N/A	N/A
nPCR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1[a]

N/A not applicable

[a]Only applies to adolescents receiving HD

Recommendation 2: Energy Requirements and Therapy

2.1: Energy requirements for children with CKD stages 2–5 and 5D should be considered to be 100% of the EER for chronological age, individually adjusted for PAL and body size (i.e., BMI). Further adjustment to energy intake is suggested based upon the response in rate of weight gain or loss. (B)

In children with CKD (excluding CKD stage 5), spontaneous energy intake decreases with deteriorating kidney function [28], but there is no evidence that children with CKD have different energy requirements than those for healthy children. In a recent study of 25 children and adolescents with CKD stage 5 on HD therapy, resting energy expenditure measured by using indirect calorimetry was the same as for healthy age-matched controls when adjusted for lean body mass [174]. In 65 children aged 2–16 years with conservatively managed CKD (GFR < 75 mL/min/1.73 m^2), regular dietetic advice with particular attention to optimizing energy intake with or without the use of supplements maintained or significantly increased the height SDS with an energy intake maintained within the normal range [156]. In 35 children younger than 5 years with CKD stages 4–5, significant weight gain and accelerated linear growth was clearly demonstrated in those starting enteral feeding at age younger than 2 years; improved weight gain and maintenance of growth was observed in those starting enteral feeds at age 2–5 years without exceeding normal energy requirements [18]. The findings are similar to an earlier study of 22 children age 0.2–10 years on long-term dialysis therapy in which there was significant improvement in both height and weight SDS with an energy intake within the normal range [154]. Improved linear growth also has been demonstrated in 12 prepubertal or early pubertal children on HD therapy with increased time on dialysis and close monitoring of nutritional intake. This was achieved with an intake of 90.6% of the recommended energy intake [150]. The importance of caloric intake has also been shown in 31 prepubertal children on dialysis therapy treated with growth hormone, with a positive correlation between energy intake and growth velocity [26].

Table 22.2 Equations to estimate energy requirements for children at healthy weights

Age	Estimate energy requirement (EER) (kcal/d) = total energy expenditures + energy deposition
0–3 months	EER = [89 × weight (kg) – 100] + 175
4–6 months	EER = [89 × weight (kg) – 100] + 56
7–12 months	EER = [89 × weight (kg) – 100] + 22
13–35 months	EER = [89 × weight (kg) – 100] + 20
3–8 years	Boys: EER = 88.5 – 61.9 × age (y) + PA × [26.7 × weight (kg) + 903 × height (m)] + 20 Girls: EER = 135.3 – 30.8 × age (y) + PA × [10 × weight (kg) + 934 × height (m)] + 20
9–18 years	Boys: EER = 88.5 – 61.9 × age (y) + PA × [26.7 × weight (kg) + 903 × height (m)] + 25 Girls: EER = 135.3 – 30.8 × age (y) + PA × [10 × weight (kg) + 934 × height (m)] + 25

Source: Ref. [175]

All children with CKD stages 2–5 and 5D should have regular dietary assessments, with the frequency dependent on the degree of renal impairment to ensure EER for age, sex, and PAL (Tables 22.2 and 22.3). If children younger than 3 years with a length- or height-for-age less than −1.88 SDS fail to achieve expected weight gain and growth when receiving EER (Table 22.2) based on chronological age, estimated requirements may be modified by using height-age.

As in the general public, the incidence of childhood obesity in those with CKD is increasing. National registry data for pediatric dialysis or transplant patients showed a significantly higher mortality rate at the upper and lower extremes of BMI-for-age [49]. Pretransplantation obesity is associated with decreased long-term renal allograft survival [176]. Prevention and treatment of obesity in patients with CKD is also important to reduce the risk of hyperlipidemia. Fat mass is less metabolically active than lean mass; therefore, energy requirements for overweight or obese children are lower and can be estimated by using equations specific for children heavier than a healthy weight [175].

Table 22.3 Physical activity coefficients for determination of energy requirements in children ages 3–18 years

Gender	Level of physical activity			
	Sedentary	Low active	Active	Very active
	Typical activities of daily living (ADL) only	ADL + 30–60 min of daily moderate activity (e.g., walking at 5–7 km/h)	ADL + ≥ 60 min of daily moderate activity	ADL + ≥ 60 min of daily moderate activity + an additional 60 min of vigorous activity or 120 min of moderate activity
Boys	1.0	1.13	1.26	1.42
Girls	1.0	1.16	1.31	1.56

Sources: Health Canada: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf. Reproduced with the permission of the Minister of Public Works and Government Services Canada 2008

In infancy, feeds should be of breast milk or a whey-based infant formula with a low renal solute load if needed. Weaning solids should be introduced at the same time as recommended for healthy children. In children, high-energy foods and drinks are recommended as part of a controlled intake, with nutritional supplements or nutritionally complete feeds introduced if necessary. Calculated energy requirements are estimates, and some children will require more or less for normal growth; therefore, all dietary prescriptions should be individualized.

Early intervention to try to prevent the development of oral hypersensitivity and food-aversive behavior often is incorporated into the feeding plan and includes the correct timing for introduction of solids with gradual inclusion of new tastes and lumpier textures, messy play and food exploration, prohibition of force feeding with self-feeding behavior promoted, and sitting with the family at meal times.

Other members of the multidisciplinary team with expertise in infant feeding issues – e.g., infant psychologists and speech, language, and occupational therapists – may be important in improving the outcome for normal feeding. However, overemphasis on maintaining the oral route to achieve an adequate nutritional intake may be counterproductive because symptoms may be exacerbated by inappropriate expectations and the critical period of intervention to ensure normal nutrition-dependent growth may be missed.

In children with CKD stage 5D on PD therapy, variable glucose absorption takes place from the dialysis fluid depending on the mode of dialysis, dialysate glucose concentration, and peritoneal membrane capacity. There are two adult studies documenting the caloric impact from dialysis fluid glucose [177, 178]. One formula using both PD modality and peritoneal equilibration test (PET) transport characteristics was shown to closely approximate measured glucose absorption, but has not been evaluated in children [177]. In a pediatric study of 31 children older than 3 years on ambulatory PD therapy, the mean energy intake derived from peritoneal glucose absorption was 9 kcal/kg/d [152]. Kaiser et al. [136] demonstrated better growth rates in children receiving CAPD versus CCPD versus HD that may have been partially explained by increased glucose absorption associated with CAPD. Because many children on PD therapy are underweight, the prescribed energy intake in those with CKD stage 5D should exclude the estimated calorie absorption from the dialysate because this may compromise the nutritional quality of the diet. However, some children – and particularly infants on PD therapy – gain weight at a faster rate than normal despite oral and/or enteral energy intakes that are lower than the average requirements. Reduced physical activity and increased exposure to dialysate glucose for fluid removal may be explanations, and in these cases, the calorie contribution from PD fluid should be taken into account when estimating energy requirements.

2.2: 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. (B)

2.3: 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. (B) When energy requirements cannot be met with oral supplementation, tube feeding should be considered. (B)

Energy requirements in infants and children include the energy needed for tissue deposition, with satisfactory growth a sensitive indicator of whether energy requirements are being met, particularly in infancy [179]. Poor energy intake and vomiting in children with CKD therefore will have an adverse effect on growth. Because short stature at dialysis therapy initiation is a marker for poor outcome in children initiating dialysis therapy, early intervention with intensive nutritional support may be critical to outcome [180]. Because calculated energy requirements are estimates, all dietary prescriptions should be individualized because some children will require more or less for normal growth. Formulas and enteral feedings may be concentrated and/or supplemented with a commercial glucose polymer powder and/or a liquid fat. Energy-dense feeds may be needed in children with CKD stage 5 with oligoanuria.

However, both poor appetite and vomiting are common in infants and children with CKD and have a negative impact on the aim of achieving the dietary prescription. Poor appetite is multifactorial in origin and includes a thirst for water rather than feed in those with polyuric CKD, the administration of multiple unpleasant medications, and a preference for salty rather than energy-dense sweetened foods. The accumulation of appetite-regulating cytokines and hormones has been implicated in the cause of both this lack of spontaneous appetite and early satiety and provides a physiological explanation for the difficulties faced by caregivers in delivering the dietary prescription [181, 182]. Gastroesophageal reflux was demonstrated in 73% of infants with chronic kidney failure, with poor feed intake and vomiting [183] and disordered gastric motility, delayed gastric emptying, and gastroesophageal reflux in 12 symptomatic children in association with increased polypeptide hormone levels [184].

Symptoms of vomiting, irritability, and discomfort suggestive of gastroesophageal reflux initially should be managed conservatively by concentrating feeds to reduce feed volume and minimizing seated and supine positions after feeds because there is some evidence of benefit in infants without CKD [185, 186]. Although there are no published data about the use of prokinetic agents (e.g., metoclopramide, a dopamine receptor antagonist; domperidone, a peripheral D_2 dopamine receptor antagonist) or gastric acid suppressants (H_2 receptor blockers or proton pump inhibitors) in children with CKD, their use may be helpful. If symptoms persist, anatomic abnormalities should be excluded radiologically, but the role of routine pH studies and tests of gastric emptying in those with CKD is not established. A fundoplication may be indicated for intractable vomiting and can be performed after a gastrostomy is placed.

When poor appetite and vomiting preclude a nutritionally adequate intake, tube feeding commonly is implemented. Although registry data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) for the use of supplemental tube feeds in children younger than 6 years at the start of dialysis therapy showed no improvement in linear growth, follow-up was for only a year and no information was available for calorie intake [187]. However, in single-center studies, tube feeding has been shown to facilitate weight gain and growth. Significant weight gain and catch-up growth were achieved in 35 children with CKD stages 4–5 and age younger than 5 years if tube feeding was started before the age of 2 years. Loss of nutrition from vomiting is variable and hard to assess; however, the improved weight gain observed in this study over 2 years with enteral feeding and without an increase in energy intake for age suggests that vomiting can be reduced by slow delivery of feeds [18]. In a large

study of 101 infants presenting with CKD who were younger than 6 months and had a GFR less than 20 mL/min/1.73 m^2 or CKD stage 5 within 2 years, 81% of the 81 survivors were tube fed and achieved a mean height SDS within the normal range by 1 year, with continued improvement thereafter [17]. In 12 infants starting PD therapy at younger than 1 year and on PD therapy for at least a year in association with enteral feeding, height, weight, and occipital head circumference SDS all improved significantly by 1 year, with continuing improvement in weight and occipital head circumference into the second year [188]. Coleman et al. [154] included older children in their study of tube feeding using gastrostomy buttons in 22 children (0.2–10.3 years old) on long-term dialysis therapy. Although growth data did not distinguish between those starting gastrostomy feeding before (n = 16) or after the age of 5 years (n = 6), mean height and weight SDS increased significantly by 18 months. However Ramage et al. [189], in a study of 15 children on PD therapy and gastrostomy fed, subdivided growth outcome into those age younger than 2.5 years (n = 8) and those older than 2.5 years (n = 7) at the start of tube feeding. There was no further decrease in height SDS in either group, with significant weight gain in both age groups by 12 months [189]. Therefore, tube feeding should be considered for infants and children younger than 3 years who do not meet their EER orally despite dietary intervention and who are underweight or growth retarded (weight or length/height < −1.88 SDS) or failing to achieve normal rates of weight gain or growth. Although there are limited data about the use of tube feeding in children older than 3 years, this approach should be considered in the individual child with intake inadequate to maintain expected weight gain to prevent malnutrition, which increases the risk of infection, reduces stamina and cognition, and compromises long-term survival [70]. However, treatment with growth hormone may be indicated if growth failure persists despite meeting nutritional requirements, particularly after early childhood, because there is currently minimal evidence that improved nutrition alone can facilitate catch-up growth.

The method of tube-feed delivery and feed composition will depend on age, the presence or absence of vomiting, nutrient requirements, mineral and electrolyte imbalances, and the assessed intake that can be achieved orally. Infants may require only boluses of the balance of their feeding after oral feeds (i.e., top-up boluses), but some may need the full prescription to be given by tube, which can then be delivered by pump as an overnight feed, with the rate adjusted as tolerated with additional daytime boluses (Table 22.4). Older children may benefit from having the majority of their feed overnight to encourage hunger and oral intake during the day and so they can be free to undertake normal daytime activities without the pressure to meet all their requirements while at school or socializing.

Dello Strogolo et al. [168] reported persistent feeding dysfunction in 8 of 12 infants with a GFR less than 35 mL/min/1.73 m^2 who were managed with nasogastric tube feeds for at least 9 months. Therefore, it is important that tube-fed infants and children be encouraged to continue some oral intake or have continued oral stimulation, e.g., sucking on a pacifier and/or positive nonthreatening contact with food. Other studies are more encouraging. In five infants on PD therapy and nasogastric feeding with persistent food refusal, intensive behavior therapy by a multidisciplinary team enabled the infants to convert to full oral feeding [190]. Although there are concerns that tube feeding will further reduce oral intake, Ledermann et al. [18] showed in children aged 0–2 years that the percentage of energy derived from the tube feed did not change over 2 years despite an increase in the absolute energy intake with age, confirming improved oral intake. The long-term outlook for normal feeding after transplantation is excellent, with reports of successful transitioning of almost all tube-fed children to oral diet and fluids within 10 months if children with significant comorbidities are excluded [169, 191].

Although the preferred method of tube feeding is by means of gastrostomy, nasogastric tubes may be used long term or as a temporary measure, particularly for infants weighing less than 4 kg or infants/children presenting with CKD stage 5 needing immediate PD therapy. Repeated

Table 22.4 Suggested Rates for Initiating and Advancing Tube Feedings

Age	Initial Hourly Infusion	Daily Increases	Goal*
Continuous Feedings			
0-1 y	10-20 mL/h or 1-2 mL/kg/h	5-10mL/8h or 1 mL/kg/h	21-54 mL/h or 6 mL/kg/h
1-6 yrs	20-30 mL/h or 2-3 mL/kg/h	10-15 mL/8h or 1 mL/kg/h	71-92 mL/h or 4-5 mL/kg/h
6-14 yrs	30-40 mL/h or 1 mL/kg/h	15-20 mL/8h or 0.5 mL/kg/h	108-130 mL/h or 3-4 mL/kg/h
>14yrs	50 mL/h or 0.5-1 mL/kg/h	25 mL/8h or 0.4-0.5 mL/kg/h	125 mL/h
Bolus Feedings			
0-1 y	60-80 mL q 4h or 10-15 mL/kg/feed	20-40 mL q 4h	80-240 mL q 4h or 20-30 mL/kg/feed
1-6 yrs	80-120 mL q 4h or 5-10 mL/kg/feed	40-60 mL q 4h	280-375 mL q 4h or 15-20 mL/kg/feed
6-14 yrs	120-160 mL q 4h or 3-5 mL/kg/feed	60-80 mL q 4h	430-520 mL q 4h or 10-20 mL/kg/feed
> 14 yrs	200 mL q 4h or 3 mL/kg/feed	100 mL q 4h	500 mL q 4h or 10 mL/kg/feed

Note: Calculating rates based on age and per kilogram body weight is useful for srnall-for-age patients
Adapted with permission
*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 tolerance

replacement due to vomiting with subsequent aversive behavior and the psychosocial problems associated with the visibility of the tube are averted by the use of gastrostomies. Gastrostomies may be placed either percutaneously (radiologically or endoscopically) or by using an open procedure. Minor complications are well documented for both approaches, particularly exit-site erythema and infections. Migration of the retention disk and enterocolic fistulae can present as significant late complications of percutaneous placement, although the latter may be avoided by radiological placement because the bowel is outlined with contrast. Gastrocutaneous fistulae may need surgical closure after gastrostomy button removal. A percutaneously placed gastrostomy should be replaced every 18–24 months by either the same size gastrostomy tube or, if the track is adequate, a button gastrostomy according to the child's and family's preference [192, 193]. Ideally, placement of a gastrostomy tube should occur before PD catheter placement. The placement of a percutaneous gastrostomy while on PD therapy should be discouraged because the risk of severe peritonitis and PD failure is high; conversely, an open Stamm gastrostomy, initially with a catheter and subsequently replaced by a button device, can be performed safely in children on PD therapy with suitable precautions (e.g., antibiotic and antifungal coverage and time off PD therapy after placement). There is no evidence of an increased incidence of bacterial or fungal peritonitis with an established gastrostomy [155, 194, 195].

A fundoplication may be performed with the gastrostomy or after initial gastrostomy placement if severe vomiting persists despite medical and nutritional management, but temporary HD therapy may be required [155, 196]. A Stamm gastrostomy can be created at the same time as PD catheter placement without additional complications [154].

The use of gastrojejunal tubes has been described by Geary and Chait [110], but the expected reduction in vomiting was not observed and the need for continuous feed delivery reduces the practical application.

Other approaches may improve the nutritional status. In adult maintenance HD patients, increasing dialysis frequency to six times per week improved both biochemical markers and weight

gain [197]. A recent report of increased growth velocity in five children with intensified daily HD allowed a "free" diet raising the possibility that nutritional status improves with a higher dialysis dose [149]. Although the appetite stimulant megestrol acetate has been used in adults on HD therapy [198, 199], there are significant side effects and few published studies or case reports of the use of appetite stimulants or anabolic agents in children with CKD.

The 3½–4-h HD session, which characteristically occurs thrice weekly, may offer an opportune time to provide oral nutritional supplementation, provided the patient is tolerant of the nutrient intake during the session. Although this is a common practice in Europe, the experience in many other centers has been less positive, prompting a philosophy against the allowance of oral intake during HD in adult and even pediatric centers alike [200–203]. The most frequent adverse outcome noted when meals have been provided is hypotension, presumably the result of either decreased cardiac output secondary to splanchnic sequestration of blood or through a decrease in splanchnic resistance leading to a reduction in systemic vascular resistance [204, 205]. A decrease in relative blood volume also has been documented [206]. However, more recently, a prospective study of 85 adults receiving maintenance HD revealed the nutritional benefit and patient tolerance of an oral supplement provided during the HD session [207]. In a subsequent retrospective study of 126 stable adult HD patients, there also was no evidence of an association between oral intake during HD and intradialytic hypotension, although the prescribed dry weight was not achieved in a substantial percentage of patients with high oral intake [208]. It is distinctly possible that the fewer comorbidities that characterize pediatric versus adult patients receiving HD are associated with decreased risk of postprandial complications. However, evidence supporting this hypothesis is not yet available and mandates close monitoring of vital signs in any patient who receives nutritional supplementation during an HD session.

2.4: A trial of IDPN to augment inadequate nutritional intake is suggested for malnourished children (BMI-for-height-age < fifth percentile) receiving maintenance HD who are unable to meet their nutritional requirements through oral and tube feeding. (C)

Malnutrition, short stature, and low BMI are independent risk factors for mortality in adult and pediatric patients [49, 70, 209]. Data from adult patients receiving maintenance HD show that anorexia is an independent risk factor for death 12 months later [210]. Children receiving MD report high rates of depression [211], poor adjustment to diagnosis and lower socioeconomic status [212], and lower health-related quality of life [213–215] than healthy controls and therefore are at risk of anorexia-induced malnutrition. One pediatric center reports that psychosocial/malnutrition-related causes account for the most frequent reason for HD patient hospitalization [58]. Advanced CKD stages are often associated with anorexia and gastrointestinal disorders, which may inhibit the ability to maintain adequate nutritional status through the oral and/or enteral route. IDPN can be provided to augment inadequate nutritional intake in a small select group of children who are malnourished and unable to meet their requirements through oral and tube feeding.

Pilot pediatric data from small cohorts suggest that IDPN can be efficacious to augment inadequate oral and/or enteral nutrition in malnourished children, leading to improvements in BMI in children with organic [58, 59, 216], but not psychosocial [59], causes of malnutrition. Optimal IDPN solution composition is unknown; however, a typical IDPN prescription contains amino acids in amounts to meet estimated daily protein requirements, as well as dextrose and 20% or 30% lipid components to increase the caloric impact of the IDPN. Substrate infusion rates are adjusted upward as tolerated to enhance caloric intake while preventing or managing hyperglycemia and hyperlipidemia (Table 22.5).

Although data assessing IDPN efficacy in adult HD patients have not shown a clear benefit of IDPN to reduce mortality [217, 218], such data may not be applicable to children, for whom adequate nutrition is requisite for normal growth and development.

Table 22.5 Nutrient content or infusion rates of IDPN reported from small pediatric cohorts

	Goldstein 2002	Orellana 2005	Krause 2002
Parameter/nutrient	(n = 3)	(n = 9)	(n = 4)
Age (years)	17–25	17–26	4–18
Protein, g/kg/treatment	1.3	1.3	0.5–1.5
Dextrose, mg/kg/min	5–9	5–9	18–46
Fat, g/kg/h	Not reported	≤ 0.2–0.3	≤0.2
kcal/kg/treatment	Not reported	11 kcal/kg from protein + dextrose; not reported for lipids	27–53

Table 22.6 Potential adverse occurrences with IDPN

Component	Adverse occurrence(s)	Monitoring schedule	Response to adverse event
Protein	None		
Carbohydrate	Hyperglycemia (>350 mg/dL)	Serum glucose before HD, 1 h into HD and at the end of HD – First week of IDPN – Week after change in dextrose rate – Symptomatic patient	Decrease dextrose rate by 2 mg/kg/min Add insulin to IDPN
Fat	Hyperlipidemia (50% rise in pre-HD TG level between two treatments)	– Serum TG levels before first and second treatment using lipids	Discontinue lipids
	Hypersensitivity (egg allergy)	– During the first administration of intravenous lipids, a test dose of 0.5 mL/min for the first 30 min of infusion	Discontinue lipids

IDPN is administered continuously during the entire course of the HD treatment and should be infused in the venous limb of the HD circuit to prevent clearance of amino acids and trace elements. More than two-thirds of the infused amino acids are retained, and the fluid used to deliver IDPN is removed through ultrafiltration. Trace element solutions can be added to provide zinc, copper, selenium, manganese, and chromium. Table 22.6 lists the potential adverse events associated with IDPN and a recommended monitoring schedule. Postinfusion hypoglycemia or symptoms suggestive of refeeding syndrome (e.g., hypokalemia, hypophosphatemia, and hypomagnesemia) have been seen rarely in children on IDPN therapy.

In the absence of pediatric criteria, discontinuation criteria for adults may provide guidance [217, 219]. Suggested criteria include clinical evidence of improving nutrition as evidenced by increased dry weight and an increase in oral intake to meet energy and protein requirements. Additional criteria for discontinuation include no improvement in nutritional status after 4–6 months of IDPN or complications or intolerance of IDPN therapy [219].

IDPN provision can require substantial resources and should be used only when adequate financial and personnel resources are available. IDPN should not be promoted as a sole nutrition source; it should be used to augment other sources. If the combination of oral and/or enteral intake and IDPN is unable to meet energy and protein requirements, daily total or partial parenteral nutrition is indicated.

2.5: A balance of calories from carbohydrate and unsaturated fats within the physiological ranges recommended as the AMDR of the DRI is suggested when prescribing oral, enteral, or parenteral energy supplementation to children with CKD stages 2–5 and 5D. (C)

Fats, carbohydrates, and proteins can substitute for one another to some extent to meet the body's energy needs. Uneven distribution of calories from each of the macronutrients may be associated with inadequacy of certain nutrients and increased risk of such chronic diseases as coronary heart disease, obesity, and diabetes. Cardiovascular disease (CVD) is the leading cause of morbidity and death in the pediatric

CKD population [220, 221]. Upper extremes of BMI-for-age are associated with higher mortality rates in children on dialysis therapy and decreased long-term allograft survival and higher mortality rates in pediatric transplant patients. Although large-scale studies of risk-factor outcomes for those with CVD have not been performed in adults or children with CKD, the high mortality rate supports the need for risk-factor reduction early in the course of CKD to reduce long-term exposure to cardiovascular insult and improve outcomes. To achieve the best risk reduction, it appears that dietary strategies should aim to prevent or minimize increased triglyceride (TG) and cholesterol levels and avoid conditions – such as obesity – that contribute to dyslipidemia.

It often is necessary to supplement an infant's formula or a child's diet with fat and carbohydrate to provide optimal calories, especially when the child is fluid restricted. In the general population, low or high proportions of calories from carbohydrate or fat are associated with nutrient inadequacies (e.g., fat-soluble vitamins) and/or chronic diseases, including heart disease, obesity, and diabetes [175].

Macronutrients are related to heart disease and obesity in many ways. Excess energy intake results directly in obesity, which increases the risk of heart disease. High intake of dietary cholesterol, saturated fat, or trans-fatty acids can increase total and low-density lipoprotein (LDL) cholesterol levels in the blood whereas monounsaturated and polyunsaturated fatty acids can decrease total and LDL blood cholesterol levels. High intakes of n-3 polyunsaturated fatty acids (omega-3 fatty acids [175], docosahexaenoic acid [175], and eicosapentaenoic acid [175]) are associated with decreasing TG levels and a decreased risk of heart disease. High carbohydrate (i.e., simple sugars) and low fat intakes tend to increase plasma TG levels and decrease high-density lipoprotein (HDL) cholesterol levels, with a carbohydrate source of monosaccharides (especially fructose) causing a more extreme effect. Hypertriglyceridemia also has been associated with enhanced glucose uptake in children on PD therapy. Dietary fiber, particularly naturally occurring viscous fiber, reduces total and LDL cholesterol levels, and high intakes have been associated with reduced rates of CVD.

As noted previously, CVD is the leading cause of morbidity and mortality in children with CKD, accounting for approximately 25% of total deaths [220, 221]. These rates are 1,000 times higher than the national pediatric cardiovascular death rate [220]. CVD in children with CKD is associated with traditional (dyslipidemia, hypertension, obesity, physical inactivity, and genetics) and nontraditional factors (uremia, uremia-related anemia, prothrombogenic factors, inflammation, fluid overload, left ventricular hypertrophy, increased homocysteine levels, and vascular calcification) [220]. Children with CKD have been identified as being in the highest risk category for pediatric CVD [173].

Dyslipidemia occurs relatively early in the progression of CKD (i.e., GFR, 30–59 mL/min/1.73 m^2) and increases in prevalence as kidney function deteriorates [222]. In children and adolescents on PD therapy, reported rates of dyslipidemia range from 29% to 87% [223]. Hypertriglyceridemia and hypercholesterolemia have been reported in 90% and 69% of children with CKD stage 5, respectively [224]. Dyslipidemia in pediatric CKD manifests primarily as increased levels of serum TG, contained predominantly in very LDLs (VLDLs) of hepatic origin [225]. This occurs in combination with high levels of VLDL and intermediate-density lipoproteins (IDLs), low levels of HDL particles, and normal or modestly increased levels of total and LDL cholesterol [226, 227]. Sometimes referred to as atherogenic dyslipidemia, the metabolic abnormalities underlying it are complex [227]. Hypertriglyceridemia is an independent contributor to the development of CVD [228–232] and may also accelerate progression of CKD to CKD stage 5, dialysis, and transplantation [233–235].

Recommended ranges for a healthy distribution of calories from protein, fat, and carbohydrate for the general pediatric population have been established by the DRI [175]. These AMDR (Table 22.7) are based on evidence that consumption greater or less than these ranges may be associated with nutrient inadequacy and increased risk of developing such chronic diseases as coronary heart disease, obesity, diabetes, and/or cancer.

Table 22.7 Acceptable macronutrient distribution ranges

Macronutrient	Children 1–3 years (%)	Children 4–18 years (%)
Carbohydrate	45–65	45–65
Fat	30–40	25–35
Protein	5–20	10–30

Source: Health Canada: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf

Table 22.8 Dietary treatment recommendations for children with dyslipidemia and CKD stages 5 and 5D, and kidney transplant

Macronutrient	Serum LDL-C >100 mg/dL	Serum TG > 150 mg/dL
Energy		If associated with excess weight, energy balance + activity recommendations for weight loss
Dietary fat	<30% of calories	Low
Dietary cholesterol	<200 mg/d	
Trans-fatty acids	Avoid	
Saturated fatty acids	<7% of calories	
Carbohydrate		Low simple carbohydrate

Source: Kavey et al. [173]

There is no information to suggest that dietary advice regarding macronutrient distribution in children with CKD should be different from that in the general population; therefore, it seems prudent to maintain a distribution of calories similar to that recommended by the AMDR for children with CKD stages 2–5 and 5D.

The DRI provide further recommendations for specific types of carbohydrate and fat to avoid or limit for the purpose of chronic disease risk reduction. Given the high risk of CVD in children with CKD, it is recommended that children and their caregivers be counseled to use sources of unsaturated fat rather than saturated or trans fats and, as much as possible, to choose complex carbohydrates instead of simple sugars.

Calorically dense formulas frequently are prescribed for infants; however, there are no AMDR for those younger than 1 year. Therefore, when advancing the caloric density of formula, the distribution of protein, fat, and carbohydrate should be kept consistent with the base formula [236], which must adhere to strict standards (7–12% protein, 40–54% fat, and 36–56% carbohydrate). Infants and young children need a somewhat greater proportion of fat in their diets to meet energy needs. Protein and electrolyte issues typically predict whether the energy density of an infant's formula can be concentrated (i.e., more formula concentrate and less water) or increased by the addition of modular components of carbohydrates (e.g., powder or liquid forms of tasteless glucose polymers) and/or fat (e.g., ordinary oil used at home, emulsified oil, or medium-chain TG). When uremia, hyperkalemia, hyperphosphatemia, or formula osmolarity prevent concentrating formulas, additions of carbohydrate and/or fat are indicated. Fat additions to formula should be in the form of heart-healthy unsaturated fats, such as canola, olive, or corn oil. Providing enteral feedings containing glucose polymers and oil emulsions in a balanced profile of fat and carbohydrate to children with CKD managed conservatively (n = 5) or by using PD (n = 5) did not enhance hyperlipidemia compared with 37 children who were not tube fed [237].

Children with CKD stages 2–5 and 5D and dyslipidemia have been identified as a high-risk population for CVD [173]. Table 22.8 lists more precise recommendations for stricter lowering of total dietary fat, cholesterol, and *trans* and saturated fats directed to toddlers, children, and adolescents with dyslipidemia and CKD stage 5, 5D, or a kidney transplant.

The KDOQI Dyslipidemia Guidelines' recommendations, endorsed by the KDOQI Cardiovascular Guidelines, recommend that the dietary and lifestyle recommendations made for

adults are also appropriate for postpubertal children and adolescents with CKD, but that prepubertal children should follow recommendations from the National Cholesterol Expert Panel in Children and Adolescents (NCEP-C) [238]. Since then, a consensus statement on dietary recommendations for children and adolescents from the -American Heart Association (AHA) [239], endorsed by the American Academy of Pediatrics, provides more current guidance than the NCEP-C recommendations for working with children and adolescents with CKD, recognizing that dietary modifications to increase calories or restrict potassium and/or phosphorus intake make macronutrient modifications more challenging to achieve.

The extent to which the macronutrient content of the diet should be manipulated must consider the child's nutritional status and other dietary mineral and/or electrolyte restrictions. The first priority for nutritional care is meeting energy, protein, and micronutrient requirements to achieve optimal growth for individual children. If a child is well nourished, adding dietary modifications for dyslipidemia prevention or management can be safely undertaken. Studies of the general pediatric population have shown that dietary fat restriction to 30% of total caloric intake is safe and, in particular, free of adverse effects on growth, development, or nutrition [240, 241].

Renal diet restrictions to control uremia (protein) and mineral and electrolyte abnormalities limit the variety and palatability of the diet, and additional (dyslipidemia) restrictions can be overwhelming and may reduce caloric intake further. In light of this, dietary intervention for treatment of dyslipidemia is not recommended for undernourished children with CKD [220, 223]; however, such simple changes as a switch to heart-healthy fats can be implemented easily.

2.6: Dietary and lifestyle changes are suggested to achieve weight control in overweight or obese children with CKD stages 2–5 and 5D. (C)

Childhood obesity is an international public health problem reaching epidemic proportions. A review of data from the US Renal Data System for more than 1,900 pediatric dialysis or transplant patients showed that mortality rates were significantly higher at the upper and lower extremes of BMI-for-age [49]. Pretransplantation obesity and increased BMI-for-age after transplantation are associated with decreased long-term renal allograft survival [176]. Prevention and treatment of obesity in patients with CKD is also important to reduce the risk of hyperlipidemia [242].

A multiorganization scientific statement on cardiovascular risk reduction in high-risk pediatric patients made the following recommendations for high-risk children, including those with CKD stages 5 and 5D and kidney transplant recipients with a BMI greater than the 95th percentile. Step 1 treatment: (a) age-appropriate reduced-calorie training for child and family; (b) specific diet/weight follow-up every 4–6 months, repeated BMI calculation at 6 months; and (c) activity counseling with a goal of 1 h or more of active play per day and screen time limited to 1 h or less per day. Step 2 treatment if follow-up BMI remains greater than the 95th percentile: weight-loss program referral plus consider referral for exercise testing and recommendations from exercise specialist appropriate for cardiac status [173]. Interventional strategies for treatment of child and adolescent overweight and obesity in the non-CKD population [45] may be helpful.

Fiber

The AI for total fiber is based on daily caloric intake, and for all children 1 year and older is 14 g/1,000 kcal/d. To normalize cholesterol levels and reduce the risk of cardiovascular heart disease, an increase in soluble fiber intake is recommended as an addition to reductions in saturated fatty acid and cholesterol intake [239, 241]. Fiber also can aid laxation and promote satiety, which can reduce energy intake and the risk of overweight.

Dietary fiber is found in most fruits, vegetables, legumes, and whole grains, which are foods restricted in low-potassium and low-phosphorus diets; therefore, meeting daily fiber recommendations for healthy children is more challenging for children with CKD who have limited intake of these foods due to low-potassium and/or low-phosphorus diet restrictions. Tasteless mineral- and electrolyte-free powdered forms of fiber (e.g.,

Unifiber®, Benefiber®) are available to add to meals or drinks if children are unable to meet their fiber intake by diet. High-fiber diets require additional fluid intake, which may not be possible for oliguric or anuric patients with strict fluid restriction.

Omega-3 Fatty Acids (n-3 FA)

Approximately 75% of children with CKD have hypertriglyceridemia, for which there is no effective therapy. Both primary and secondary prevention studies provide strong evidence that consumption of fish and fish oils rich in the n-3 FAs EPA and DHA reduce all-cause mortality and various CVD outcomes in adults [243, 244]. By far, the strongest most consistent evidence of the cardioprotective benefits of n-3 FA is for the lowering of serum TG levels that is dose dependent and similar in various (adult) populations [244, 245]. Adults with CKD who were treated with n-3 FA for 8 weeks had significant decreases in TG levels ranging from 20% to 50% compared with controls [246–248]. Pediatric data for the TG-lowering effect of n-3 FA are limited to several pre/post-studies [249, 250]. Eighteen children (7–18 years old) on dialysis therapy experienced a 27% decrease in TG levels from 236 ± 31 to 171 ± 21 mg/dL after 8 weeks of EPA plus DHA supplementation [251]. In a trial of n-3 FA and alternate-day prednisone on progression of disease in children and young adults (age, 7.4–39.7 years) with immunoglobulin A (IgA) nephropathy, a 17% decrease in TG level was observed after 2 years of therapy with 3.36 g/d of EPA plus DHA [252].

EPA and DHA can be synthesized in vivo through the elongation and desaturation of a-linolenic acid; however, this process occurs slowly and is inefficient. Therefore, EPA and DHA, found almost exclusively in fish and marine sources, must be provided in the diet; the highest sources are fatty fish (e.g., tuna, mackerel, trout, salmon, herring, sardines, and anchovies) [253]. Adults on dialysis therapy consume fish in amounts far less than recommendations and have lower tissue EPA plus DHA stores compared with healthy people [254]. The higher mercury content of certain fatty fish (shark, swordfish, marlin, orange roughy, king mackerel, escolar [254], tilefish, and albacore or "white" tuna) has led various regulatory bodies to issue recommendations about the maximum intake of these fish for young children, who are considered to be more susceptible than adults to the adverse health effects of methyl mercury.

Several safety concerns around the use of n-3 FA have been raised, including prolonged bleeding times, worsening glycemic control in patients with diabetes, small increases in LDL cholesterol levels, and environmental contaminants in fish-oil products. Despite these concerns, n-3 FAs have been found to be extremely safe by both Health Canada and the US Food and Drug Administration.

At this time, there is insufficient evidence to recommend routine use of n-3 FAs to treat hypertriglyceridemia in children with CKD.

Recommendation 3: Protein Requirements and Therapy

3.1: It is suggested to maintain dietary protein intake at 100–140% of the DRI for ideal body weight in children with CKD stage 3 and at 100–120% of the DRI in children with CKD stages 4–5. (C)

Progressive CKD is generally associated with a reduction in spontaneous dietary intake of both protein and energy. In a study comparing 50 children with CKD stages 3–4 with healthy controls, protein intake was found to be 33% lower and energy intake was 10% lower in patients with CKD [255]. However, whereas spontaneous energy intake tends to be critically low, e.g., less than 80–85% of the RDA, DPI in those with CKD is far in excess of the average requirements, typically 150–200% of the RDA [9, 255, 256].

The efficacy of low-protein diets in reducing the rate of CKD progression has been assessed in randomized prospective trials in both adult and pediatric patients. In the MDRD trial, no significant beneficial effect of decreasing DPI from 1.3 to either 0.58 or 0.3 g/kg/d, supplemented with essential keto acids, could be demonstrated; subtle signs of a suboptimal nutritional status were noted with these diets [257]. In a

Table 22.9 Recommended dietary protein intake in children with CKD stages 3–5 and 5D

Age	DRI (g/kg/d)	Recommended for CKD stage 3 (g/kg/d) (100–140% DRI)	Recommended for CKD stages 4–5 (g/kg/d) (100–120% DRI)	Recommended for HD (g/kg/d)[a]	Recommended for PD (g/kg/d)[b]
0–6 months	1.5	1.5–2.1	1.5–1.8	1.6	1.8
7–12 months	1.2	1.2–1.7	1.2–1.5	1.3	1.5
1–3 years	1.05	1.05–1.5	1.05–1.25	1.15	1.3
4–13 years	0.95	0.95–1.35	0.95–1.15	1.05	1.1
14–18 years	0.85	0.85–1.2	0.85–1.05	0.95	1.0

[a]DRI + 0.1 g/kg/d to compensate for dialytic losses
[b]DRI + 0.15–0.3 g/kg/d depending on patient age to compensate for peritoneal losses

pediatric trial involving 191 children with CKD stages 3–4, a reduction in protein intake aiming at 100% (0.8–1.1 g/kg ideal body weight [257]) and achieving 120% of the dietary intake recommended by WHO did not alter the rate of CKD progression compared with a cohort with ad libitum protein intake (mean, 181% of RDA) [256, 258]. The reduction in protein intake, with maintenance of energy intake at greater than 80% of the RDA in both groups, did not affect statural growth, weight gain, body composition, or serum albumin levels within the observation period of 2–3 years.

Hence, although there is no evidence for a nephroprotective effect of dietary protein restriction, protein intake can be restricted safely to 0.8–1.1 g/kg/d in children with CKD. Because dietary protein restriction reduces the accumulation of nitrogenous waste products and facilitates lowering dietary phosphorus intake, it appears appropriate to gradually lower DPI toward 100% of the DRI in children advancing from CKD stage 3 to stage 5. This should delay the onset of signs and symptoms of uremia, although it should be noted that in the pediatric trial cited, the time of initiation of kidney replacement therapy was not delayed significantly in the low-protein cohort. Moreover, implementation and maintenance of a strict low-protein diet requires a major lifestyle change that may not be acceptable to many families. Hence, moderate protein restriction aiming at 100–140% of the DRI in CKD stage 3 and 100–120% of the DRI in CKD stages 4–5 may be a reasonable compromise in most cases (Table 22.9).

These protein recommendations refer to a stable child and assume that energy intake is adequate (i.e., it meets 100% of estimated requirements). Inadequate caloric intake results in the inefficient use of dietary protein as a calorie source, with increased generation of urea. Ensuring caloric needs are met is an important step in assessing protein requirements and modifying protein intake.

Protein requirements may be increased in patients with proteinuria and during recovery from intercurrent illness. Modification of protein recommendations also may be necessary in obese or stunted children. Obese individuals have a greater percentage of body fat, which is much less metabolically active than lean mass. Therefore, it is believed that basing protein (and energy) requirements of obese individuals on their actual weight may overestimate requirements. Conversely, using ideal body weight for an obese person does not take into account the increase in body protein needed for structural support of extra fat tissue. Therefore, a common practice is to estimate protein requirements of obese individuals based on an "adjusted" weight (i.e., adjusted weight = ideal weight-for-height + 25% × [256, 258], where 25% represents the percentage of body fat tissue that is metabolically active) rather than their actual body weight [259]. This formula is based on physiological theory rather than scientific evidence. In young children (i.e., age <3 years) or stunted children (i.e., length- or height-for-age <−1.88 SDS), protein requirements initially should be estimated by using chronological age, but may be reestimated by using height-age if there are indications of inadequate protein intake (see Recommendation 3.3).

3.2 In children with CKD stage 5D, it is suggested to maintain dietary protein intake at 100% of the DRI for ideal body weight plus an allowance for dialytic protein and amino acid losses. (C)

Our recommendations for DPI in dialyzed children differ from previous adult and pediatric guidelines based on several lines of reasoning.

First, the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences in 2002 replaced the RDA of 1989 with DRI values for the intake of nutrients by Americans and Canadians. For protein, the DRI values are lower than the RDA across all age groups [175].

Second, previous recommendations for dialyzed patients were based on the concept that in addition to replacements for dialytic amino acid and protein losses, at least 0.3–0.4 g/kg of dietary protein should be added to the intake recommended for healthy subjects [62]. The evidence base for this notion is weak and primarily based on adult literature.

The widespread notion that dialysis induces generalized protein catabolism through generalized protein degradation resulting from cytokine release induced by exposure to bioincompatible membranes (in HD) or dialysis fluids (in PD) has not been universally confirmed by metabolic studies. Net protein "catabolism" seems to be limited to the dialytic removal of amino acids and/or protein and a slightly reduced protein synthesis during HD sessions. Whole-body protein breakdown is not increased [260].

Observational studies showing a correlation between high-protein intake and better outcomes in adult dialysis patients [261, 262] do not prove that a high-protein intake by itself stimulates tissue anabolism. Reviews of nitrogen-balance studies performed in adult dialysis patients with different protein intakes [56, 263–270] conclude that HD patients are in neutral nitrogen balance with a protein intake as low as 0.75–0.87 g/kg/d, and PD patients with 0.9–1.0 g/kg/d. A single nitrogen-balance study has been performed in dialyzed children [152]. In 31 pediatric patients receiving automated PD, the investigators observed a positive correlation between nitrogen balance and DPI and concluded that DPI should be at least 144% of RDA. However, nitrogen balance also positively correlated with total energy intake, and no multivariate analysis was performed to address whether energy intake, protein intake, or both were independent effectors of nitrogen balance.

A single randomized prospective study in adults [271] and several trials in children have addressed the effect of selectively increasing amino acid supply in patients on PD therapy. Despite increases in amino acid and dietary protein intake, no significant beneficial effects on nutritional status and longitudinal growth in children were achieved by this intervention, whereas urea concentrations frequently increased [272–276]. These results are compatible with the interpretation that it is not possible to induce tissue anabolism by selectively increasing protein and amino acid ingestion except in subjects with subnormal baseline protein intake. If more protein is ingested than needed for metabolic purposes, all the excess is oxidized and results in accumulation of nitrogenous-containing end products.

Third, although evidence for beneficial effects of a high DPI is lacking, there is growing concern that it may even be harmful to dialyzed children. In a DXA study of body composition in 20 children on long-term PD therapy and a mean DPI of 144% of the RDA, protein intake inversely correlated with bone mineral density, bone mineral content, and fat-free mass, and also with plasma bicarbonate level, suggesting that a high-protein intake may cause tissue catabolism and bone loss through aggravating metabolic acidosis [277].

Finally, the most convincing argument for limiting DPI in dialyzed children is derived from the solid evidence for a key etiologic role of dietary phosphorus load in the pathogenesis of dialysis-associated calcifying arteriopathy in pediatric and adult patients. Several studies of children and adults with childhood-onset CKD stage 5 have demonstrated correlations between serum phosphorus levels and cumulative phosphate-binder requirements and arteriopathy [278–282], which, in turn, is linked to the excessive cardiovascular mortality of patients with CKD [283, 284].

There is a nearly linear relationship between protein and phosphorus intake [285], which deter-

Table 22.10 Average ratio of phosphorus to protein content in various protein-rich foods

Food category	Ratio of mg phosphorus to g protein	Ratio adjusted for digestion/absorption
Egg white	1.4	1
Meat	9	6
Tofu	12	7
Egg	14	10
Legumes	17	10
Lentils	20	12
Nuts	25	15
Milk	29	21
Seeds	50	29

Note: Mathematical estimations based on protein digestibility-corrected amino acid scores (PDCAA) and data on estimated phosphorus bioavailability

mines a frequent association of high protein in the diet with hyperphosphatemia [286]. Whereas hyperphosphatemia is a powerful independent predictor of mortality on dialysis therapy [287], evidence for any benefit from high-protein diets is lacking [288]. Hence, it appears mandatory to limit protein intake to the safe levels known to ensure adequate growth and nutrition in healthy children.

The adverse impact of hyperphosphatemia on cardiovascular, bone, and endocrine function in children with CKD mandates the preferential selection of protein sources that are relatively low in phosphorus. The lowest amount of phosphorus in proportion to the quantity and quality of protein comes from animal-flesh proteins (average, 11 mg of phosphorus per 1 g of protein), whereas eggs, dairy products, legumes, and lentils have higher phosphorus-protein ratios (average, 20 mg of phosphorus per 1 g of protein; Table 22.10). Complexity is added by the variable digestibility of dietary protein and bioavailability of dietary phosphorus. Protein digestibility from animal proteins is 95%, whereas protein digestibility from plant proteins (85%) and mixed meals (85–95%) is lower. Whereas phosphorus in animal meat is stored as organic phosphates in intracellular compartments that are easily hydrolyzed and readily absorbed, 75% of phosphorus in plants is in the form of phytic acid. Because humans do not express the degrading enzyme phytase, the bioavailability of phosphorus from plant-derived food is very low. Phosphorus availability from animal products is greater than 70%, whereas availability from plant products (50%) and mixed meals (50–70%) is lower. Hence, despite their higher specific phosphorus content, some plant sources of protein may actually result in a lower rate of phosphorus uptake per mass of protein than meat-based foods [289]. If healthy humans are administered an equivalent amount of either animal or plant protein, urinary phosphorus excretion is higher with the meat-based diet [290]. Moreover, meat products are frequently "enhanced" by the addition of phosphate salts; these additions may markedly increase the total phosphorus load. Hence, a mixed composition of dietary protein with a strong contribution of vegetable protein rich in phytic acid should be encouraged.

Although dialyzed children require larger amounts of protein per unit of body weight than adults to grow in size and lean body mass, this demand is fully accounted for by the age-adjusted pediatric DRI. Hence, the only additional dietary protein requirement justified by evidence is the replacement of dialytic nitrogen losses. In those on long-term PD therapy, daily peritoneal protein losses decrease with age across childhood from an average of 0.28 g/kg in the first year of life to less than 0.1 g/kg in adolescents [292]. Peritoneal amino acid losses add approximately one-third to the nitrogen lost with protein, resulting in a total additional dietary protein requirement ranging from 0.15 to 0.35 mg/kg, depending on patient age (see Table 22.8).

Peritoneal permeability for protein shows large interindividual variation, but appears to be relatively constant within subjects. Transperitoneal protein transport correlated with small-molecule transport rates; the peritoneal transporter status as assessed by using the PET provides some indication of the level of peritoneal protein losses. High peritoneal transporters tend to have low serum albumin levels; these patients may be at need for increased dietary protein supply. Because dialytic protein concentrations can be measured easily, consideration should be given to regular monitoring of peritoneal protein excretion and individual adaptation of the dietary protein prescription according to actual peritoneal losses.

Amino acid and protein losses during HD vary according to dialyzer membrane characteristics and reuse. Losses have not been quantified in children. In adults, an average of 8–10 g of amino acids and less than 1–3 g of protein are lost per HD session [288, 293, 293a, 293b]. On the basis of three HD sessions per week for a 70-kg adult, this equates to 0.08 g/kg/day.[1] Assuming that dialytic amino acid losses are in linear relationship to urea kinetics, children can be expected to have similar or slightly higher amino acid losses than adults. An added DPI of 0.1 g/kg/d should be appropriate to compensate for pediatric hemodialytic losses (see Table 22.9). Under all conditions, at least 50% of dietary protein intake should be of high biological value[2] to protect body protein and minimize urea generation.

In patients undergoing intensified HD modalities, in particular, extended nocturnal HD, the removal of nitrogenous waste products and phosphorus is almost doubled, frequently resulting in a need for phosphorus substitution [294]. Appetite and spontaneous dietary energy and protein intake reportedly increase in these patients. The excellent nitrogen and phosphorus clearances achieved with intensified treatment schedules and the concomitantly increased amino acid losses permit and require liberalization of DPI.

These recommendations for DPI refer to dialyzed children in stable clinical condition. Protein requirements may be increased in patients with proteinuria, during and after peritonitis episodes, and during recovery from intercurrent illness.

3.3: The use of protein supplements to augment inadequate oral and/or enteral protein intake should be considered when children with CKD stages 2–5 and 5D are unable to meet their protein requirements through food and fluids alone. (B)

Occasionally, protein intake may be inadequate in children with CKD because of anorexia, chewing problems, or the need for very stringent phosphorus restriction. Suggested signs of inadequate protein intake include abnormally low serum urea levels, an undesirable downward trend in nPCR for adolescents on HD therapy (see Recommendation 1, nPCR), and/or documentation of low-protein intake by using food records, food questionnaires, or diet recall. Powdered protein modules can be added to expressed breast milk, infant formula, beverages, pureed foods, or other moist foods to boost their protein content, and minced or chopped meat, chicken, fish, egg, tofu, or skim milk powder can be added to soups, pasta, or casseroles. Liquid protein-rich renal supplements can also be used orally or enterally to boost protein intake.

Recommendation 4: Vitamin and Trace Element Requirements and Therapy

4.1: The provision of a dietary intake consisting of at least 100% of the DRI for thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8), cobalamin (B12), ascorbic acid (C), retinol (A), a-tocopherol (E), vitamin K, folic acid, copper,

[1](13 g AA and protein × 3 sessions) ÷ 7 days per week ÷ 70 kg = 0.08 g/kg/d.

[2]Protein containing the nine essential amino acids in a proportion similar to that required by humans has high biological value. When one or more essential amino acids are scarce, the protein is said to have low biological value. Animal sources of protein (e.g., meat, poultry, fish, eggs, milk, cheese, and yogurt) provide high biological value protein. Protein found in plants, legumes, grains, nuts, seeds, and vegetables are of low biological value.

Table 22.11 Dietary reference intake: recommended daily allowance and adequate intake

	Infants	Infants	Children	Children	Males	Males	Females	Females
	0–6 months	7–12 months	1–3 years	4–8 years	9–13 years	14–18 years	9–13 years	14–18 years
Vitamin A (μg/d)	400	500	**300**	**400**	**600**	**900**	**600**	**700**
Vitamin C (mg/d)	40	50	**15**	**25**	**45**	**75**	**45**	**65**
Vitamin E (mg/d)	4	5	**6**	**7**	**11**	**15**	**11**	**15**
Vitamin K (μg/d)	2.0	2.5	30	55	60	75	60	75
Thiamin (mg/d)	0.2	0.3	**0.5**	**0.6**	**0.9**	**1.2**	**0.9**	**1.0**
Riboflavin (mg/d)	0.3	0.4	**0.5**	**0.6**	**0.9**	**1.3**	**0.9**	**1.0**
Niacin (mg/d; NE)	2[a]	4	**6**	**8**	**12**	**16**	**12**	**14**
Vitamin B_6 (mg/d)	0.1	0.3	**0.5**	**0.6**	**1.0**	**1.3**	**1.0**	**1.2**
Folate (μg/d)	65	80	**150**	**200**	**300**	**400**	**300**	**400**
Vitamin B_{12} (μg/d)	0.4	0.5	**0.9**	**1.2**	**1.8**	**2.4**	**1.8**	**2.4**
Pantothenic acid (mg/d)	1.7	1.8	2	3	4	5	4	5
Biotin (μg/d)	5	6	8	12	20	25	20	25
Copper (μg/d)	200	220	**340**	**440**	**700**	**890**	**700**	**890**
Selenium (μg/d)	15	20	**20**	**30**	**40**	**55**	**40**	**55**
Zinc (mg/d)	2	**3**	**3**	**5**	**8**	**11**	**8**	**9**

Note: RDAs are in bold type; also are in ordinary type
Source: Health Canada: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf
[a]As preformed niacin, not niacin equivalents (NE) for this age group

and zinc should be considered for children with CKD stages 2–5 and 5D. (B)

Little information exists about the vitamin and trace element needs specific to children with CKD and those on dialysis therapy. However, in view of the important role of these nutrients as cofactors in a number of metabolic reactions, and recognizing that achieving the DRI should reduce the risk of developing a condition that is associated with the nutrient in question that has a negative functional outcome [298, 299], the practice has been to target 100% of the DRI as the goal for children with CKD stages 2–5 and on dialysis therapy (Table 22.11).

The B vitamins are essential for carbohydrate, protein, and fat metabolism; oxidation–reduction reactions; transamination and decarboxylation; glycolysis; and blood formation. Most thiamin in the body is present as thiamin pyrophosphate, which is a coenzyme for the oxidative decarboxylation of a-keto acids. The metabolism of riboflavin resulting in functional flavoproteins is important because the flavoenzymes are important factors involved in oxidation–reduction reactions that are necessary for a variety of metabolic pathways, including energy production. Pantothenic acid is necessary for the synthesis of such compounds as fatty acids, cholesterol, and steroid hormones and for energy extraction during oxidation of amino acids. Pyridoxine is a coenzyme for nearly 100 enzymatic reactions and is essential for gluconeogenesis and niacin formation. Biotin has an important role in the metabolism of carbohydrates, fatty acids, and some amino acids. Finally, cobalamin has a key role in the metabolism of folic acid.

Ascorbic acid is involved in collagen synthesis through its role as a reversible reducing agent, whereas retinol is necessary for normal night vision. a-tocopherol is the main antioxidant in biological membranes and vitamin K is a coenzyme for the posttranslational carboxylation of glutamate residues that ultimately influence the coagulation cascade. Folic acid is required for DNA synthesis, and copper functions as a cofactor in several physiologically important enzymes, such as lysyl oxidase, elastase, ceruloplasmin, and superoxide dismutase, as does zinc.

The DRIs were established by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, as an expansion of the periodic RDA reports. Most studies examining vitamin status in

children and adults with CKD occurred before the release of the DRI and hence report intake relative to the earlier RDA. The DRIs apply to the apparently healthy general population and are based on nutrient balance studies, biochemical measurement of tissue saturation or molecular function, and extrapolation from animal studies. Unfortunately, only limited data exist about the vitamin needs for infants and children, and there is no assurance that meeting the DRI will meet the needs of patients with kidney disease.

4.2: It is suggested that supplementation of vitamins and trace elements be provided to children with CKD stages 2–5 if dietary intake alone does not meet 100% of the DRI or if clinical evidence of a deficiency, possibly confirmed by low blood levels of the vitamin or trace element, is present. (C)

4.3: It is suggested that children with CKD stage 5D receive a water-soluble vitamin supplement. (C)

Children with CKD and those on dialysis therapy are at risk of alterations in vitamin and trace element levels or function as a result of decreased intake secondary to anorexia or dietary restrictions, increased degradation or clearance from blood, loss per dialysis, or interference with absorption, excretion, or metabolism (Tables 22.12 and 22.13).

Although limited, most data about the subject are derived from studies of adult populations. Whereas studies conducted in children receiving dialysis have documented dietary intake of most water-soluble vitamins, zinc, and copper that has been less than the RDA, the combination of dietary intake and supplemental intake has routinely met or exceeded the RDA [300–303]. In large part, this is due to the rarity of a vitamin and mineral supplement specifically formulated for infants and children on dialysis therapy and the resultant need to use one of the proprietary renal supplements available [304–306]. Caution should be exercised when using these supplements to not exceed the UL for the contents of the preparation when the intake of diet and supplement is combined. In older children and adolescents, daily vitamin supplementation is feasible without providing excessive vitamin intake. For smaller dosing in infants and toddlers, less frequent dosing (e.g., every 2–3 days) or partial dosing (e.g., half tablet) may be required if a liquid product or easily divisible tablet is not available. Children with healthy appetites for a variety of nutritious foods and children receiving the majority or all of their energy requirements from adult renal formulas generally meet 100% of the DRI for vitamins and trace elements and may not require vitamin supplementation.

Water-Soluble Vitamins

Thiamin (Vitamin B1)

Adult patients with CKD ingesting a low-protein diet have demonstrated borderline low thiamin levels [307]. In one study of children receiving dialysis, the spontaneous dietary intake was below the RDA in 28 of 30 patients [301]. Whereas a substantial quantity of thiamin is removed by HD, little appears to be lost by the peritoneal route in patients receiving chronic PD (CPD) [308, 309]. In most cases, the combination of dietary intake and daily supplement to equal the DRI will prevent deficiency. Thiamin stores can be assessed indirectly by means of erythrocyte transketolase activity or directly by means of high-performance liquid chromatography (HPLC) [310–312].

Riboflavin (Vitamin B2)

A low-protein diet may contain inadequate quantities of riboflavin [312], and both Pereira et al. [301] and Kriley and Warady [300] have documented spontaneous intake of riboflavin less than the RDA in children receiving dialysis. However, riboflavin deficiency is uncommon in patients being treated with HD or CPD and who receive a combined diet/supplement intake that meets or exceeds the DRI. Erythrocyte glutathione reductase activity is used to evaluate riboflavin status [312].

Niacin (Vitamin B3)

There are limited data about the niacin status of patients with CKD, with or without the use of dialysis. The metabolic clearance of niacin is

Table 22.12 Physiological effects and sources of vitamins

Name	Effects of deficiency	Effects of excess	Food sources
Biotin	Seborrheic dermatitis, anorexia, nausea, pallor, alopecia, myalgias, paresthesias	Unknown	Liver, egg yolk, soybeans, milk, meat
Cyanocobalamin (vitamin B_{12})	Pernicious anemia, neurologic deterioration, methyl-malonic acidemia	Unknown	Animal foods only: meat, fish, poultry, cheese, milk, eggs, vitamin B_{12} fortified soy milk
Folacin group of compounds	Megaloblastic anemia, impaired cellular immunity, irritability, paranoid behavior, neural tube defects in fetus of pregnant women	Masking of B_{12} deficiency symptoms in patients with pernicious anemia not receiving cyanocobalamin	Yeast, liver leafy green vegetables, oranges, cantaloupe, seeds, fortified breads and cereal (grains)
Niacin (vitamin B_3)	Pellagra, dementia, diarrhea, dermatitis	Flushing pruritis, liver abnormalities, hyperuricemia, decreased LDL and increased HDL cholesterol	Milk, eggs, poultry, meat, fish, whole grains, enriched cereal and grains
Pantothenic acid	Observed only with use of antagonists; depression, fatigue, muscle weakness, hypotension, abdominal pain	Unknown	Organ meats, yeast, egg yolk, fresh vegetables, whole grains, legumes
Pyridoxine (vitamin B_6)	Irritability, depression, dermatitis, glossitis, cheilosis, peripheral neuritis; in infants, irritability, convulsions, microcytic anemia	Neuropathy, photosensitivity	Liver, meat, whole grains, legumes, potatoes
Riboflavin (vitamin B_2)	Photophobia, cheilosis, glossitis, corneal vascularization, poor growth	Unknown	Meat, dairy products, green vegetables, whole grains, enriched breads and cereals
Thiamin (vitamin B_1)	Beriberi: neuritis, edema cardiac failure, hoarseness, anorexia, restlessness, aphonia	Unknown	Enriched cereals and breads, lean pork, whole grains, legumes, in small amounts in most nutritious foods
Ascorbic acid (vitamin C)	Osmotic diarrhea, bleeding gums, perifollicular hemorrhage, frank scurvy	Massive doses predispose to kidney stones, nausea, abdominal pain, rebound scurvy when massive doses stopped	Papaya, citrus fruits, tomatoes, cabbage, potatoes, cantaloupe, strawberries
Retinol (vitamin A)	Night blindness, xerophthalmia, keratomalacia, poor bone growth, impaired resistance to infection, follicular hyperkeratosis	Hyperostosis, hepatomegaly, hepatic fibrosis, alopecia, increased cerebrospinal fluid pressure, hypercalcemia	Fortified milk, liver, egg, cheese, yellow fruits and vegetables (carotenoid precursors)
Vitamin E	Hemolytic anemia in premature infants; fat malabsorption causes deficiency; hyporeflexia, and spinocerebellar and retinal degeneration	Bleeding, impaired leukocyte function	Sardines, green and leafy vegetables, vegetable oils, wheat germ, whole grains, butter, liver, egg yolk
Vitamin K	Primary deficiency rare; hemorrhagic manifestations, possible effect on bone mineral density	Water-soluble analogs only: hyperbilirubinemia, hemolysis	Cow milk, green leafy vegetables, pork, liver

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Table 22.13 Physiological effects and sources of trace elements

Name	Effects of deficiency	Effects of excess	Food sources
Zinc	Anorexia, hypogeusia, retarded growth, delayed sexual maturation, impaired wound healing, skin lesions	Few toxic effects; may aggravate marginal copper deficiency	Oysters, liver, meat, cheese, legumes, whole grains
Selenium	Cardiomyopathy, anemia, myositis	Irritation of mucous membranes, pallor, irritability, indigestion	Seafood, meat, whole grains
Copper	Sideroblastic anemia, retarded growth, osteoporosis, neutropenia, decreased pigmentation	Few toxic effects; Wilson disease, liver dysfunction	Shellfish, meat, legumes, nuts, cheese

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rapid, and thus it is believed that losses into dialysate are likely to be low. Prior studies have demonstrated the intake of niacin to be less than or equivalent to the RDA in patients prescribed a low-protein diet [314]. Whereas Pereira et al. [301] found the spontaneous intake of niacin to be less than the RDA in 27 of 30 children receiving dialysis, the combined dietary and supplement intake exceeded the RDA in all cases. Thus, it is recommended that the DRI for niacin be provided per diet and/or supplement.

Pantothenic Acid (Vitamin B_5)

There are few data available about the status of pantothenic acid in adult patients with CKD or those receiving dialysis, and no data are available for children. However, the vitamin is removed by HD, and normal, low, and high levels have been found in adult dialysis patients [315–317]. Accordingly, patients on HD and CPD therapy likely should receive 100% of the DRI for this vitamin. Pantothenic acid levels are measured by means of radioimmunoassay.

Pyridoxine (Vitamin B_6)

Low pyridoxine intake has been documented in a number of adult surveys of dialysis patients. In children, low intake of pyridoxine in children with CKD was reported by Foreman et al. [9]. Stockberger et al. [318] found intake to be lower than 59% of the RDA in 67% of children receiving CPD, and Pereira et al. [301] noted intake less than the RDA in 26 of 30 pediatric dialysis patients. In a study of infants receiving CPD, Warady et al. [303] documented dietary pyridoxine intake of only 60% RDA. There are also a host of medicines that can interfere with pyridoxine (and folic acid) metabolism [308].

Low blood levels (measured as plasma pyridoxal-5-phosphate by means of HPLC) have been documented in HD and CPD patients, and dialysis removal of the nutrient likely contributes to the deficiency. A daily pyridoxine-HCl supplement of 10 mg has been recommended for adult HD and CPD patients because this is the lowest dose that has been proved to correct pyridoxine deficiency. Lower supplemental doses, in addition to that provided by diet, likely would be sufficient in infants and young children based on the marked increase in blood level that has occurred with a 10-mg supplement in this population [300]. Supplements that equate to the RDA have previously been recommended [302, 319]. Functional tests (e.g., erythrocyte oxaloacetate transaminase) have been used to assess vitamin B6 deficiency. As noted, direct measurement of total pyridoxine by means of HPLC also can be performed.

Biotin (Vitamin B_8)

The intake of biotin has been estimated to be less than the RDA in adult patients with CKD prescribed with a low-protein diet [316]. In addition, intestinal absorption of biotin may be compromised in patients with CKD. The impact of HD on biotin status is poorly understood because both high and low blood levels have been reported [320, 321]. Although there is no information

regarding the influence of CPD on biotin losses and there is no information at all from children with kidney disorders, intake equal to the DRI should be provided per diet and/or supplement. Plasma biotin is measured by using microbiological assays.

Folic Acid (Vitamin B_9)

Litwin et al. [321a] documented normal folic acid levels in 18 children with CKD and Pereira et al. [301] found the dietary intake of folic acid to be greater than the RDA in 21 of 30 pediatric dialysis patients. Low folic acid levels have been reported in adult patients receiving CPD, with an average dialysis loss of 107 µg/d in one study [322, 323]. Folic acid status (red blood cell and plasma) may be compromised by inhibitors of folic acid absorption. Folic acid (along with vitamins B_6 and B_{12}) also has a key role in the handling of plasma homocysteine. Whereas some data have suggested that increased plasma homocysteine levels are a risk factor for CVD, other more recent studies have suggested otherwise [324, 325]. Studies conducted in children have all demonstrated lowering of the plasma homocysteine level (the normal plasma concentration of homocysteine is ~5–10 µmol/L) following the provision of folic acid [326–329]. Thus, most children with CKD and those on dialysis therapy should receive the DRI, whereas adults are prescribed 1.0 mg/d [330, 331]. If lowering plasma homocysteine level is the clinical goal, children with increased plasma homocysteine levels probably should receive 2.5–5.0 mg/d of folic acid [305, 310–313, 315, 317]. However, in dialysis patients, administration of folate and vitamins B_6 and B_{12} has been reported to lower, but not normalize, plasma homocysteine levels [332, 333]. Red blood cell folate levels are most indicative of body stores [334]. The reduced form of folic acid, tetrahydrofolate, may be measured by using a radioimmunologic technique.

Cobalamin (Vitamin B_{12})

Most adult and pediatric patients with CKD and dialysis patients have been reported to have normal cobalamin levels, regardless of whether they receive a supplement [300, 303, 309, 322, 323]. Dietary intake also appears to meet or exceed the DRI in most, but not all, dialysis patients [300, 301, 303, 335]. Serum vitamin B_{12} levels can be determined by using radioassay methods.

Ascorbic Acid (Vitamin C)

Decreased vitamin C levels have been reported in patients with CKD, as well as those receiving HD and CPD [335–337]. The low levels seen in dialysis patients are the result of low intake (e.g., restricted intake of fruits) and dialysis losses [301, 322, 335–337]. In children, Pereira et al. [301] found that 24 of 30 children received less than the RDA by diet alone. Warady et al. [303] reported a negative mass transfer of 32 mg/d in children receiving APD, an amount compensated for by oral supplementation. However, in a study of infants receiving APD, Warady et al. [303] reported dietary intake to be 140% of RDA, increasing to 180% of RDA with the addition of a 15-mg/d supplement. Excessive vitamin C intake (e.g., 0.5–1 g/d in adults) can result in increased oxalate concentrations in plasma and soft tissues [338, 339]. Thus, recommended combined dietary and supplement intake should not greatly exceed the DRI, with caution exercised when providing supplementation. Plasma ascorbic acid levels reflect dietary intake, and leukocytes levels estimate the body pool.

Fat-Soluble Vitamins

Retinol (Vitamin A)

Vitamin A is not removed by dialysis, and elevated serum levels are present in patients with CKD and on dialysis therapy without supplementation [300, 302, 303, 309]. Whereas retinol-binding protein (the transport protein for vitamin A) is catabolized in the renal tubules in individuals with normal kidney function, both vitamin A and retinol-binding protein accumulate when the GFR is reduced and there is impaired renal tubular activity [340, 341]. Kriley and Warady [300] documented serum vitamin A levels in pediatric dialysis patients without supplements that were threefold greater than control patients. Because the risk of developing vitamin A toxicity is high when supplements

with vitamin A are provided, total intake of vitamin A should be limited to the DRI, with supplementation rarely recommended and limited to those with very low dietary intake. Plasma vitamin A levels are measured by means of HPLC.

Vitamin K

There is no need for an intake of vitamin K greater than the DRI unless the patient is eating poorly and receiving long-term antibiotic therapy [309, 342, 343]. Plasma vitamin K levels are measured by means of liquid chromatography.

α-Tocopherol (Vitamin E)

Plasma vitamin E levels in patients receiving HD have been reported as low, normal, and high [344–346]. No differences in levels were found comparing predialysis and postdialysis samples, and no α-tocopherol was found in dialysis effluent [347, 348]. Studies of CPD patients have also reported both low and high levels of α-tocopherol [335, 349, 350]. Nevertheless, because of its ability to alleviate oxidative stress in patients at risk of CVD, patients with CKD and dialysis patients (aged <9 years) should receive the DRI of vitamin E [351, 352]. Serum vitamin E levels are measured by means of HPLC.

Trace Elements

Copper

Dietary intake less than the DRI has been noted for copper in children receiving CPD [353]. Although copper excess is associated most commonly with CKD, low serum copper and ceruloplasmin levels also have been reported in children receiving HD [303]. Intake should be monitored every 4–6 months because supplementation to the DRI may be required in patients with particularly low dietary intake. Assessment of serum copper levels may be beneficial when clinical signs of overload or deficiency are present.

Selenium

Although selenium is normally excreted by the kidney and not removed by dialysis, low serum levels occur in patients with CKD or those receiving maintenance HD [337, 354]. The selenium content of food is dependent on the selenium content of soil on which crops have grown or animals have grazed [309]. Selenium-dependent glutathione peroxidase activity in the blood, an integral component of the antioxidant defense, has also been found to be lower in patients with CKD than in healthy subjects, and the reduction worsens with increasing severity of disease. Supplementation of selenium in patients with CKD has resulted in a minimal increase in selenium-dependent glutathione peroxidase activity in patients with CKD, but not dialysis patients. Whereas routine supplementation is not recommended, patients should receive a daily dietary intake that meets the DRI.

Zinc

Low serum zinc levels result from removal by dialysis and poor intake. Intake less than the RDA has been documented in children receiving CPD [353]. Children and adults should receive the DRI for zinc, with supplementation reserved for treatment of clinical manifestations of zinc deficiency after laboratory confirmation.

Recommendation 5: Bone Mineral and Vitamin D Requirements and Therapy

5.1: Calcium

5.1.1 In children with CKD stages 2–5 and 5D, it is suggested that the total oral and/or enteral calcium intake from nutritional sources and phosphate binders be in the range of 100–200% of the DRI for calcium for age. (C)

Adequate dietary calcium intake during childhood is necessary for skeletal development, including acquisition of an optimal peak bone mass during puberty [355]. Both insufficient and excessive oral and/or enteral calcium supply may occur in children with CKD. Intestinal calcium absorption is increasingly impaired in those with CKD as endogenous production of calcitriol (1,25-dihydroxyvitamin D; 1,25[OH]$_2$D) decreases, but is readily stimulated by vitamin D

Table 22.14 Recommended calcium intake for children with CKD stages 2–5 and 5D

Age	DRI	Upper limit (for healthy children)	Upper limit for CKD stages 2–5, 5D (dietary + phosphate binders[a])
0–6 months	210	ND	≤420
7–12 months	270	ND	≤540
1–3 years	500	2,500	≤1,000
4–8 years	800	2,500	≤1,600
9–18 years	1,300	2,500	≤2,500

Abbreviation: ND, not determined
[a]Determined as 200% of the DRI, to a maximum of 2,500 mg elemental calcium

therapy. Spontaneous calcium intake frequently is insufficient in adolescent patients in whom acceptance of high-calcium foods is limited and in children on phosphorus-restricted diets. The homeostatic mechanisms for regulating calcium balance are impaired most severely in children with CKD stage 5 and on dialysis therapy. Calcium absorption cannot be adjusted because of the kidney's inability to produce $1,25(OH)_2D$. Also, vitamin D receptor expression may be reduced.

However, therapy with high doses of active vitamin D sterols (e.g., calcitriol, alfacalcidol) may boost intestinal calcium absorption. Oral and/or enteral treatment with calcium-containing phosphate binders and absorption from dialysis fluids with supraphysiological calcium content markedly enhance the calcium load. Increasing evidence suggests that the resulting strongly positive calcium balance is a major contributor to soft-tissue calcifications. Although it is impossible to accurately assess the actual absorption of calcium derived from diet and binders in this setting, it appears reasonable to limit total oral and/or enteral calcium ingestion.

Intake of 100% of the DRI for calcium is a reasonable starting point for children with CKD (Table 22.14). Although the safe limit of dietary calcium intake in children of different ages has not been defined by study evidence, it appears logical to scale maximal calcium intake relative to the age-specific DRI. The safe UL of dietary calcium intake in healthy individuals older than 1 year is 2,500 mg/d. For adults and children 9 years and older, this is approximately two times the DRI.

A number of measures are effective to improve low oral and/or enteral calcium intake and absorption: increased consumption of calcium-rich and/or calcium-fortified foods or tube feedings, supplementation with calcium-containing pharmacological agents between meals or bolus tube feedings, use of calcium-containing phosphorus binders for managing hyperphosphatemia, and supplementation with vitamin D.

If spontaneous intestinal calcium absorption is low, as typically observed in early stages of CKD, vitamin D should be supplemented to augment plasma $1,25(OH)_2D$ synthesis and maximize calcium absorption.

If plasma calcium levels and urinary calcium excretion remain low and dietary assessment suggests inadequate calcium intake, consumption of foods with high endogenous calcium content (e.g., milk, yogurt, cheese, Chinese cabbage, kale, and broccoli) and calcium-fortified food products should be encouraged. The bioavailability of calcium from milk and dairy products generally is high; however, the high phosphorus content of these products must be considered in children who require dietary phosphorus restriction. Some foods high in phytates, such as bran cereal, may have poor bioavailability of calcium [356–358]. Fortified products seem to provide calcium bioavailability comparable to milk [359–361].

If dietary intake alone does not meet the DRI, use of oral and/or enteral calcium supplements should be considered (Table 22.15). Salts of calcium – gluconate (9% elemental calcium), lactate (13% elemental calcium), acetate (25% elemental calcium), or carbonate (40% elemental calcium) – are usually well tolerated by children of all ages. Calcium-containing phosphate binders can be applied easily and effectively in infants. Conversely, calcium chloride should be avoided as a supplement in patients with CKD due to the possible development of metabolic acidosis. Calcium citrate should not be given because citrate augments

Table 22.15 Calcium content of common calcium-based binders or supplements

Compound	Brand name	Compound content (mg)	% calcium	Elemental calcium (mg)	No. of pills to equal ~1,500 mg elemental calcium
Calcium acetate	PhosLo™	667	25%	167	9
Calcium carbonate	Children's Mylanta	400	40%	160	9
	Chooz™ (Gum)	500	40%	200	7.5
	TUMS™				
	TUMS EX™ (extra strength)	750	40%	300	5
	TUMS Ultra™	1,000	40%	400	3.75
	LiquiCal	1,200	40%	480	3
	CalciChew™	1,250	40%	500	3
	CalciMix™				
	Oscal 500™				
	TUMS 500™				
	Caltrate 600™	1,500	40%	600	2.5
	NephroCalci™				
Calcium citrate	Citracal™	Not recommended			
Calcium acetate + magnesium carbonate	MagneBind™ 200	200 magnesium carbonate		(Magnesium = 57 mg)	13
		450 calcium acetate		113 mg	
	MagneBind™	300 magnesium carbonate		(Magnesium = 85 mg)	20
		300 calcium acetate		76 mg	

Adapted with permission [121]

aluminum absorption [362]. Maximal absorption of calcium supplements is achieved when calcium salts are taken between meals and separate from iron supplements [363, 364].

As CKD progresses, increasing phosphate retention creates the need for oral and/or enteral phosphate-binder therapy. Calcium carbonate and calcium acetate are effective phosphate binders in children and should be used as first-choice therapy in patients with low dietary calcium intake [365–370]. Calcium carbonate and calcium acetate easily can be crushed, dissolved in formula milk, and administered through enteral tubes. However, hypercalcemic episodes occur in approximately 25% of patients, depending on the type and dose of the calcium-containing binder and the coadministration of active vitamin D sterols (e.g., calcitriol and alfacalcidol). Calcium acetate has a higher specific phosphorus-binding efficacy than calcium carbonate [371] and causes fewer hypercalcemic episodes than calcium carbonate at a given phosphate-binder dose [372–374]. Hence, calcium carbonate should be preferred in children with insufficient dietary calcium intake and no need for active vitamin D therapy, whereas calcium acetate is the preferable phosphate binder in children considered at moderate risk of calcium overload. In contrast to the use of calcium salts as supplements, calcium-containing phosphate binders should be taken with meals to obtain maximal phosphorus-binding efficacy and minimal intestinal absorption of free calcium. For calcium acetate, fecal excretion of phosphate has been shown to be higher when the phosphate binder is given with meals [375].

The use of any calcium-containing phosphate binder should be limited by the maximally acceptable total oral and enteral calcium intake. For example, in a dialyzed 8-year-old with a typical spontaneous dietary calcium intake of 700 mg/d,

a maximum of 900 mg of elemental calcium ingested as phosphate binders should be administered to stay within the recommended maximal total calcium intake of 1,600 mg (200% of the DRI). This would correspond to a prescription of four to five tablets containing 500 mg of calcium carbonate (200 mg of elemental calcium) or five tablets containing 667 mg of calcium acetate (167 mg of elemental calcium) per day. If dietary calcium intake is higher, calcium-containing phosphate-binder intake and/or dialysate calcium concentration need to be reduced, and the use of calcium-free phosphate binders should be considered. In a 1-year-old anuric child with an upper limit of 750 mg/d of calcium intake, a maximum of 875 mg of calcium carbonate (i.e., 350 mg of elemental calcium) per day would be acceptable if dietary calcium intake is 400 mg.

These model calculations should be viewed as a general principle of dietary calcium prescription and may not always be applicable in clinical practice. Also, they do not consider confounding factors, such as treatment with active vitamin D sterols, which has been found to increase calcium absorption (reported to be 35–40% in those with CKD [377]) by 30% [378]. The dosage of calcium-based phosphate binders should be reduced in dialysis patients with low PTH levels because these patients commonly have low-turnover bone disease with a reduced capacity of the bone to incorporate a calcium load [379].

To avoid the critical accumulation of calcium, oligoanuric children on dialysis therapy may require a further reduction in total oral and enteral calcium intake from nutritional sources and phosphate binders. In those with CKD stage 5, urinary calcium excretion – the major physiological elimination pathway – is severely impaired or absent. An anuric child receiving HD or PD with a neutral dialysate calcium concentration is incapable of disposing of any calcium exceeding the amounts required for bone formation by any mechanism other than soft-tissue precipitation. Hence, the upper limit of dietary calcium intake considered safe in healthy subjects may not be applicable to oligoanuric patients. In these children, further limitation of oral and enteral calcium intake from both dietary sources and calcium-containing phosphate binders should be considered, although evidence to support this further restriction is not yet available. Modification to decrease the calcium concentration in the dialysate is an additional therapeutic option to be considered in both HD and PD patients. Calcium balance during PD usually is negative with the use of 2.5 mEq/L calcium dialysate and positive with 3.0–3.5 mEq/L calcium dialysate [380–384]. Calcium balance during HD may be neutral or negative with the use of a 2.5 mEq/L calcium dialysate [385, 386]. Dietary and pharmacological interventions should aim at avoiding both hypo- and hypercalcemic episodes.

5.2: Vitamin D

5.2.1 In children with CKD stages 2–5 and 5D, it is suggested that serum 25-hydroxyvitamin D levels be measured once per year. (C)

5.2.2 If the serum level of 25-hydroxyvitamin D is less than 30 ng/mL (75 nmol/L), supplementation with vitamin D_2 (ergocalciferol) or vitamin D3 (cholecalciferol) is suggested. (C)

5.2.3 In the repletion phase, it is suggested that serum levels of corrected total calcium and phosphorus be measured at 1 month following initiation or change in dose of vitamin D and at least every 3 months thereafter. (C)

5.2.4 When patients are replete with vitamin D, it is suggested to supplement vitamin D continuously and to monitor serum levels of 25-hydroxyvitamin D yearly. (C)

A decrease in serum calcidol (25-hydroxyvitamin D; 25[OH]D), the substrate for renal synthesis of $1,25(OH)_2D$, induces secondary hyperparathyroidism in individuals with normal kidney function [387, 388] and may aggravate secondary hyperparathyroidism in patients with CKD [389, 390]. The critical lower limit of the serum vitamin D concentration is not well defined. Serum concentrations show considerable seasonal and regional variation. Although severe manifestations of vitamin D deficiency, such as osteomalacia and hypocalcemia, are seen only with 25(OH)D concentrations less than 5 ng/mL

(<12 nmol/L), levels less than 30 ng/mL (75 nmol/L) are suggestive of vitamin D "insufficiency" as manifested by hyperparathyroidism and increased risk of bone demineralization and hip fractures [391, 392]. Supplementation with vitamin D, 800 IU/d, along with a modest dietary calcium supplement, reduced the hip fracture rate by 43% in a double-blinded placebo-controlled trial in elderly women [393].

Vitamin D insufficiency is observed in a large proportion (typically 80–90%) of patients with CKD [394, 395]. In a population-based study of patients hospitalized in New England, CKD was a major risk factor for low serum 25(OH)D levels [396]. Vitamin D insufficiency may be more relevant in those with CKD than in healthy individuals because, in contrast to healthy subjects in whom 25(OH)D is not rate limiting for calcitriol synthesis [397], $1,25(OH)_2D$ levels correlated with 25(OH)D levels in patients with CKD [394, 395]. This probably is explained by impaired compensatory upregulation of renal 1-α-hydroxylase and an increased contribution of strictly substrate-dependent extrarenal calcitriol synthesis in patients with impaired kidney function [398, 399].

Reasons for the high prevalence of low vitamin D levels in patients with CKD include their sedentary lifestyle with reduced exposure to sunlight, limited ingestion of foods rich in vitamin D (cod liver oil, fish, liver, egg yolk, fortified milk, and fortified margarine), reduced endogenous synthesis of vitamin D_3 in the skin in patients with uremia [287], and urinary losses of 25(OH)D and vitamin D–binding protein in nephrotic patients [400].

Even in patients with CKD stage 5D with little or no residual renal 1-α-hydroxylase activity, vitamin D deficiency is associated with more marked secondary hyperparathyroidism [401]. In anephric individuals, high doses of ergocalciferol (D_2) or alfacalcidol (25[401]D) can increase serum calcitriol levels, pointing to a significant role of extrarenal 1-α-hydroxylase activity [402–404]. However, the role of 25(OH)D deficiency and its correction in patients on maintenance dialysis (MD) therapy is controversial because the ability to generate adequate levels of $1,25(OH)_2D$ is markedly reduced or absent. However, 25(OH)D has been claimed to exert specific effects on cell metabolism. 25(OH)D, but not $1,25(OH)_2D$, improved muscular function and phosphate content [405].

In patients with CKD, nutritional vitamin D deficiency and insufficiency can be prevented or corrected by supplementation with vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol). Cholecalciferol appears to have higher bioefficacy than ergocalciferol, although long-term comparative trials are lacking in humans [406, 407]. The DRI for prevention of vitamin D deficiency in children and adolescents is 200 IU [376]. This value, published more than a decade ago, is 50% lower than the RDA that it replaced and, given increasing reports of vitamin D insufficiency in the general public, is controversial. The required daily vitamin D intake for patients of any age with CKD is unknown. In individuals with normal kidney function, the recommended upper limit of vitamin D is 1,000 IU/d in neonates and infants younger than 12 months and 2,000 IU/d for all other ages [376]. The equivalent of this dose can be achieved by administering one capsule (50,000 IU) once a month [408]. Daily doses of 10,000 IU of ergocalciferol have been administered in adult patients with advanced CKD for periods longer than 1 year with no evidence of vitamin D overload or renal toxicity [409, 410]. Whereas signs of vitamin D intoxication would be the exception at doses recommended in this guideline, the development of hypercalcemia would be the evidence of excessive dosing.

We recommend treating vitamin D deficiency and insufficiency, with the specific dosing regimen dependent on the severity of the disorder (Table 22.16). Smaller doses of vitamin D probably are sufficient in children younger than 1 year. When repletion (i.e., serum 25[OH]D ≥30 ng/mL) has been accomplished, vitamin D homeostasis should be maintained by once-daily administration of 200–1,000 IU.

Calcitriol, alfacalcidol, or other synthetic active vitamin D analogs (e.g., doxercalciferol and paracalcitol) should not be used to treat 25(OH)D deficiency.

Table 22.16 Recommended supplementation for vitamin D deficiency/insufficiency in children with CKD

Serum 25 (OH)D (ng/mL)	Definition	Ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) dosing	Duration (months)
<5	Severe vitamin D deficiency	8,000 IU/d orally or enterally × 4 wk or (50,000 IU/wk × 4 wk); then 4,000 IU/d or (50,000 IU twice per mo for 2 mo) × 2 mo	3
5–15	Mild vitamin D deficiency	4,000 IU/d orally or enterally × 12 wk or (50,000 IU every other wk, for 12 wk)	3
16–30	Vitamin D insufficiency	2,000 IU daily or (50,000 IU every 4 wk)	3

Note: Conversion factor for serum 25(OH)D: ng/mL × 2.496 = nmol/L
Adapted with permission [121]

5.3: Phosphorus

5.3.1 In children with CKD stages 3–5 and 5D, reducing dietary phosphorus intake to 100% of the DRI for age is suggested when the serum PTH concentration is above the target range for CKD stage and the serum phosphorus concentration is within the normal reference range for age. (C)

5.3.2 In children with CKD stages 3–5 and 5D, reducing dietary phosphorus intake to 80% of the DRI for age is suggested when the serum PTH concentration is above the target range for CKD stage and the serum phosphorus concentration exceeds the normal reference range for age. (C)

5.3.3 After initiation of dietary phosphorus restriction, it is suggested that serum phosphorus concentration be monitored at least every 3 months in children with CKD stages 3–4 and monthly in children with CKD stages 5 and 5D. (C) In all CKD stages, it is suggested to avoid serum phosphorus concentrations both above and below the normal reference range for age. (C)

Epidemiological studies of adult patients with CKD have demonstrated a positive association, albeit not a causal link, between hyperphosphatemia and morbidity and mortality independent of CKD stage. Although the benefits of lowering serum phosphorus level on patient-level clinical outcomes have not been demonstrated in prospective interventional studies, it is generally accepted and biologically plausible that increased serum phosphorus levels be avoided in patients with CKD stages 3–5 and 5D in an effort to control CKD-associated bone disease and CVD. Associations between hyperphosphatemia and CKD-associated vasculopathy have also been observed in children with CKD stage 5 [282, 411].

Although serum phosphorus levels usually are not increased in the early stages of progressive CKD [363, 412–414], the dietary phosphorus load is an important determinant of the severity of hyperparathyroidism, even in those with mild renal insufficiency. In children and adults with CKD stage 3, dietary phosphorus restriction decreases increased PTH levels and increases 1,25(OH)2D production, whereas dietary phosphorus intakes approximately twice the DRI for age aggravate hyperparathyroidism despite little or no change in serum phosphorus levels [413, 415, 416]. Also, bone biopsy studies showed marked improvement in bone resorption and defects in bone mineralization by using dietary phosphate restriction [415]. In four studies in children, dietary phosphate restriction did not lead to impaired statural growth [256, 417–419]. Studies in adult and pediatric patients provided no evidence for any adverse effect of dietary phosphate restriction on nutritional status [256, 257, 420–423]. However, severe restriction of dietary phosphorus in children with moderate and severe CKD leading to subnormal serum phosphorus levels was associated with histological findings of worsening osteomalacia [415].

Table 22.17 Recommended maximum oral and/or enteral phosphorus intake for children with CKD

Recommended phosphorus intake (mg/d)			
Age	DRI (mg/d)	High PTH and normal phosphorus[a]	High PTH and high phosphorus[b]
0–6 months	100	≤100	≤80
7–12 months	275	≤275	≤220
1–3 years	460	≤460	≤370
4–8 years	500	≤500	≤400
9–18 years	1,250	≤1,250	≤1,000

Source: Health Canada: http://www.hc-sc-gc.ca/fn-an/alt_formats/hpfp-dgpsa/pdf/nutrition/dri_tables-eng.pdg. Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2008
[a]≤100% of the DRI
[b]≤80% of the DRI

Table 22.18 Age-specific normal ranges of blood ionized calcium, total calcium and phosphorus

Age	Ionized calcium (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)
0–5 months	1.22–1.40	8.7–11.3	5.2–8.4
6–12 months	1.20–1.40	8.7–11.0	5.0–7.8
1–5 years	1.22–1.32	9.4–10.8	4.5–6.5
6–12 years	1.15–1.32	9.4–10.3	3.6–5.8
13–20 years	1.12–1.30	8.8–10.2	2.3–4.5

Conversion factor for calcium and ionized calcium: mg/dL × 0.25 = mmol/L
Conversion factor for phosphorus: mg/dL × 0.323 = mmol/L

Hence, a solid body of evidence suggests that moderate dietary phosphate restriction is beneficial with respect to the prevention and treatment of hyperparathyroidism and safe with respect to growth, nutrition, and bone mineralization. We recommend limiting dietary phosphorus intake to 100% of the DRI (Table 22.17) in normophosphatemic patients (using/not using phosphorus-lowering medications) if serum PTH concentration exceeds the target range. Although similar PTH target ranges have been recommended by two expert work groups [121, 424], the optimal range is controversial and may be lower than previously believed [425]. In CKD stages 4 and 5, when serum phosphorus levels increase to greater than the target normal range for age (Table 22.18) and hyperparathyroidism is already established, phosphorus restriction to approximately 80% of the DRI is recommended.

Higher physiological serum concentrations of calcium and phosphorus are observed in healthy infants and young children, presumably reflecting the increased requirements of these minerals by the rapidly growing skeleton. Rickets due to phosphorus deficiency occurs in preterm infants fed insufficient amounts of phosphorus and in infants and children with hypophosphatemia due to inherited disorders of renal phosphate transport [426]. Hence, when dietary phosphorus is restricted to control hyperphosphatemia and secondary hyperparathyroidism in children with CKD, subnormal serum phosphorus values should be avoided (Table 22.18).

The dietary prescription should aim at minimizing phosphate intake while ensuring an adequate protein intake. To achieve this aim, protein sources with low specific phosphorus content should be prescribed (see Table 22.10, Recommendation 3). Most food sources exhibit good phosphate bioavailability with the exception of plant seeds (beans, peas, cereals, and nuts) that contain phosphate in phytic acid.

Milk and dairy products are a major source of dietary phosphorus. In young infants with CKD, phosphorus control can be achieved easily by using formulas with a low-phosphorus content.

It usually is feasible, and common clinical practice, to continue oral and/or enteral use of a low-phosphorus formula and delay the introduction of phosphorus-rich cow's milk until the age of 18–36 months.

Dietary phosphate restriction can be hindered by the inadvertent consumption of food containing phosphate additives, which can increase phosphorus intake up to twofold compared with unprocessed foods. This is a particular problem in patients with CKD who rely heavily on processed foods [427, 428]

Unfortunately, most available nutrient databases do not consider the impact of additives on total phosphorus content of foods. An exception is the USDA National Nutrient Database for Standard Reference, which lists more than 60 phosphate-containing food additives.

The aspects mentioned illustrate that dietary modification of phosphorus intake is a complex and challenging task. Multiple pitfalls, including nonadherence in older children and adolescents, may result in inefficient lowering of phosphorus intake; conversely, overrestriction may lead to signs of phosphate deficiency, particularly in young infants. Hence, involvement of an experienced pediatric dietitian is key to phosphorus management in children with CKD.

A recent randomized clinical trial assessed the efficacy of a low-phosphorus diet compared with additional treatment with different phosphate binders in adults with CKD stages 3–5. Coronary calcification increased in patients on the low-phosphorus diet alone, to a lesser extent in calcium carbonate-treated patients, and not at all in sevelamer-treated patients [429]. Notably, urinary phosphorus excretion did not decrease by the institution of the low-phosphorus diet alone and increased by 50% during the 2-year follow-up. These results highlight the difficulty of implementing and maintaining a phosphorus-restricted diet in clinical practice. Hence, dietary phosphate restriction should be considered an important, but not solitary, component in the management of uremic bone and vascular disease in association with vitamin D and phosphate-binder therapy and dialytic removal.

The link between hyperphosphatemia and patient mortality observed in adult studies [287, 430–432] and the associations between serum phosphorus level and surrogate markers of vascular morbidity in adult and pediatric patients with CKD [282, 433, 434] provide a rationale to lower serum phosphorus levels pharmacologically if dietary phosphorus restriction is insufficient to maintain normophosphatemia. The current goal to target normal phosphorus levels is different from the allowance for slightly higher phosphorus values within the KDOQI Pediatric Bone Guidelines [121]. Oral and enteral phosphate binders are effective in lowering serum phosphorus concentrations in children with CKD [365–371]. It should be noted that the association between bone and mineral metabolism disorders and cardiovascular risk and mortality are largely reported from either in vitro or retrospective cohort studies, which can prove association, but not cause and effect.

If total intestinal calcium load becomes excessive or hypercalcemia exists with the use of calcium-containing phosphate binders, these should be reduced in dose or replaced by calcium- and aluminum-free phosphate binders. The only calcium- and aluminum-free phosphate binder with proven efficacy and safety in children is sevelamer, which has been assessed in two randomized controlled clinical trials studying a total of 47 children. In one study, 29 hemodialyzed children were assigned to either sevelamer or calcium carbonate, and either calcitriol or doxercalciferol, as well. Although serum phosphorus levels were equally well controlled in the sevelamer and calcium-carbonate arms at the end of the 8-month study period, serum calcium and calcium-phosphorus ion product levels were significantly higher and hypercalcemia episodes were more frequent in the calcium-carbonate group, with no significant difference in serum PTH levels [435]. The second trial used a crossover design to compare sevelamer with calcium acetate in 18 children with CKD stages 3–4 or 5D during 8-week observation periods. Phosphorus and PTH control were similar with both treatments, whereas hypercalcemia occurred more frequently with calcium acetate. A decrease in LDL cholesterol levels by 34% and a greater incidence of metabolic acidosis were observed with sevelamer [436].

Sevelamer is a resin that, in aqueous solution, attains a gel-like consistency and cannot be applied through feeding tubes without a high risk of tube blockage. However, it is possible to pretreat breast milk [437], infant formula, and cow's milk [438] by dissolving sevelamer, waiting for precipitation, decanting, and feeding the supernatant of the processed fluid. This maneuver reduces phosphorus content by 80–90%.

Larger comparative trials in adults consistently observed lower serum calcium and higher PTH levels with sevelamer than with calcium-containing phosphate binders [256, 422, 426–429, 435–437, 439–441]. In adult patients with CKD stages 3–5 and 5D, randomized controlled trials have provided evidence that the use of sevelamer attenuates the progression of arterial calcifications compared with patients receiving calcium-based phosphate binders [429, 439–441].

Whereas neither cardiovascular nor all-cause mortality was reduced significantly by using sevelamer therapy in 1,068 patients completing the Dialysis Clinical Outcomes Revisited Study, the Renagel in New Dialysis Patients trial suggested a significant mortality reduction in incident dialysis patients receiving sevelamer for a median of 44 months [439, 440].

Lanthanum carbonate recently has become available as an alternative calcium- and aluminum-free binder with high affinity for phosphate and minimal intestinal absorption. In a randomized study in adult patients, lanthanum carbonate controlled plasma phosphate levels well and induced less adynamic bone disease than calcium carbonate [442]. However, no long-term data about the effect of lanthanum on the functions of liver and kidney and bone, in which lanthanum accumulates [443], and its safety profile in children are available.

It should be emphasized that any phosphate-binder therapy introduces a major pill burden. The need to swallow several large tablets or capsules with each meal is a major physical and psychological challenge to many patients that can seriously compromise long-term adherence to this and other medications. Hence, phosphate-binder therapy should be individualized realizing that in some patients lowering of serum phosphate levels into the normal range may not be possible or may lead to an unacceptable decrease in quality of life. In these cases, other options, such as intensified dialysis protocols, should be evaluated.

Recommendation 6: Fluid and Electrolyte Requirements and Therapy

6.1: Supplemental free water and sodium supplements should be considered for children with CKD stages 2–5 and 5D and polyuria to avoid chronic intravascular depletion and to promote optimal growth. (B)

The primary cause of CKD needs to be considered when initiating dietary modification of fluids and sodium. Although restriction of sodium and/or fluids is appropriate in children with CKD associated with sodium and water retention, the most common causes of CKD in children are associated with excessive loss of sodium and chloride. Infants and children with obstructive uropathy or renal dysplasia have polyuria, polydypsia, and difficulty conserving sodium chloride. These children develop a salt-wasting state and require salt supplementation [119]. In addition to its effect on extracellular volume, sodium depletion also adversely affects growth and nitrogen retention [445]. Sodium intake supports normal expansion of the ECF volume needed for muscle development and mineralization of bone [446]. Therefore, infants and children with polyuric salt-wasting forms of CKD who do not have their sodium and water losses corrected may experience vomiting, constipation, and significant growth retardation associated with chronic intravascular volume depletion and a negative sodium balance [111]. It is important to note that normal serum sodium levels do not rule out sodium depletion and the need for supplementation.

Individualized therapy can be accomplished by first prescribing at least the age-related DRI of sodium and chloride (Table 22.19) [119]. In two small cohort studies, infants with polyuric salt-wasting CKD stages 3–5 who were given

Table 22.19 DRI for healthy children for water, sodium, chloride, and potassium

	Total water[a] (L/d)		Sodium[b] (mg/d)		Chloride (mg/d)		Potassium (mg/d)	
Age	AI	Upper limit	AI	Upper limit	AI	Upper limit	AI	Upper limit
0–6 months	0.7	ND	120	ND	180	ND	400	ND
7–12 months	0.8	ND	370	ND	570	ND	700	ND
1–3 years	1.3	ND	1,000	1,500	1,500	2,300	3,000	ND
4–8 years	1.7	ND	1,200	1,900	1,900	2,900	3,800	ND
9–13 years	2.4	ND	1,500	2,200	2,300	3,400	4,500	ND
14–18 years	3.3	ND	1,500	2,300	2,300	3,600	4,700	ND

Abbreviation: ND, not determined
Sources: Health Canada: http://www.hc-sc-gc.ca/fn-an/alt_formats/hpfp-dgpsa/pdf/nutrition/dri_tables-eng.pdg. Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2008
[a]Total water includes drinking water, water in beverages, and water that is part of food
[b]Grams of sodium × 2.53 = grams of salt; 1 teaspoon of salt = 2,300 mg sodium

nutritional support with generous fluids and sodium supplements achieved better growth compared with published data for nonsupplemented infants with CKD. The dosage of sodium supplements used by the two studies varied between 2 and 4 mmol of sodium (Na)/100 mL formula added to 180–240 mL/kg/d of formula [111] and 1–5 mmol Na/kg body weight/d [120] and was adjusted according to blood biochemistry test results. The average dose used in the first study was Na, 3.2 ± 1.04 mmol/kg [111]. Nasogastric or gastrostomy tube feedings were used [111] or suggested for critical periods [120].

Sodium given as alkali therapy should be considered as part of the daily sodium allowance [119].

Home preparation of sodium chloride supplements using table salt generally is not recommended due to potential errors in formulation that could result in hypo- or hypernatremia [447].

6.2: Sodium supplements should be considered for all infants with CKD stage 5D on PD therapy. (B)

Infants on PD therapy are predisposed to substantial sodium losses, even when anuric. High ultrafiltration requirements per kilogram of body weight result in removal of significant amounts of sodium chloride. These losses cannot be replaced through the low sodium content of breast milk (160 mg/L or 7 mmol/L) or standard commercial infant formulas (160–185 mg/L or 7–8 mmol/L) [449]. Consequences of hyponatremia include cerebral edema and blindness; therefore, neutral sodium balance must be maintained. Therapy should be individualized based on clinical symptoms, including hypotension, hyponatremia, and/or abnormal serum chloride levels. Sodium balance measurements, determined from dietary and medication intake and dialysate effluent losses, should be considered every 6 months concurrent with the measurement of dialysis adequacy. More frequent measurement is indicated after significant changes to the dialysis prescription or clinical status.

6.3: Restriction of sodium intake should be considered for children with CKD stages 2–5 and 5D who have hypertension (systolic and/or diastolic blood pressure ≥95th percentile) or prehypertension (systolic and/or diastolic blood pressure ≥90th percentile and <95th percentile). (B)

When kidney function is impaired, ECF volume increases, edema occurs, and blood pressure increases. Hypertension is already common in the early stages of CKD, with 48–63% of children affected [444, 450]. More than 50% of children on dialysis therapy have uncontrolled hypertension [450, 451], and an additional 20% have controlled hypertension [63, 451–454]. Children with severe hypertension are at increased risk of hypertensive encephalopathy, seizures, cerebrovascular events, and congestive

heart failure [455]. Less severe hypertension can contribute to progression of CKD. Therefore, dietary modification is encouraged for children and adolescents who have blood pressures in the prehypertensive range, as well as those with hypertension [455].

A systematic review of pediatric clinical trials demonstrated that modest dietary sodium restriction reduces blood pressure in hypertensive children without CKD [456]. In dialysis patients, many observational and interventional studies of patients with CKD have shown that restricting sodium intake is an essential tool for volume and blood pressure control [457–459]. Aside from preventing acute complications of hypertension, optimal control of blood pressure reduces further kidney damage and modifies progression of disease.

The KDOQI Clinical Guidelines for Hypertension [444], CVD [220], and Dialysis Adequacy [63] are all in agreement that dietary sodium restriction is an important component of a comprehensive strategy for volume and blood pressure control in adults and children with CKD. The earliest recommendation from the Hypertension Guidelines was to limit daily sodium intake to less than 2,400 mg (<104 mmol) [444]. The more recent Cardiovascular and Adequacy Guidelines have lowered the recommendation to less than 2,000 mg (<87 mmol) of sodium per day [450, 459]. The most recent 2005 Dietary Guidelines for Americans older than 2 years [460] recommend that individuals with hypertension, blacks, and middle-aged and older adults aim to consume no more than 1,500 mg (65 mmol) of sodium per day. To provide more size-appropriate guidelines for infants and young children, based on a standard 60–70-kg adult, 1,500–2,400 mg/d of sodium would be the equivalent of sodium, 1–2 mmol/kg/d. This degree of restriction is reasonably consistent with the age-appropriate DRI for healthy children (Table 22.19).

The average daily intake of sodium in healthy children is far above recommended levels. In a national community health survey, 77% of children aged 1–3 years exceeded the recommended upper limit for sodium (1,500 mg/d), with a mean intake of 1,918 mg/d [461]. In children 4–8 years old, daily intake averaged 2,700 mg and 93% had consumed more than the recommended upper limit. For most of these children, adding salt at the table did not contribute to their high-sodium intakes because 69% of those aged 1–3 years and 52% of those aged 4–8 years "never" added salt to their food. Salt intakes of adolescents exceeded recommended upper limits by 27–79%; the intake of males was significantly higher than that of females.

Sodium occurring naturally in food accounts for only about 10% of total intake, whereas salt added at the table or while cooking provides another 5–10% of total intake [462]. The majority (75%) of sodium in the diet comes from salt added by manufacturers during processing [462] to enhance flavor, control the growth of bacteria, provide certain functional characteristics, or act as a preservative. By weight, salt is composed of 40% sodium and 60% chloride. One teaspoon of salt contains about 2,300 mg of sodium.

Reduction of sodium intake can be achieved by replacing processed and canned foods with fresh foods; reading food labels to identify less salty foods; reducing salt added to foods at the table; in cooking, substituting fresh herbs and spices to flavor foods; and eating fast foods less often. The nutrition facts panel on food labels lists sodium content as actual amount (mg) and percent of the recommended daily value (% DV). Foods containing less than 140 mg or 5% DV are considered low in sodium [460], and foods that have no more than 170–280 mg of sodium or 6–10% of the DV for sodium should be chosen. Salt substitutes, also referred to as light salts, typically replace all or some of the sodium with another mineral. Salt substitutes replacing Na chloride (NaCl) with potassium chloride (KCl) are contraindicated in children with hyperkalemia.

Certain medications (e.g., antacids, laxatives, and nonsteroidal anti-inflammatory drugs) can be a significant source of sodium. Kayexalate® (sodium polystyrene sulfonate) contains 100 mg (4.3 mmol) of sodium per 100 g of powder. Where available, non-sodium-containing potassium binders (e.g., calcium polystyrene sulfonate) should be used for children with severe hypertension and hyperkalemia.

Restriction of salt and fluid intake requires considerable patient motivation, which is often a problem in the adolescent population. The KDOQI Hypertension Guidelines recommend dietary education by a dietitian every 3 months [444]. Patients used to a high-sodium intake may lose their appetite and become malnourished if sodium restriction is instituted too abruptly and too strictly [63]. In these patients, sodium restriction should be introduced gradually to provide time for taste adjustment. By cutting back gradually, most patients find that they do not miss the salt.

6.4: Fluid intake should be restricted in children with CKD stages 3–5 and 5D who are oligoanuric to prevent the complications of fluid overload. (A)

Children with oliguria or anuria need to limit their fluid intake to avoid associated complications of altered fluid status, including hypertension. Fluid restriction for oligoanuric children on HD therapy is also indicated, and an interdialytic increase above their "dry" weight (≤5% of their dry weight) is expected and desirable. Severe restriction of food (and fluid) intake by children for the purpose of avoiding extra HD sessions fosters malnutrition and should be discouraged.

Daily fluid restriction = insensible fluid losses (Table 22.20) + urine output + amount to replace additional losses (e.g., vomiting, diarrhea, enterostomy output) − amount to be deficited.

To restrict fluid intake, children should be advised to reduce their intake of beverages, as well as foods that are liquid or semiliquid at room temperature (e.g., ice, soup, Jell-O, ice cream, yogurt, pudding, and gravy). This can be achieved by drinking only when thirsty, taking small amounts throughout the day using small cups or glasses, quenching thirst by sucking on crushed ice, eating cold fruit, chewing gum, gargling or using breath sprays/sheets, and avoiding high-sodium or very sweet foods. About 80% of an individual's total water intake comes from drinking water and beverages and the other 20% is derived from food [448]. Many fruits and vegetables contain lots of water and can inconspicuously add to a child's fluid intake. These foods are not restricted routinely. The free water content of infant formulas (~90% by volume) and enteral feedings (70–85%) should be considered when formulating feeding regimens for fluid-restricted children.

Table 22.20 Insensible fluid losses

Age group	Fluid loss
Preterm infants	40 mL/kg/d
Neonates	20–30 mL/kg/d
Children and adolescents	20 mL/kg/d or 400 mL/m²

Attempts at fluid restriction may be futile if sodium is not restricted at the same time [63]. Reducing fluid intake alone is not practical most of the time because the increased ECF osmolality brought about by the excessive sodium ingestion will stimulate thirst, followed by further fluid ingestion and isotonic fluid gain [63, 463, 464].

6.5: Potassium intake should be limited for children with CKD stages 2–5 and 5D who have or are at risk of hyperkalemia. (A)

Ninety-eight percent of the body's potassium is contained in cells, whereas only 2% is in the extracellular compartment. Potassium moves rapidly between the intra- and extracellular compartments to maintain normal serum levels. Because of the uneven distribution between compartments, small shifts can result in major changes in serum potassium concentrations. Maintaining a normal serum potassium concentration depends on these shifts, as well as excretion of potassium from the body. Intestinal excretion accounts for approximately 10% of potassium excretion, whereas the remainder is excreted in urine. Renal potassium excretion typically is maintained until GFR decreases to less than 10–15 mL/min/1.73 m^2. The risk of hyperkalemia is also increased by urinary obstruction, rhabdomyolysis, hemolysis (e.g., blood transfusions and tumor lysis), acidosis, or treatment with potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers.

Extracellular potassium influences muscle activity, especially the heart. Both hypokalemia and hyperkalemia cause alterations in all muscle

function (skeletal, myocardial, and smooth muscle contractility) and cardiac arrhythmias. Hyperkalemia is common in patients with CKD stage 5 and when severe, can rapidly lead to death from cardiac arrest or paralysis of muscles that control ventilation. Therefore, control of serum potassium is a critically important part of dietary management in patients with CKD.

When the kidney loses its ability to filter potassium (K), counseling children and caretakers to limit dietary potassium is critical to prevent and manage hyperkalemia. There are no data for the degree of dietary potassium restriction required for children with hyperkalemia. Suggested dietary management of hyperkalemia in adults limits intake to less than 2,000–3,000 mg (<50–75 mmol/d) of K daily [444, 465, 466]. Based on a 70-kg standard adult, this is the equivalent of less than 30–40 mg/kg/d (<0.8–1 mmol/kg/d). For infants and young children, 40–120 mg (1–3 mmol/kg/d) of K may be a reasonable place to start. Breast milk (mature) has the lowest potassium content (546 mg/L; 14 mmol/L) compared with standard commercial cow's milk–based infant formulas (700–740 mg/L; 18–19 mmol/L). Volumes of infant formula of 165 mL/kg or greater will exceed 120 mg (3 mmol) K/kg and may aggravate hyperkalemia. Children can lower potassium intake by restricting intake of such high-potassium foods as bananas, oranges, potatoes and potato chips, tomato products, legumes and lentils, yogurt, and chocolate [460]. The nutrition facts panel on food labels is not required to list potassium, but may provide potassium content as actual amount (mg) and % DV. Foods containing less than 100 mg or less than 3% DV are considered low in potassium. Foods containing 200–250 mg or greater than 6% DV are considered high in potassium. If potassium is not listed, it does not mean that the food does not contain potassium. Presoaking root vegetables, including potatoes, effectively lowers potassium content by 50–75% [468, 469].

Salt substitutes, also referred to as light salts, typically replace all or some of the sodium with another mineral, such as potassium or magnesium. Salt substitutes that contain potassium may cause hyperkalemia with life-threatening consequences in individuals with hyperkalemia or a tendency toward it [470]. Potassium-containing salt substitutes are inappropriate for people who need to limit both salt and potassium.

When hyperkalemia persists, despite strict adherence to dietary potassium restriction, nondietary causes of hyperkalemia – such as spurious values, hemolysis, metabolic acidosis, other exogenous potassium sources, constipation, inadequate dialysis, medications (angiotensin-converting enzyme, inhibitors, angiotensin-receptor blockers, nonsteroidal anti-inflammatory agents, and potassium-sparing diuretics), and tissue destruction due to catabolism, infection, surgery, or chemotherapy – should be investigated further [471, 472].

Moderate to severe hyperkalemia may require treatment with a potassium binder. When oral, enteral, or rectal administration of potassium-binding resins is ineffective, undesirable, or not feasible, infant formula, enteral feedings, or other fluids can be pretreated to safely and effectively reduce their potassium content. Depending on the dosage of potassium binder used, this process lowers the potassium content of the feeding by 12–78% [473–477]. This process also may be indicated when there are concerns about obstruction of an enteral feeding tube. In addition to reducing potassium content, other reported changes associated with binder use include an increase or reduction in other nutrients, such as sodium and calcium.

Children on PD or frequent HD therapy (i.e., >5 sessions/week) rarely need dietary potassium restriction and may actually develop hypokalemia. Normokalemia may be achieved through counseling and frequent reinforcement of a high-potassium diet [478], KCl supplements, or addition of potassium to the dialysate.

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References

1. Teitelbaum D, Guenter P, Howell WH, Kochevar ME, Roth J, Seidner DL: Definition of terms, style, and conventions used in A.S.P.E.N. guidelines and standards. Nutr Clin Pract 20:281–285, 2005
2. Arnold WC, Danford D, Holliday MA: Effects of caloric supplementation on growth in children with uremia. Kidney Int 24:205–209, 1983
3. Betts PR, Magrath G: Growth pattern and dietary intake of children with chronic renal insufficiency. Br Med J 2:189–193, 1974
4. Simmons JM, Wilson CJ, Potter DE, Holliday MA: Relation of calorie deficiency to growth failure in children on hemodialysis and the growth response to calorie supplementation. N Engl J Med 285:653–656, 1971
5. Sylvestre LC, Fonseca KP, Stinghen AE, Pereira AM, Meneses RP, Pecoits-Filho R: The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. Pediatr Nephrol 22:864–873, 2007
6. Peterson KE, Chen LC: Defining undernutrition for public health purposes in the United States. J Nutr 120:933–942, 1990
7. Baur LA, Knight JF, Crawford BA, et al: Total body nitrogen in children with chronic renal failure and short stature. Eur J Clin Nutr 48:433–441, 1994
8. El-Bishti M, Burke J, Gill D, Jones RW, Counahan R, Chantler C: Body composition in children on regular hemodialysis. Clin Nephrol 15:53–60, 1981
9. Foreman JW, Abitbol CL, Trachtman H, 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 15:579–585, 1996
10. Jones RW, Rigden SP, Barratt TM, Chantler C: The effects of chronic renal failure in infancy on growth, nutritional status and body composition. Pediatr Res 16:784–791, 1982
11. Rashid R, Neill E, Smith W, et al: Body composition and nutritional intake in children with chronic kidney disease. Pediatr Nephrol 21:1730–1738, 2006
12. Salusky IB, Fine RN, Nelson P, Blumenkrantz MJ, Kopple JD: Nutritional status of children undergoing continuous ambulatory peritoneal dialysis. Am J Clin Nutr 38:599–611, 1983
13. Karlberg J: On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr 78: 26–37, 1989
14. 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 76:478–488, 1987
15. 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 337:S12-S29, 1987
16. 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 10:283–287, 1996
17. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L: Outcome and growth of infants with severe chronic renal failure. Kidney Int 57:1681–1687, 2000
18. Ledermann SE, Shaw V, Trompeter RS: Long-term enteral nutrition in infants and young children with chronic renal failure. Pediatr Nephrol 13:870–875, 1999
19. 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 112:714–719, 1988
20. Filler G, Reimao SM, Kathiravelu A, Grimmer J, Feber J, Drukker A: Pediatric nephrology patients are overweight: 20 Years' experience in a single Canadian tertiary pediatric nephrology clinic. Int Urol Nephrol 39:1235–1240, 2007
21. Hanevold CD, Ho PL, Talley L, Mitsnefes MM: Obesity and renal transplant outcome: A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics 115:352–356, 2005
22. Omoloja A, Stolfi A, Mitsnefes M: Pediatric obesity at renal transplantation: A single center experience. Pediatr Transplant 9:770–772, 2005
23. Bandini LG, Cyr H, Must A, Dietz WH: Validity of reported energy intake in preadolescent girls. Am J Clin Nutr 65:S1138-S1141, 1997 (suppl 4)
24. Champagne CM, Baker NB, DeLany JP, Harsha DW, Bray GA: Assessment of energy intake underreporting by doubly labeled water and observations on reported nutrient intakes in children. J Am Diet Assoc 98:426–433, 1998
25. Livingstone MB, Robson PJ: Measurement of dietary intake in children. Proc Nutr Soc 59:279–293, 2000
26. Zadik Z, Frishberg Y, Drukker A, 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 47:264–268, 1998
27. Abitbol CL, Warady BA, Massie MD, et al: Linear growth and anthropometric and nutritional measurements in children with mild to moderate renal insufficiency: A report of the Growth Failure in Children with Renal Diseases Study. J Pediatr 116:S46-S54, 1990
28. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR: Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol 15:259–265, 2000
29. Schaefer F, Seidel C, Binding A, et al: Pubertal growth in chronic renal failure. Pediatr Res 28:5–10, 1990
30. 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 10:288–293, 1996
31. Donckerwolcke R, Yang WN, Chan JC: Growth failure in children with renal tubular acidosis. Semin Nephrol 9:72–74, 1989
32. 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 343:923–930, 2000
33. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al: CDC growth charts: United States. Adv Data Report no. 314:1–27, 2000
34. World Health Organization: WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age. Methods and Development. Geneva, Switzerland, World Health Organization, 2006, p 332
35. Tanner JM, Goldstein H, Whitehouse RH: Standards for children's height at ages 2–9 years allowing for heights of parents. Arch Dis Child 45:755–762, 1970
36. Nelson M, Bingham SA: Assessment of food consumption and nutrient intake, in Margetts BM, Nelson M (eds): Design Concepts in Nutritional Epidemiology (ed 2). New York, NY, Oxford University, 1997, pp 123–169
37. Baumgartner RN, Roche AF, Himes JH: Incremental growth tables: Supplementary to previously published charts. Am J Clin Nutr 43:711–722, 1986
38. Foster BJ, Leonard MB: Measuring nutritional status in children with chronic kidney disease. Am J Clin Nutr 80:801–814, 2004
39. Roche AF: Anthropometry and ultrasound, in Roche AF, Heymsfield SB, Lohman TG (eds): Human Body Composition. Champaign, IL, Human Kinetics, 1996, pp 167–182
40. Michael M, Brewer ED, Goldstein SL: Blood volume monitoring to achieve target weight in pediatric hemodialysis patients. Pediatr Nephrol 19:432–437, 2004
41. Hattori K, Hirohara T: Age change of power in weight/height(p) indices used as indicators of adiposity in Japanese. Am J Hum Biol 14:275–279, 2002
42. Kuczmarski RJ, Ogden CL, Guo SS, et al: 2000 CDC Growth Charts for the United States: Methods and development. Vital Health Stat 11:1–190, 2002
43. Cole TJ, Flegal KM, Nicholls D, Jackson AA: Body mass index cut offs to define thinness in children and adolescents: International survey. BMJ 335:194, 2007
44. World Health Organization: Physical status: The use and interpretation of anthropometry. Report of a WHO Expert Committee. Geneva, Switzerland, World Health Organization, 1995
45. Barlow SE: Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. Pediatrics 120:S164-S192, 2007 (suppl 4)
46. 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 31:997–1006, 1998
47. Pifer TB, McCullough KP, Port FK, et al: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int 62:2238–2245, 2002
48. Kaizu Y, Tsunega Y, Yoneyama T, et al: Overweight as another nutritional risk factor for the long-term survival of non-diabetic hemodialysis patients. Clin Nephrol 50:44–50, 1998
49. Wong CS, Gipson DS, Gillen DL, et al: Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis 36:811–819, 2000
50. So SK, Chang PN, Najarian JS, Mauer SM, Simmons RL, Nevins TE: Growth and development in infants after renal transplantation. J Pediatr 110:343–350, 1987
51. Warady BA, Belden B, Kohaut E: Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol 13:759–765, 1999
52. World Health Organization: WHO Child Growth Standards: Head Circumference-for-Age, Arm Circumference-for-Age, Triceps Skinfold-for-Age and Subscapular Skinfold-for-Age. Methods and Development. Geneva, Switzerland, World Health Organization, 2007, p 234
53. Grupe WE, Harmon WE, Spinozzi NS: Protein and energy requirements in children receiving chronic hemodialysis. Kidney Int Suppl 15:S6-S10, 1983
54. Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 28:526–534, 1985
55. Goldstein SL: Hemodialysis in the pediatric patient: State of the art. Adv Ren Replace Ther 8:173–179, 2001
56. Borah MF, Schoenfeld PY, Gotch FA, Sargent JA, Wolfsen M, Humphreys MH: Nitrogen balance during intermittent dialysis therapy of uremia. Kidney Int 14:491–500, 1978
57. Depner TA, Cheer A: Modeling urea kinetics with two vs. three BUN measurements. A critical comparison. ASAIO Trans 35:499–502, 1989
58. Goldstein SL, Baronette S, Gambrell TV, Currier H, Brewer ED: nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients. Pediatr Nephrol 17:531–534, 2002
59. 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 15:312–317, 2005
60. Juarez-Congelosi M, Orellana P, Goldstein SL: Normalized protein catabolic rate versus serum albumin as a nutrition status marker in pediatric patients receiving hemodialysis. J Ren Nutr 17:269–274, 2007

61. Goldstein SL: Prescribing and monitoring hemodialysis, in Warady BA, Schaefer FR, Fine RN, Alexander SR (eds): Pediatric Dialysis. Dordrecht, The Netherlands, Kluwer, 2004, pp 135–146
62. National Kidney Foundation: K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 35:S1-S140, 2000 (suppl 2)
63. National Kidney Foundation: KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. Am J Kidney Dis 48:S1-S322, 2006 (suppl 1)
64. Kopple JD, Jones MR, Keshaviah PR, et al: A proposed glossary for dialysis kinetics. Am J Kidney Dis 26:963–981, 1995
65. Mendley SR, Majkowski NL: Urea and nitrogen excretion in pediatric peritoneal dialysis patients. Kidney Int 58:2564–2570, 2000
66. Edefonti A, Picca M, Damiani B, et al: Models to assess nitrogen losses in pediatric patients on chronic peritoneal dialysis. Pediatr Nephrol 15:25–30, 2000
67. 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 15:458–482, 1990
68. Qureshi AR, Alvestrand A, Divino-Filho JC, et al: Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol 13:S28-S36, 2002 (suppl 1)
69. Stenvinkel P, Barany P, Chung SH, Lindholm B, Heimburger O: A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. Nephrol Dial Transplant 17:1266–1274, 2002
70. Wong CS, Hingorani S, Gillen DL, et al: Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int 61:630–637, 2002
71. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality: An integrated point of view. Am J Kidney Dis 32:834–841, 1998
72. Graf L, Candelaria S, Doyle M, Kaskel F: Nutrition assessment and hormonal influences on body composition in children with chronic kidney disease. Adv Chronic Kidney Dis 14:215–223, 2007
73. Jones CH, Wells L, Stoves J, Farquhar F, Woodrow G: Can a reduction in extracellular fluid volume result in increased serum albumin in peritoneal dialysis patients? Am J Kidney Dis 39:872–875, 2002
74. Kalantar-Zadeh K, Kopple JD: Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis 38:1343–1350, 2001
75. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 38:1251–1263, 2001
76. Kaysen GA: Malnutrition and the acute-phase reaction in dialysis patients—How to measure and how to distinguish. Nephrol Dial Transplant 15:1521–1524, 2000
77. Yeun JY, Levine RA, Mantadilok V, Kaysen GA: C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 35:469–476, 2000
78. Wang J, Thornton JC, Kolesnik S, Pierson RN Jr: Anthropometry in body composition. An overview. Ann N Y Acad Sci 904:317–326, 2000
79. Zivicnjak M, Franke D, Ehrich JH, Filler G: Does growth hormone therapy harmonize distorted morphology and body composition in chronic renal failure? Pediatr Nephrol 15:229–235, 2000
80. Rayner HC, Stroud DB, Salamon KM, et al: Anthropometry underestimates body protein depletion in haemodialysis patients. Nephron 59:33–40, 1991
81. Pietrobelli A, Formica C, Wang Z, Heymsfield SB: Dual-energy X-ray absorptiometry body composition model: Review of physical concepts. Am J Physiol 271:E941-E951, 1996
82. Boot AM, Nauta J, de Jong MC, et al: Bone mineral density, bone metabolism and body composition of children with chronic renal failure, with and without growth hormone treatment. Clin Endocrinol (Oxf) 49:665–672, 1998
83. Cochat P, Braillon P, Feber J, et al: Body composition in children with renal disease: Use of dual energy X-ray absorptiometry. Pediatr Nephrol 10:264–268, 1996
84. Dumler F: Use of bioelectric impedance analysis and dual-energy X-ray absorptiometry for monitoring the nutritional status of dialysis patients. ASAIO J 43:256–260, 1997
85. O'Sullivan AJ, Lawson JA, Chan M, Kelly JJ: Body composition and energy metabolism in chronic renal insufficiency. Am J Kidney Dis 39:369–375, 2002
86. Woodrow G, Oldroyd B, Turney JH, Tompkins L, Brownjohn AM, Smith MA: Whole body and regional body composition in patients with chronic renal failure. Nephrol Dial Transplant 11:1613–1618, 1996
87. Schoeller DA: Bioelectrical impedance analysis. What does it measure? Ann N Y Acad Sci 904:159–162, 2000
88. Bradbury MG, Smye SW, Brocklebank JT: Assessment of the sensitivity of bioimpedance to volume changes in body water. Pediatr Nephrol 9:337–340, 1995
89. Dietel T, Filler G, Grenda R, Wolfish N: Bioimpedance and inferior vena cava diameter for assessment of dialysis dry weight. Pediatr Nephrol 14:903–907, 2000
90. Ellis KJ, Shypailo RJ, Wong WW: Measurement of body water by multifrequency bioelectrical impedance spectroscopy in a multiethnic pediatric population. Am J Clin Nutr 70:847–853, 1999

91. Smye SW, Norwood HM, Buur T, Bradbury M, Brocklebank JT: Comparison of extra-cellular fluid volume measurement in children by 99Tcm-DPTA clearance and multi-frequency impedance techniques. Physiol Meas 15:251–260, 1994
92. Sun SS, Chumlea WC, Heymsfield SB, et al: Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys. Am J Clin Nutr 77:331–340, 2003
93. Wuhl E, Fusch C, Scharer K, Mehls O, Schaefer F: Assessment of total body water in paediatric patients on dialysis. Nephrol Dial Transplant 11:75–80, 1996
94. Baumgartner RN, Chumlea WC, Roche AF: Bioelectric impedance phase angle and body composition. Am J Clin Nutr 48:16–23, 1988
95. Chertow GM, Lazarus JM, Lew NL, Ma L, Lowrie EG: Bioimpedance norms for the hemodialysis population. Kidney Int 52:1617–1621, 1997
96. Nagano M, Suita S, Yamanouchi T: The validity of bioelectrical impedance phase angle for nutritional assessment in children. J Pediatr Surg 35:1035–1039, 2000
97. De Lorenzo A, Andreoli A, Matthie J, Withers P: Predicting body cell mass with bioimpedance by using theoretical methods: A technological review. J Appl Physiol 82:1542–1558, 1997
98. Fenech M, Maasrani M, Jaffrin MY: Fluid volumes determination by impedance spectroscopy and hematocrit monitoring: Application to pediatric hemodialysis. Artif Organs 25:89–98, 2001
99. Zhu F, Schneditz D, Wang E, Martin K, Morris AT, Levin NW: Validation of changes in extracellular volume measured during hemodialysis using a segmental bioimpedance technique. ASAIO J 44:M541-M545, 1998
100. Chamney PW, Kramer M, Rode C, Kleinekofort W, Wizemann V: A new technique for establishing dry weight in hemodialysis patients via whole body bioimpedance. Kidney Int 61:2250–2258, 2002
101. Zhu F, Kuhlmann MK, Sarkar S, et al: Adjustment of dry weight in hemodialysis patients using intradialytic continuous multifrequency bioimpedance of the calf. Int J Artif Organs 27:104–109, 2004
102. Edefonti A, Picca M, Damiani B, et al: Prevalence of malnutrition assessed by bioimpedance analysis and anthropometry in children on peritoneal dialysis. Perit Dial Int 21:172–179, 2001
103. Edefonti A, Picca M, Paglialonga F, et al: A novel objective nutritional score for children on chronic peritoneal dialysis. Perit Dial Int 22:602–607, 2002
104. 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 14:191–200, 2004
105. Detsky AS, McLaughlin JR, Baker JP, et al: What is Subjective Global Assessment of nutritional status? JPEN J Parenter Enteral Nutr 11:8–13, 1987
106. Detsky AS, Smalley PS, Chang J: The rational clinical examination. Is this patient malnourished? JAMA 271:54–58, 1994
107. Secker DJ, Jeejeebhoy KN: Subjective Global Nutritional Assessment for children. Am J Clin Nutr 85:1083–1089, 2007
108. Dietitians of Canada CPS, The College of Family Physicians of Canada, and Community Health Nurses Association of Canada: The use of growth charts for assessing and monitoring growth in Canadian infants and children. Paedr Child Health 9:171–180, 2004
109. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Bright Futures Steering Committee: Recommendations for preventive pediatric health care. Pediatrics 120:1376, 2007
110. Geary DF, Chait PG: Tube feeding in infants on peritoneal dialysis. Perit Dial Int 16:S517-S520, 1996 (suppl 1)
111. 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 12:2418–2426, 2001
112. Mahan JD, Warady BA: Assessment and treatment of short stature in pediatric patients with chronic kidney disease: A consensus statement. Pediatr Nephrol 21:917–930, 2006
113. Kaskel F: Chronic renal disease: A growing problem. Kidney Int 64:1141–1151, 2003
114. Betts PR, Magrath G, White RH: Role of dietary energy supplementation in growth of children with chronic renal insufficiency. Br Med J 1:416–418, 1977
115. Greenbaum LA, Del Rio M, Bamgbola F, Kaskel F: Rationale for growth hormone therapy in children with chronic kidney disease. Adv Chronic Kidney Dis 11:377–386, 2004
116. Wingen AM, Mehls O: Nutrition in children with preterminal chronic renal failure. Myth or important therapeutic aid? Pediatr Nephrol 17:111–120, 2002
117. Warady BA, Fischbach M, Geary D, Goldstein SL: Frequent hemodialysis in children. Adv Chronic Kidney Dis 14:297–303, 2007
118. Kuizon BD, Salusky IB: Growth retardation in children with chronic renal failure. J Bone Miner Res 14:1680–1690, 1999
119. Rodriguez-Soriano J, Arant BS, Brodehl J, Norman ME: Fluid and electrolyte imbalances in children with chronic renal failure. Am J Kidney Dis 7:268–274, 1986
120. Van Dyck M, Bilem N, Proesmans W: Conservative treatment for chronic renal failure from birth: A 3-year follow-up study. Pediatr Nephrol 13:865–869, 1999
121. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis 46: S1-S122, 2005 (suppl 1)

122. Tonshoff B, Mehls O: Interaction between glucocorticoids and the somatotrophic axis. Acta Paediatr Suppl 417:S72-S75, 1996
123. Mehls O, Wuhl E, Tonshoff B, Schaefer F, Nissel R, Haffner D: Growth hormone treatment in short children with chronic kidney disease. Acta Paediatr 97:1159–1164, 2008
124. Brungger M, Hulter HN, Krapf R: Effect of chronic metabolic acidosis on thyroid hormone homeostasis in humans. Am J Physiol 272:F648-F653, 1997
125. 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 51:216–221, 1997
126. Challa A, Krieg RJ Jr, Thabet MA, Veldhuis JD, Chan JC: Metabolic acidosis inhibits growth hormone secretion in rats: Mechanism of growth retardation. Am J Physiol 265:E547-E553, 1993
127. Challa A, Chan W, Krieg RJ Jr, et al: Effect of metabolic acidosis on the expression of insulin-like growth factor and growth hormone receptor. Kidney Int 44:1224–1227, 1993
128. Hanna JD, Santos F, Foreman JW, Chan JC, Han VK: Insulin-like growth factor-I gene expression in the tibial epiphyseal growth plate of growth hormone-treated uremic rats. Kidney Int 47:1374–1382, 1995
129. 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 58:236–241, 2000
130. Maniar S, Laouari D, Caldas A, Kleinknecht C: Protein synthesis and growth in uremic rats with and without chronic metabolic acidosis. Miner Electrolyte Metab 18:250–252, 1992
131. Bushinsky DA, Frick KK: The effects of acid on bone. Curr Opin Nephrol Hypertens 9:369–379, 2000
132. Bushinsky DA, Goldring JM, Coe FL: Cellular contribution to pH-mediated calcium flux in neonatal mouse calvariae. Am J Physiol 248:F785-F789, 1985
133. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J: Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int 65:1031–1040, 2004
134. Caldas A, Broyer M, Dechaux M, Kleinknecht C: Primary distal tubular acidosis in childhood: Clinical study and long-term follow-up of 28 patients. J Pediatr 121:233–241, 1992
135. McSherry E, Morris RC Jr: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. J Clin Invest 61:509–527, 1978
136. Kaiser BA, Polinsky MS, Stover J, Morgenstern BZ, Baluarte HJ: Growth of children following the initiation of dialysis: A comparison of three dialysis modalities. Pediatr Nephrol 8:733–738, 1994
137. Mahesh S, Kaskel F: Growth hormone axis in chronic kidney disease. Pediatr Nephrol 23:41–48, 2008
138. 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 5:539–544, 1991
139. 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 108:467–475, 2001
140. Tonshoff B, Cronin MJ, Reichert M, 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 82:1007–1013, 1997
141. Tonshoff B, Kiepe D, Ciarmatori S: Growth hormone/insulin-like growth factor system in children with chronic renal failure. Pediatr Nephrol 20:279–289, 2005
142. Vimalachandra D, Hodson EM, Willis NS, Craig JC, Cowell C, Knight JF: Growth hormone for children with chronic kidney disease. Cochrane Database Syst Rev 3:CD003264.pub003262, 2006
143. Nissel R, Lindberg A, Mehls O, Haffner D: Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. J Clin Endocrinol Metab 93:1359–1365, 2008
144. Berard E, Andre JL, Guest G, et al: Long-term results of rhGH treatment in children with renal failure: Experience of the French Society of Pediatric Nephrology. Pediatr Nephrol 23:2031–2038, 2008
145. 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 14:701–706, 2000
146. Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D: Stature in children with chronic kidney disease: Analysis of NAPRTCS database. Pediatr Nephrol 21:793–799, 2006
147. Fine RN, Stablein D, Cohen AH, Tejani A, Kohaut E: Recombinant human growth hormone post-renal transplantation in children: A randomized controlled study of the NAPRTCS. Kidney Int 62:688–696, 2002
148. Greenbaum LA, Hidalgo G, Chand D, et al: Obstacles to the prescribing of growth hormone in children with chronic kidney disease. Pediatr Nephrol 23:1531–1535, 2008
149. Fischbach M, Terzic J, Menouer S, et al: Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol 21:1746–1752, 2006

150. Tom A, McCauley L, Bell L, et al: Growth during maintenance hemodialysis: Impact of enhanced nutrition and clearance. J Pediatr 134:464–471, 1999
151. Canepa A, Perfumo F, Carrea A, et al: Protein and calorie intake, nitrogen losses, and nitrogen balance in children undergoing chronic peritoneal dialysis. Adv Perit Dial 12:326–329, 1996
152. Edefonti A, Picca M, Damiani B, et al: Dietary prescription based on estimated nitrogen balance during peritoneal dialysis. Pediatr Nephrol 13:253–258, 1999
153. Orejas G, Santos F, Malaga S, Rey C, Cobo A, Simarro M: Nutritional status of children with moderate chronic renal failure. Pediatr Nephrol 9:52–56, 1995
154. Coleman JE, Watson AR, Rance CH, Moore E: Gastrostomy buttons for nutritional support on chronic dialysis. Nephrol Dial Transplant 13:2041–2046, 1998
155. Ledermann SE, Spitz L, Moloney J, Rees L, Trompeter RS: Gastrostomy feeding in infants and children on peritoneal dialysis. Pediatr Nephrol 17:246–250, 2002
156. Norman LJ, Macdonald IA, Watson AR: Optimising nutrition in chronic renal insufficiency—Growth. Pediatr Nephrol 19:1245–1252, 2004
157. Koehler S, Sichert-Hellert W, Kersting M: Measuring the effects of nutritional counseling on total infant diet in a randomized controlled intervention trial. J Pediatr Gastroenterol Nutr 45:106–113, 2007
158. Obarzanek E, Kimm SY, Barton BA, et al: Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: Seven-year results of the Dietary Intervention Study in Children (DISC). Pediatrics 107:256–264, 2001
159. Santos I, Victora CG, Martines J, et al: Nutrition counseling increases weight gain among Brazilian children. J Nutr 131:2866–2873, 2001
160. Campbell KL, Ash S, Davies PS, Bauer JD: Randomized controlled trial of nutritional counseling on body composition and dietary intake in severe CKD. Am J Kidney Dis 51:748–758, 2008
161. Burrowes JD: Incorporating ethnic and cultural food preferences in the renal diet. Adv Ren Replace Ther 11:97–104, 2004
162. Coyne T, Olson M, Bradham K, Garcon M, Gregory P, Scherch L: Dietary satisfaction correlated with adherence in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 95:1301–1306, 1995
163. Morales Lopez C, Burrowes JD, Gizis F, Brommage D: Dietary adherence in Hispanic patients receiving hemodialysis. J Ren Nutr 17:138–147, 2007
164. Coleman JE, Norman LJ, Watson AR: Provision of dietetic care in children on chronic peritoneal dialysis. J Ren Nutr 9:145–148, 1999
165. Norman LJ, Macdonald IA, Watson AR: Optimising nutrition in chronic renal insufficiency—Progression of disease. Pediatr Nephrol 19:1253–1261, 2004
166. Levey AS, Adler S, Caggiula AW, et al: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. Am J Kidney Dis 27:652–663, 1996
167. Dolecek TA, Olson MB, Caggiula AW, et al: Registered dietitian time requirements in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 95:1307–1312, 1995
168. Dello Strologo L, Principato F, Sinibaldi D, et al: Feeding dysfunction in infants with severe chronic renal failure after long-term nasogastric tube feeding. Pediatr Nephrol 11:84–86, 1997
169. Pugh P, Watson AR: Transition from gastrostomy to oral feeding following renal transplantation. Adv Perit Dial 22:153–157, 2006
170. Magrab PR, Papadopoulou ZL: The effect of a token economy on dietary compliance for children on hemodialysis. J Appl Behav Anal 10:573–578, 1977
171. Harvey E, Secker D, Braj B, Picone G, Balfe JW: The team approach to the management of children on chronic peritoneal dialysis. Adv Ren Replace Ther 3:3–13, 1996
172. Hodson E: Evaluation and management of nutrition in children. Nephrology 10:S215-S217, 2005 (suppl 5)
173. Kavey RE, Allada V, Daniels SR, 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 114:2710–2738, 2006
174. Marques de Aquino T, Avesani CM, Brasileiro RS, de Abreu Carvalhaes JT: Resting energy expenditure of children and adolescents undergoing hemodialysis. J Ren Nutr 18:312–319, 2008
175. Food and Nutrition Board: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Food and Nutrition Board. Washington, DC, National Academies, 2002
176. Mitsnefes MM, Khoury P, McEnery PT: Body mass index and allograft function in pediatric renal transplantation. Pediatr Nephrol 17:535–539, 2002
177. Bodnar DM, Busch S, Fuchs J, Piedmonte M, Schreiber M: Estimating glucose absorption in peritoneal dialysis using peritoneal equilibration tests. Adv Perit Dial 9:114–118, 1993
178. Grodstein GP, Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW: Glucose absorption during continuous ambulatory peritoneal dialysis. Kidney Int 19:564–567, 1981
179. Butte NF, Wong WW, Hopkinson JM, Heinz CJ, Mehta NR, Smith EO: Energy requirements derived from total energy expenditure and energy deposition

during the first 2 y of life. Am J Clin Nutr 72:1558–1569, 2000
180. 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 109:909–913, 2002
181. Daschner M, Tonshoff B, Blum WF, 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 9:1074–1079, 1998
182. Mak RH, Cheung W, Cone RD, Marks DL: Leptin and inflammation-associated cachexia in chronic kidney disease. Kidney Int 69:794–797, 2006
183. 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 3:424–429, 1989
184. Ravelli AM, Ledermann SE, Bisset WM, Trompeter RS, Barratt TM, Milla PJ: Foregut motor function in chronic renal failure. Arch Dis Child 67:1343–1347, 1992
185. Orenstein SR, McGowan JD: Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. J Pediatr 152:310–314, 2008
186. Rudolph CD, Mazur LJ, Liptak GS, et al: Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: Recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 32:S1-31, 2001 (suppl 2)
187. Ellis EN, Yiu V, Harley F, 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 16:404–408, 2001
188. Ledermann SE, Scanes ME, Fernando ON, Duffy PG, Madden SJ, Trompeter RS: Long-term outcome of peritoneal dialysis in infants. J Pediatr 136:24–29, 2000
189. 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 19:231–236, 1999
190. 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 6:265–268, 1990
191. Ledermann S: When should gastrostomy tubes be removed following successful renal transplantation? Pediatr Transplant 9:553–554, 2005
192. Chang PF, Ni YH, Chang MH: Percutaneous endoscopic gastrostomy to set up a long-term enteral feeding route in children: An encouraging result. Pediatr Surg Int 19:283–285, 2003
193. Davies BW, Watson AR, Coleman JE, Rance CH: Do gastrostomies close spontaneously? A review of the fate of gastrostomies following successful renal transplantation in children. Pediatr Surg Int 17:326–328, 2001
194. Warady BA, Bashir M, Donaldson LA: Fungal peritonitis in children receiving peritoneal dialysis: A report of the NAPRTCS. Kidney Int 58:384–389, 2000
195. Ramage IJ, Harvey E, Geary DF, Hebert D, Balfe JA, Balfe JW: Complications of gastrostomy feeding in children receiving peritoneal dialysis. Pediatr Nephrol 13:249–252, 1999
196. von Schnakenburg C, Feneberg R, Plank C, et al: Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int 26:69–77, 2006
197. Galland R, Traeger J, Arkouche W, Cleaud C, Delawari E, Fouque D: Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. Kidney Int 60:1555–1560, 2001
198. Boccanfuso JA, Hutton M, McAllister B: The effects of megestrol acetate on nutritional parameters in a dialysis population. J Ren Nutr 10:36–43, 2000
199. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossein C: Megestrol acetate in a moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. J Ren Nutr 15:345–355, 2005
200. Davenport A: Intradialytic complications during hemodialysis. Hemodial Int 10:162–167, 2006
201. Sherman RA, Torres F, Cody RP: Postprandial blood pressure changes during hemodialysis. Am J Kidney Dis 12:37–39, 1988
202. Strong J, Burgett M, Buss ML, Carver M, Kwankin S, Walker D: Effects of calorie and fluid intake on adverse events during hemodialysis. J Ren Nutr 11:97–100, 2001
203. Veeneman JM, Kingma HA, Boer TS, et al: Protein intake during hemodialysis maintains a positive whole body protein balance in chronic hemodialysis patients. Am J Physiol Endocrinol Metab 284:E954-E965, 2003
204. Barakat MM, Nawab ZM, Yu AW, Lau AH, Ing TS, Daugirdas JT: Hemodynamic effects of intradialytic food ingestion and the effects of caffeine. J Am Soc Nephrol 3:1813–1818, 1993
205. Shibagaki Y, Takaichi K: Significant reduction of the large-vessel blood volume by food intake during hemodialysis. Clin Nephrol 49:49–54, 1998
206. Sivalingam M, Banerjee A, Nevett G, Farrington K: Haemodynamic effects of food intake during haemodialysis. Blood Purif 26:157–162, 2008
207. Caglar K, Fedje L, Dimmitt R, Hakim RM, Shyr Y, Ikizler TA: Therapeutic effects of oral nutritional supplementation during hemodialysis. Kidney Int 62:1054–1059, 2002
208. Benaroia M, Iliescu EA: Oral intake during hemodialysis: Is there an association with intradialytic hypotension? Hemodial Int 12:62–65, 2008
209. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 63:793–808, 2003

210. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD: Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr 80:299–307, 2004
211. Simoni JM, Asarnow JR, Munford PR, Koprowski CM, Belin TR, Salusky IB: Psychological distress and treatment adherence among children on dialysis. Pediatr Nephrol 11:604–606, 1997
212. Brownbridge G, Fielding DM: Psychosocial adjustment and adherence to dialysis treatment regimes. Pediatr Nephrol 8:744–749, 1994
213. Gerson A, Hwang W, Fiorenza J, et al: Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis 44:1017–1023, 2004
214. Goldstein SL, Gerson AC, Goldman CW, Furth S: Quality of life for children with chronic kidney disease. Semin Nephrol 26:114–117, 2006
215. Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW: Health-related quality of life in pediatric patients with ESRD. Pediatr Nephrol 21:846–850, 2006
216. Krause I, Shamir R, Davidovits M, et al: Intradialytic parenteral nutrition in malnourished children treated with hemodialysis. J Ren Nutr 12:55–59, 2002
217. Cano NJ, Fouque D, Roth H, et al: Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: A 2-year multicenter, prospective, randomized study. J Am Soc Nephrol 18:2583–2591, 2007
218. Foulks CJ: An evidence-based evaluation of intradialytic parenteral nutrition. Am J Kidney Dis 33:186–192, 1999
219. Moore E, Celano J: Challenges of providing nutrition support in the outpatient dialysis setting. Nutr Clin Pract 20:202–212, 2005
220. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis 45:S1-S153, 2005 (suppl 3)
221. Filler G, Payne RP, Orrbine E, Clifford T, Drukker A, McLaine PN: Changing trends in the referral patterns of pediatric nephrology patients. Pediatr Nephrol 20:603–608, 2005
222. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1)
223. National Kidney Foundation: K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 41:S1-S91, 2003 (suppl 3)
224. Querfeld U, Salusky IB, Nelson P, Foley J, Fine RN: Hyperlipidemia in pediatric patients undergoing peritoneal dialysis. Pediatr Nephrol 2:447–452, 1988
225. Saland JM, Ginsberg HN: Lipoprotein metabolism in chronic renal insufficiency. Pediatr Nephrol 22:1095–1112, 2007
226. Querfeld U: Disturbances of lipid metabolism in children with chronic renal failure. Pediatr Nephrol 7:749–757, 1993
227. Saland JM, Ginsberg H, Fisher EA: Dyslipidemia in pediatric renal disease: Epidemiology, pathophysiology, and management. Curr Opin Pediatr 14:197–204, 2002
228. Austin MA, Hokanson JE, Edwards KL: Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol 81:7B-12B, 1998
229. Hokanson JE, Austin MA: Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta-analysis of population-based prospective studies. J Cardiovasc Risk 3:213–219, 1996
230. Sprecher DL, Stevens M: Triglycerides and HDL-cholesterol in pediatric patients. Prog Pediatr Cardiol 17:151–158, 2003
231. Tirosh A, Rudich A, Shochat T, et al: Changes in triglyceride levels and risk for coronary heart disease in young men. Ann Intern Med 147:377–385, 2007
232. Yuan G, Al-Shali KZ, Hegele RA: Hypertriglyceridemia: Its etiology, effects and treatment. CMAJ 176:1113–1120, 2007
233. Abrass CK: Cellular lipid metabolism and the role of lipids in progressive renal disease. Am J Nephrol 24:46–53, 2004
234. Crook ED, Thallapureddy A, Migdal S, et al: Lipid abnormalities and renal disease: Is dyslipidemia a predictor of progression of renal disease? Am J Med Sci 325:340–348, 2003
235. Fried LF, Orchard TJ, Kasiske BL: Effect of lipid reduction on the progression of renal disease: A meta-analysis. Kidney Int 59:260–269, 2001
236. Spinozzi NS, Nelson PA: Nutrition support in the newborn intensive care unit. J Ren Nutr 1996:188–197, 1996
237. Kari JA, Shaw V, Vallance DT, Rees L: Effect of enteral feeding on lipid subfractions in children with chronic renal failure. Pediatr Nephrol 12:401–404, 1998
238. American Academy of Pediatrics National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 89:525–584, 1992
239. Gidding SS, Dennison BA, Birch LL, et al: Dietary recommendations for children and adolescents: A guide for practitioners: Consensus statement from the American Heart Association. Circulation 112:2061–2075, 2005
240. Kwiterovich PO Jr, Barton BA, McMahon RP, et al: Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty: The Dietary Intervention Study in Children (DISC). Circulation 96:2526–2533, 1997
241. Niinikoski H, Lapinleimu H, Viikari J, et al: Growth until 3 years of age in a prospective, randomized trial of a diet with reduced saturated fat and cholesterol. Pediatrics 99:687–694, 1997

242. Skinner AC, Mayer ML, Flower K, Weinberger M: Health status and health care expenditures in a nationally representative sample: How do overweight and healthy-weight children compare? Pediatrics 121:e269-e277, 2008
243. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J: Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review. Atherosclerosis 189:19–30, 2006
244. Wang C, Harris WS, Chung M, et al: n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: A systematic review. Am J Clin Nutr 84:5–17, 2006
245. Balk E, Chung M, Lichtenstein A, et al: Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ) Report no. 93:1–6, 2004
246. McKenney JM, Sica D: Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia. Am J Health Syst Pharm 64:595–605, 2007
247. Rylance PB, Gordge MP, Saynor R, Parsons V, Weston MJ: Fish oil modifies lipids and reduces platelet aggregability in haemodialysis patients. Nephron 43:196–202, 1986
248. Svensson M, Christensen JH, Solling J, Schmidt EB: The effect of n-3 fatty acids on plasma lipids and lipoproteins and blood pressure in patients with CRF. Am J Kidney Dis 44:77–83, 2004
249. Agostoni C, Riva E, Biasucci G, et al: The effects of n-3 and n-6 polyunsaturated fatty acids on plasma lipids and fatty acids of treated phenylketonuric children. Prostaglandins Leukot Essent Fatty Acids 53:401–404, 1995
250. Ilowite NT, Copperman N, Leicht T, Kwong T, Jacobson MS: Effects of dietary modification and fish oil supplementation on dyslipoproteinemia in pediatric systemic lupus erythematosus. J Rheumatol 22:1347–1351, 1995
251. Goren A, Stankiewicz H, Goldstein R, Drukker A: Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. Pediatrics 88:265–268, 1991
252. Hogg RJ, Lee J, Nardelli N, et al: Clinical trial to evaluate omega-3 fatty acids and alternate day prednisone in patients with IgA nephropathy: Report from the Southwest Pediatric Nephrology Study Group. Clin J Am Soc Nephrol 1:467–474, 2006
253. Oomen CM, Feskens EJM, Räsänen L, et al: Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. Am J Epidemiol 151:999–1006, 2000
254. Friedman AN, Moe SM, Perkins SM, Li Y, Watkins BA: Fish consumption and omega-3 fatty acid status and determinants in long-term hemodialysis. Am J Kidney Dis 47:1064–1071, 2006
255. Ratsch IM, Catassi C, Verrina E, 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 151:701–705, 1992
256. 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 349:1117–1123, 1997
257. Kopple JD, Levey AS, Greene T, et al: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. Kidney Int 52:778–791, 1997
258. Chaturvedi S, Jones C: Protein restriction for children with chronic renal failure. Cochrane Database Syst Rev CD006863, 2007
259. Krenitsky J: Adjusted body weight, pro: Evidence to support the use of adjusted body weight in calculating calorie requirements. Nutr Clin Pract 20:468–473, 2005
260. Lim VS, Ikizler TA, Raj DS, Flanigan MJ: Does hemodialysis increase protein breakdown? Dissociation between whole-body amino acid turnover and regional muscle kinetics. J Am Soc Nephrol 16:862–868, 2005
261. Acchiardo SR, Moore LW, Latour PA: Malnutrition as the main factor in morbidity and mortality of hemodialysis patients. Kidney Int Suppl 16:S199-S203, 1983
262. Hakim RM, Breyer J, Ismail N, Schulman G: Effects of dose of dialysis on morbidity and mortality. Am J Kidney Dis 23:661–669, 1994
263. Bergstrom J, Furst P, Alvestrand A, Lindholm B: Protein and energy intake, nitrogen balance and nitrogen losses in patients treated with continuous ambulatory peritoneal dialysis. Kidney Int 44:1048–1057, 1993
264. Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW: Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. Kidney Int 21:849–861, 1982
265. Buchwald R, Pena JC: Evaluation of nutritional status in patients on continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 9:295–301, 1989
266. Ginn HE, Frost A, Lacy WW: Nitrogen balance in hemodialysis patients. Am J Clin Nutr 21:385–393, 1968
267. Giordano C, De Santo NG, Pluvio M, et al: Protein requirement of patients on CAPD: A study on nitrogen balance. Int J Artif Organs 3:11–14, 1980
268. Kopple JD, Shinaberger JH, Coburn JW, Sorensen MK, Rubini ME: Optimal dietary protein treatment during chronic hemodialysis. Trans Am Soc Artif Intern Organs 15:302–308, 1969
269. Mandolfo S, Zucchi A, Cavalieri D'Oro L, Corradi B, Imbasciati E: Protein nitrogen appearance in CAPD patients: What is the best formula? Nephrol Dial Transplant 11:1592–1596, 1996

270. von Baeyer H, Gahl GM, Riedinger H, Borowzak B, Kessel M: Nutritional behaviour of patients on continuous ambulatory peritoneal dialysis. Proc Eur Dial Transplant Assoc 18:193–198, 1981
271. Misra M, Ashworth J, Reaveley DA, Muller B, Brown EA: Nutritional effects of amino acid dialysate (Nutrineal) in CAPD patients. Adv Perit Dial 12:311–314, 1996
272. Canepa A, Perfumo F, Carrea A, et al: Long-term effect of amino-acid dialysis solution in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol 5:215–219, 1991
273. Canepa A, Perfumo F, Carrea A, et al: Continuous ambulatory peritoneal dialysis (CAPD) of children with amino acid solutions: Technical and metabolic aspects. Perit Dial Int 10:215–220, 1990
274. 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 46:22–30, 1987
275. 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 14:34–41, 1994
276. Qamar IU, Secker D, Levin L, Balfe JA, Zlotkin S, Balfe JW: Effects of amino acid dialysis compared to dextrose dialysis in children on continuous cycling peritoneal dialysis. Perit Dial Int 19: 237–247, 1999
277. Azocar MA, Cano FJ, Marin V, Delucchi MA, Rodriguez EE: Body composition in children on peritoneal dialysis. Adv Perit Dial 20:231–236, 2004
278. Civilibal M, Caliskan S, Adaletli I, et al: Coronary artery calcifications in children with end-stage renal disease. Pediatr Nephrol 21:1426–1433, 2006
279. 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 342:1478–1483, 2000
280. Litwin M, Wuhl E, Jourdan C, et al: Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant 23:2552–2557, 2008
281. 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 16:1494–1500, 2005
282. Oh J, Wunsch R, Turzer M, et al: Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation 106:100–105, 2002
283. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H: Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 18:1731–1740, 2003
284. Siirtola A, Virtanen SM, Ala-Houhala M, et al: Diet does not explain the high prevalence of dyslipidaemia in paediatric renal transplant recipients. Pediatr Nephrol 23:297–305, 2008
285. Boaz M, Smetana S: Regression equation predicts dietary phosphorus intake from estimate of dietary protein intake. J Am Diet Assoc 96:1268–1270, 1996
286. Sedlacek M, Dimaano F, Uribarri J: Relationship between phosphorus and creatinine clearance in peritoneal dialysis: Clinical implications. Am J Kidney Dis 36:1020–1024, 2000
287. 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 31:607–617, 1998
288. Uribarri J: The obsession with high dietary protein intake in ESRD patients on dialysis: Is it justified? Nephron 86:105–108, 2000
289. Uribarri J: Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. Semin Dial 20:295–301, 2007
290. Karp HJ, Vaihia KP, Karkkainen MU, Niemisto MJ, Lamberg-Allardt CJ: Acute effects of different phosphorus sources on calcium and bone metabolism in young women: A whole-foods approach. Calcif Tissue Int 80:251–258, 2007
291. American Dietetic Association: Vegetarian Diets in Renal Disease. Vegetarian Nutrition Update. Chicago, IL, Vegetarian Nutrition DPG, American Dietetic Association, 1998
292. Quan A, Baum M: Protein losses in children on continuous cycler peritoneal dialysis. Pediatr Nephrol 10:728–731, 1996
293. Wolfson M, Jones MR, Kopple JD: Amino acid losses during hemodialysis with infusion of amino acids and glucose. Kidney Int 21:500–506, 1982
293a. Chazot C, Shahmir E, Matias B, Laidlaw S, Kopple J: Dialytic nutrition: provision of amino acids in dialysate during hemodialysis. Kidney Int 52:1663–1670, 1997
293b. Ikizler T, Flakoll P, Parker R, Hakim R: Amino acid and albumin losses during hemodialysis. Kidney Int 46:830–837, 1994
294. Kooienga L: Phosphorus balance with daily dialysis. Semin Dial 20:342–345, 2007
295. Canepa A, Carrea A, Menoni S, et al: Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. Kidney Int 59:1967–1973, 2001
296. Tjiong HL, Rietveld T, Wattimena JL, et al: Peritoneal dialysis with solutions containing amino acids plus glucose promotes protein synthesis during oral feeding. Clin J Am Soc Nephrol 2:74–80, 2007
297. Tjiong HL, van den Berg JW, Wattimena JL, 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 16:1486–1493, 2005

298. Kleinman RE: Pediatric Nutrition Handbook. Elk Grove, IL, American Academy of Pediatrics, 2004
299. Otten JJ, Hellwig JP, Meyers LD (eds): Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC, National Academies, 2006
300. Kriley M, Warady BA: Vitamin status of pediatric patients receiving long-term peritoneal dialysis. Am J Clin Nutr 53:1476–1479, 1991
301. Pereira AM, Hamani N, Nogueira PC, Carvalhaes JT: Oral vitamin intake in children receiving long-term dialysis. J Ren Nutr 10:24–29, 2000
302. Rees L, Shaw V: Nutrition in children with CRF and on dialysis. Pediatr Nephrol 22:1689–1702, 2007
303. Warady BA, Kriley M, Alon U, Hellerstein S: Vitamin status of infants receiving long-term peritoneal dialysis. Pediatr Nephrol 8:354–356, 1994
304. Coleman JE, Watson AR: Micronutrient supplementation in children on continuous cycling peritoneal dialysis (CCPD). Adv Perit Dial 8:396–401, 1992
305. Coleman JE, Watson AR, Chowdhury S, Thurlby D, Wardell J: Comparison of two micronutrient supplements in children with chronic renal failure. J Ren Nutr 12:244–247, 2002
306. Filler G: The DOQI pediatric nutritional guidelines—Critical remarks. Perit Dial Int 21:S192-S194, 2001 (suppl 3)
307. Kopple JD, Dirige OV, Jacob M, Wang M, Swendseid ME: Transketolase activity in red blood cells in chronic uremia. Trans Am Soc Artif Intern Organs 18:250–256, 266, 1972
308. Chazot C, Kopple JD: Vitamin metabolism and requirements in renal disease and renal failure, in Kopple JD, Massry SG (eds): Kopple and Massry's Nutritional Management of Renal Disease (ed 2). Philadelphia, PA, Lippincott Williams & Wilkins, 2003, pp 415–478
309. Fouque D, Vennegoor M, ter Wee P, et al: EBPG guideline on nutrition. Nephrol Dial Transplant 22:Sii45-Sii87, 2007 (suppl 2)
310. Laschi-Loquerie A, Vallas S, Viollet J, Leclercq M, Fayol V: High performance liquid chromatographic determination of total thiamine in biological and food products. Int J Vitam Nutr Res 62:248–251, 1992
311. Lynch PL, Young IS: Determination of thiamine by high-performance liquid chromatography. J Chromatogr A 881:267–284, 2000
312. Vuilleumier JP, Keller HE, Rettenmaier R, Hunziker F: Clinical chemical methods for the routine assessment of the vitamin status in human populations. Part II: The water-soluble vitamins B1, B2 and B6. Int J Vitam Nutr Res 53:359–370, 1983
313. Gentile MG, Manna GM, D'Amico G, Testolin G, Porrini M, Simonetti P: Vitamin nutrition in patients with chronic renal failure and dietary manipulation. Contrib Nephrol 65:43–50, 1988
314. Kopple JD, Swendseid ME: Vitamin nutrition in patients undergoing maintenance hemodialysis. Kidney Int Suppl:S79-S84, 1975
315. DeBari VA, Frank O, Baker H, Needle MA: Water soluble vitamins in granulocytes, erythrocytes, and plasma obtained from chronic hemodialysis patients. Am J Clin Nutr 39:410–415, 1984
316. Mackenzie J, Ford J, Waters A, Harding N, Cattell W, Anderson B: Erythropoiesis in patients undergoing regular dialysis treatment (R.D.T.) without transfusion. Proc Eur Dial Transplant Assoc 5:172–178, 1968
317. Sterzel RB, Semar M, Lonergan ET, Treser G, Lange K: Relationship of nervous tissue transketolase to the neuropathy in chronic uremia. J Clin Invest 50:2295–2304, 1971
318. Stockberger R, Parrott K, Alexander S, Miller L, Leklem J, Jenkins R: Vitamin B-6 status of children undergoing continuous ambulatory peritoneal dialysis. Nutr Res 7:1021–1030, 1987
319. Coleman JE, Edefonti A, Watson AR: Guidelines by an ad hoc European committee on the assessment of growth and nutritional status in children on chronic peritoneal dialysis. International Society for Peritoneal Dialysis, 2001, 14 pp
320. Lasker N, Harvey A, Baker H: Vitamin levels in hemodialysis and intermittent peritoneal dialysis. Trans Am Soc Artif Intern Organs 9:51–56, 1963
321. Yatzidis H, Koutsicos D, Alaveras AG, Papastephanidis C, Frangos-Plemenos M: Biotin for neurologic disorders of uremia. N Engl J Med 305:764, 1981
321a. Litwin M, Abuauba M, Wawer ZT, Grenda R, Kuryt T, Pietraszek E. Folate, vitamin B12, and sulfur amino acid levels in patients with renal failure. Pediatr Nephrol 16:127–132, 2001
322. Boeschoten EW, Schrijver J, Krediet RT, Schreurs WH, Arisz L: Deficiencies of vitamins in CAPD patients: The effect of supplementation. Nephrol Dial Transplant 3:187–193, 1988
323. Descombes E, Hanck AB, Fellay G: Water soluble vitamins in chronic hemodialysis patients and need for supplementation. Kidney Int 43:1319–1328, 1993
324. Jamison RL, Hartigan P, Kaufman JS, et al: Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: A randomized controlled trial. JAMA 298:1163–1170, 2007
325. Sunder-Plassmann G, Winkelmayer WC, Fodinger M: Approaching the end of the homocysteine hype? Am J Kidney Dis 51:549–553, 2008
326. Feinstein S, Sela BA, Drukker A, et al: Hyperhomocysteinemia in children on renal replacement therapy. Pediatr Nephrol 17:515–519, 2002
327. Kang HG, Lee BS, Hahn H, et al: Reduction of plasma homocysteine by folic acid in children with chronic renal failure. Pediatr Nephrol 17:511–514, 2002
328. Schroder CH, de Boer AW, Giesen AM, Monnens LA, Blom H: Treatment of hyperhomocysteinemia in children on dialysis by folic acid. Pediatr Nephrol 13:583–585, 1999

329. Bennett-Richards K, Kattenhorn M, Donald A, et al: Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure? Circulation 105:1810–1815, 2002
330. Bamgbola OF, Kaskel F: Role of folate deficiency on erythropoietin resistance in pediatric and adolescent patients on chronic dialysis. Pediatr Nephrol 20:1622–1629, 2005
331. Merouani A, Lambert M, Delvin EE, Genest J Jr, Robitaille P, Rozen R: Plasma homocysteine concentration in children with chronic renal failure. Pediatr Nephrol 16:805–811, 2001
332. Clarke R, Armitage J: Vitamin supplements and cardiovascular risk: Review of the randomized trials of homocysteine-lowering vitamin supplements. Semin Thromb Hemost 26:341–348, 2000
333. Spence JD, Cordy P, Kortas C, Freeman D: Effect of usual doses of folate supplementation on elevated plasma homocyst(e)ine in hemodialysis patients: No difference between 1 and 5 mg daily. Am J Nephrol 19:405–410, 1999
334. Pollock C, Voss D, Hodson E, Crompton C: The CARI guidelines. Nutrition and growth in kidney disease. Nephrology (Carlton) 10:S177-S230, 2005 (suppl 5)
335. Blumberg A, Hanck A, Sander G: Vitamin nutrition in patients on continuous ambulatory peritoneal dialysis (CAPD). Clin Nephrol 20:244–250, 1983
336. 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 7:745–750, 1996
337. Wiggins KL (ed): Renal Care: Resources and Practical Applications. Chicago, IL, American Dietetic Association, 2004
338. Ono K: Secondary hyperoxalemia caused by vitamin C supplementation in regular hemodialysis patients. Clin Nephrol 26:239–243, 1986
339. Rolton HA, McConnell KM, Modi KS, Macdougall AI: The effect of vitamin C intake on plasma oxalate in patients on regular haemodialysis. Nephrol Dial Transplant 6:440–443, 1991
340. Gentile MG, Fellin G, Manna GM, et al: Vitamin A and retinol binding protein in chronic renal insufficiency. Int J Artif Organs 11:403–404, 1988
341. Vannucchi MT, Vannucchi H, Humphreys M: Serum levels of vitamin A and retinol binding protein in chronic renal patients treated by continuous ambulatorial peritoneal dialysis. Int J Vitam Nutr Res 62:107–112, 1992
342. Kopple JD: Dietary considerations in patients with advanced chronic renal failure, acute renal failure, and transplantation, in Shrier RW, Gottschalk CW (eds): Diseases of the Kidney (ed 4). Boston, MA, Little, Brown, 1988, pp 3167–3210
343. Makoff R: Vitamin supplementation in patients with renal disease. Dial Transplant 21:18–36, 1992
344. de Cavanagh EM, Ferder L, Carrasquedo F, et al: Higher levels of antioxidant defenses in enalapril-treated versus non-enalapril-treated hemodialysis patients. Am J Kidney Dis 34:445–455, 1999
345. Giardini O, Cantani A, Donfrancesco A: Vitamin E therapy in homozygous beta-thalassemia. N Engl J Med 305:644, 1981
346. Stein G, Sperschneider H, Koppe S: Vitamin levels in chronic renal failure and need for supplementation. Blood Purif 3:52–62, 1985
347. De Bevere VO, Nelis HJ, De Leenheer AP, Lambert WE, De Paepe M, Ringoir S: Vitamin E levels in hemodialysis patients. JAMA 247:2371, 1982
348. Hultqvist M, Hegbrant J, Nilsson-Thorell C, et al: Plasma concentrations of vitamin C, vitamin E and/or malondialdehyde as markers of oxygen free radical production during hemodialysis. Clin Nephrol 47:37–46, 1997
349. Bonnefont-Rousselot D, Jaudon MC, Issad B, et al: Antioxidant status of elderly chronic renal patients treated by continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 12:1399–1405, 1997
350. Nikolakakis N, Kounali D, Tornaritis M, et al: Adipose tissue fatty acid composition, serum lipids, and serum alpha-tocopherol in continuous ambulatory peritoneal dialysis patients living on the island of Crete. Perit Dial Int 19:154–159, 1999
351. Nemeth I, Turi S, Haszon I, Bereczki C: Vitamin E alleviates the oxidative stress of erythropoietin in uremic children on hemodialysis. Pediatr Nephrol 14:13–17, 2000
352. Thabet MA, Chan JC: Vitamin E in renal therapeutic regiments. Pediatr Nephrol 21:1790–1801, 2006
353. Tamura T, Vaughn WH, Waldo FB, Kohaut EC: Zinc and copper balance in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol 3:309–313, 1989
354. Zachara BA, Gromadzinska J, Wasowicz W, Zbrog Z: Red blood cell and plasma glutathione peroxidase activities and selenium concentration in patients with chronic kidney disease: A review. Acta Biochim Pol 53:663–677, 2006
355. Baker SS, Cochran WJ, Flores CA, et al: American Academy of Pediatrics, Committee on Nutrition. Calcium requirements of infants, children, and adolescents. Pediatrics 104:1152–1157, 1999
356. Weaver CM: Calcium bioavailability and its relation to osteoporosis. Proc Soc Exp Biol Med 200:157–160, 1992
357. Weaver CM, Plawecki KL: Dietary calcium: Adequacy of a vegetarian diet. Am J Clin Nutr 59:S1238-S1241, 1994 (suppl 5)
358. Weaver CM, Proulx WR, Heaney R: Choices for achieving adequate dietary calcium with a vegetarian diet. Am J Clin Nutr 70:S543-S548, 1999 (suppl 3)
359. Andon MB, Peacock M, Kanerva RL, De Castro JA: Calcium absorption from apple and orange juice fortified with calcium citrate malate (CCM). J Am Coll Nutr 15:313–316, 1996
360. Hsu CH: Are we mismanaging calcium and phosphate metabolism in renal failure? Am J Kidney Dis 29:641–649, 1997

361. Raper NR, Zissa C, Rourke J: Nutrient Content of the US Food Supply, 1909–1988: Home Economics Research Report. Washington, DC, US Department of Agriculture, 1992
362. Coburn JW, Mischel MG, Goodman WG, Salusky IB: Calcium citrate markedly enhances aluminum absorption from aluminum hydroxide. Am J Kidney Dis 17:708–711, 1991
363. Coburn JW, Koppel MH, Brickman AS, Massry SG: Study of intestinal absorption of calcium in patients with renal failure. Kidney Int 3:264–272, 1973
364. Recker RR, Saville PD: Calcium absorption in renal failure: Its relationship to blood urea nitrogen, dietary calcium intake, time on dialysis, and other variables. J Lab Clin Med 78:380–388, 1971
365. Alon U, Davidai G, Bentur L, Berant M, Better OS: Oral calcium carbonate as phosphate-binder in infants and children with chronic renal failure. Miner Electrolyte Metab 12:320–325, 1986
366. Andreoli SP, Dunson JW, Bergstein JM: Calcium carbonate is an effective phosphorus binder in children with chronic renal failure. Am J Kidney Dis 9:206–210, 1987
367. Salusky IB, Coburn JW, Foley J, Nelson P, Fine RN: Effects of oral calcium carbonate on control of serum phosphorus and changes in plasma aluminum levels after discontinuation of aluminum-containing gels in children receiving dialysis. J Pediatr 108:767–770, 1986
368. Sieniawska M, Roszkowska-Blaim M, Weglarska J, Jablczynska A, Welc-Dobies J: Calcium carbonate as a phosphate binder in children on continuous ambulatory peritoneal dialysis and hemodialysis. Mater Med Pol 23:203–208, 1991
369. Tamanaha K, Mak RH, Rigden SP, et al: Long-term suppression of hyperparathyroidism by phosphate binders in uremic children. Pediatr Nephrol 1:145–149, 1987
370. Wallot M, Bonzel KE, Winter A, Georger B, Lettgen B, Bald M: Calcium acetate versus calcium carbonate as oral phosphate binder in pediatric and adolescent hemodialysis patients. Pediatr Nephrol 10:625–630, 1996
371. Sheikh MS, Maguire JA, Emmett M, et al: Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical, in vitro, and in vivo study. J Clin Invest 83:66–73, 1989
372. Janssen MJ, van der Kuy A, ter Wee PM, van Boven WP: Aluminum hydroxide, calcium carbonate and calcium acetate in chronic intermittent hemodialysis patients. Clin Nephrol 45:111–119, 1996
373. Pflanz S, Henderson IS, McElduff N, Jones MC: Calcium acetate versus calcium carbonate as phosphate-binding agents in chronic haemodialysis. Nephrol Dial Transplant 9:1121–1124, 1994
374. Ring T, Nielsen C, Andersen SP, Behrens JK, Sodemann B, Kornerup HJ: Calcium acetate versus calcium carbonate as phosphorus binders in patients on chronic haemodialysis: A controlled study. Nephrol Dial Transplant 8:341–346, 1993
375. Schiller LR, Santa Ana CA, Sheikh MS, Emmett M, Fordtran JS: Effect of the time of administration of calcium acetate on phosphorus binding. N Engl J Med 320:1110–1113, 1989
376. Food and Nutrition Board: Dietary Reference Intakes For Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Food and Nutrition Board. Washington, DC, National Academy, 1997
377. Chanard JM, Drueke T, Zingraff J, Man NK, Russo-Marie F, Funck-Brentano JL: Effects of haemodialysis on fractional intestinal absorption of calcium in uraemia. Eur J Clin Invest 6:261–264, 1976
378. Ardissino G, Schmitt CP, Bianchi ML, Dacco V, Claris-Appiani A, Mehls O: No difference in intestinal strontium absorption after oral or IV calcitriol in children with secondary hyperparathyroidism. The European Study Group on Vitamin D in Children with Renal Failure. Kidney Int 58: 981–988, 2000
379. Kurz P, Monier-Faugere MC, Bognar B, et al: Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. Kidney Int 46:855–861, 1994
380. 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 9:271–273, 1993
381. Malberti F, Corradi B, Imbasciati E: Calcium mass transfer and kinetics in CAPD using calcium-free solutions. Adv Perit Dial 9:274–279, 1993
382. Piraino B, Bernardini J, Holley J, Johnston JR, Perlmutter JA, Martis L: Calcium mass transfer in peritoneal dialysis patients using 2.5 mEq/l calcium dialysate. Clin Nephrol 37:48–51, 1992
383. Sieniawska M, Roszkowska-Blaim M, Wojciechowska B: The influence of dialysate calcium concentration on the PTH level in children undergoing CAPD. Perit Dial Int 16:S567-S569, 1996 (suppl 1)
384. Weinreich T, Colombi A, Echterhoff HH, et al: Transperitoneal calcium mass transfer using dialysate with a low calcium concentration (1.0 mM). Perit Dial Int 13:S467-S470, 1993 (suppl 2)
385. Fabrizi F, Bacchini G, Di Filippo S, Pontoriero G, Locatelli F: Intradialytic calcium balances with different calcium dialysate levels. Effects on cardiovascular stability and parathyroid function. Nephron 72:530–535, 1996
386. Fernandez E, Borras M, Pais B, Montoliu J: Low-calcium dialysate stimulates parathormone secretion and its long-term use worsens secondary hyperparathyroidism. J Am Soc Nephrol 6:132–135, 1995
387. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK: Vitamin D status in the elderly: Seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. Am J Clin Nutr 45:755–763, 1987
388. Khaw KT, Sneyd MJ, Compston J: Bone density parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ 305:273–277, 1992

389. Eastwood JB, Stamp TC, De Wardener HE, Bordier PJ, Arnaud CD: The effect of 25-hydroxy vitamin D3 in the osteomalacia of chronic renal failure. Clin Sci Mol Med 52:499–508, 1977
390. Eastwood JB, Stamp TC, Harris E, de Wardener HE: Vitamin-D deficiency in the osteomalacia of chronic renal failure. Lancet 2:1209–1211, 1976
391. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J: Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 281:1505–1511, 1999
392. Lips P, van Ginkel FC, Jongen MJ, Rubertus F, van der Vijgh WJ, Netelenbos JC: Determinants of vitamin D status in patients with hip fracture and in elderly control subjects. Am J Clin Nutr 46:1005–1010, 1987
393. Chapuy MC, Arlot ME, Duboeuf F, et al: Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 327:1637–1642, 1992
394. Ishimura E, Nishizawa Y, Inaba M, et al: Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. Kidney Int 55:1019–1027, 1999
395. Reichel H, Deibert B, Schmidt-Gayk H, Ritz E: Calcium metabolism in early chronic renal failure: Implications for the pathogenesis of hyperparathyroidism. Nephrol Dial Transplant 6:162–169, 1991
396. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al: Hypovitaminosis D in medical inpatients. N Engl J Med 338:777–783, 1998
397. Papapoulos SE, Clemens TL, Fraher LJ, Gleed J, O'Riordan JL: Metabolites of vitamin D in human vitamin-D deficiency: Effect of vitamin D3 or 1,25-dihydroxycholecalciferol. Lancet 2:612–615, 1980
398. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42:S1-S201, 2003 (suppl 3)
399. Holick MF: Vitamin D and the kidney. Kidney Int 32:912–929, 1987
400. Saha H: Calcium and vitamin D homeostasis in patients with heavy proteinuria. Clin Nephrol 41:290–296, 1994
401. Ghazali A, Fardellone P, Pruna A, et al: Is low plasma 25-(OH)vitamin D a major risk factor for hyperparathyroidism and Looser's zones independent of calcitriol? Kidney Int 55:2169–2177, 1999
402. Dusso A, Lopez-Hilker S, Rapp N, Slatopolsky E: Extra-renal production of calcitriol in chronic renal failure. Kidney Int 34:368–375, 1988
403. Dusso AS, Finch J, Brown A, et al: Extrarenal production of calcitriol in normal and uremic humans. J Clin Endocrinol Metab 72:157–164, 1991
404. Lambert PW, Stern PH, Avioli RC, et al: Evidence for extrarenal production of 1 alpha,25-dihydroxyvitamin D in man. J Clin Invest 69:722–725, 1982
405. Birge SJ, Haddad JG: 25-hydroxycholecalciferol stimulation of muscle metabolism. J Clin Invest 56:1100–1107, 1975
406. Houghton LA, Vieth R: The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 84:694–697, 2006
407. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R: Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr 68:854–858, 1998
408. Shah BR, Finberg L: Single-day therapy for nutritional vitamin D-deficiency rickets: A preferred method. J Pediatr 125:487–490, 1994
409. Combe C, Aparicio M: Phosphorus and protein restriction and parathyroid function in chronic renal failure. Kidney Int 46:1381–1386, 1994
410. Lafage MH, Combe C, Fournier A, Aparicio M: Ketodiet, physiological calcium intake and native vitamin D improve renal osteodystrophy. Kidney Int 42:1217–1225, 1992
411. Shroff RC, Donald AE, Hiorns MP, et al: Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol 18:2996–3003, 2007
412. Llach F, Massry SG, Singer FR, Kurokawa K, Kaye JH, Coburn JW: Skeletal resistance to endogenous parathyroid hormone in patients with early renal failure. A possible cause for secondary hyperparathyroidism. J Clin Endocrinol Metab 41:339–345, 1975
413. 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 73:1580–1589, 1984
414. Portale AA, Booth BE, Tsai HC, Morris RC Jr: Reduced plasma concentration of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. Kidney Int 21:627–632, 1982
415. Llach F, Massry SG: On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. J Clin Endocrinol Metab 61:601–606, 1985
416. Turner C, Compston J, Mak RH, et al: Bone turnover and 1,25-dihydroxycholecalciferol during treatment with phosphate binders. Kidney Int 33:989–995, 1988
417. Jureidini KF, Hogg RJ, van Renen MJ, et al: Evaluation of long-term aggressive dietary management of chronic renal failure in children. Pediatr Nephrol 4:1–10, 1990
418. Kist-van Holthe tot Echten JE, Nauta J, Hop WC, et al: Protein restriction in chronic renal failure. Arch Dis Child 68:371–375, 1993
419. Uauy RD, Hogg RJ, Brewer ED, Reisch JS, Cunningham C, Holliday MA: Dietary protein and growth in infants with chronic renal insufficiency: A report from the Southwest Pediatric Nephrology Study Group and the University of California, San Francisco. Pediatr Nephrol 8:45–50, 1994
420. Ihle BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid-Smith PS: The effect of protein restriction on the progression of renal insufficiency. N Engl J Med 321:1773–1777, 1989

421. Mahmoud MD, Bouche V, Collin P, Girault A: Effects of keto-analogues on phosphocalcic and aminoacid metabolism in dialysed patients: A cross-over study. Int J Artif Organs 12:692–696, 1989
422. Williams PS, Stevens ME, Fass G, Irons L, Bone JM: Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: A prospective, randomized, controlled trial. Q J Med 81:837–855, 1991
423. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 324:78–84, 1991
424. Klaus G, Watson A, Edefonti A, et al: Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol 21:151–159, 2006
425. Rees L: What parathyroid hormone levels should we aim for in children with stage 5 chronic kidney disease; What is the evidence? Pediatr Nephrol 23:179–184, 2008
426. Tenenhouse HS, Murer H: Disorders of renal tubular phosphate transport. J Am Soc Nephrol 14:240–248, 2003
427. Sullivan CM, Leon JB, Sehgal AR: Phosphorus-containing food additives and the accuracy of nutrient databases: Implications for renal patients. J Ren Nutr 17:350–354, 2007
428. Uribarri J, Calvo MS: Hidden sources of phosphorus in the typical American diet: Does it matter in nephrology? Semin Dial 16:186–188, 2003
429. Russo D, Miranda I, Ruocco C, et al: The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int 72:1255–1261, 2007
430. Levin NW, Gotch FA, Kuhlmann MK: Factors for increased morbidity and mortality in uremia: Hyperphosphatemia. Semin Nephrol 24:396–400, 2004
431. Rodriguez-Benot A, Martin-Malo A, Alvarez-Lara MA, Rodriguez M, Aljama P: Mild hyperphosphatemia and mortality in hemodialysis patients. Am J Kidney Dis 46:68–77, 2005
432. Voormolen N, Noordzij M, Grootendorst DC, et al: High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant 22:2909–2916, 2007
433. Cozzolino M, Brancaccio D, Gallieni M, Slatopolsky E: Pathogenesis of vascular calcification in chronic kidney disease. Kidney Int 68:429–436, 2005
434. Giachelli CM: Vascular calcification: In vitro evidence for the role of inorganic phosphate. J Am Soc Nephrol 14: S300-S304, 2003 (suppl 4)
435. Salusky IB, Goodman WG, Sahney S, 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 16:2501–2508, 2005
436. Pieper AK, Haffner D, Hoppe B, et al: A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. Am J Kidney Dis 47:625–635, 2006
437. Ferrara E, Lemire J, Reznik VM, Grimm PC: Dietary phosphorus reduction by pretreatment of human breast milk with sevelamer. Pediatr Nephrol 19:775–779, 2004
438. Raaijmakers R, Willems J, Houkes B, Heuvel CS, Monnens LA: Pretreatment of various dairy products with sevelamer: Effective P reduction but also a rise in pH. Perit Dial Int 29:S15A, 2008 (suppl 4; abstr)
439. Block GA, Spiegel DM, Ehrlich J, et al: Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 68:1815–1824, 2005
440. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 62:245–252, 2002
441. Suki WN, Zabaneh R, Cangiano JL, et al: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int 72:1130–1137, 2007
442. Hutchison AJ, Maes B, Vanwalleghem J, et al: Efficacy, tolerability, and safety of lanthanum carbonate in hyperphosphatemia: A 6-month, randomized, comparative trial versus calcium carbonate. Nephron Clin Pract 100:c8-c19, 2005
443. Lacour B, Lucas A, Auchere D, Ruellan N, de Serre Patey NM, Drueke TB: Chronic renal failure is associated with increased tissue deposition of lanthanum after 28-day oral administration. Kidney Int 67:1062–1069, 2005
444. National Kidney Foundation: K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:S1-S290, 2004 (suppl 1)
445. Wassner SJ, Kulin HE: Diminished linear growth associated with chronic salt depletion. Clin Pediatr (Phila) 29:719–721, 1990
446. Ray PE, Lyon RC, Ruley EJ, Holliday MA: Sodium or chloride deficiency lowers muscle intracellular pH in growing rats. Pediatr Nephrol 10:33–37, 1996
447. Parekh R, Smoyer WE, Milne JL, et al: Letter from the authors of "Improved Growth in Young Children with Severe Chronic Renal Insufficiency Who Use Specified Nutritional Therapy." J Am Soc Nephrol 13:1421–1422, 2002
448. Food and Nutrition Board: Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC, The National Academies, 2004
449. Paulson WD, Bock GH, Nelson AP, Moxey-Mims MM, Crim LM: Hyponatremia in the very young chronic peritoneal dialysis patient. Am J Kidney Dis 14:196–199, 1989
450. Hadtstein C, Schaefer F: Hypertension in children with chronic kidney disease: Pathophysiology and management. Pediatr Nephrol 23:363–371, 2008

451. 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 45:309–315, 2005
452. Lerner GR, Warady BA, Sullivan EK, Alexander SR: Chronic dialysis in children and adolescents. The 1996 annual report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 13:404–417, 1999
453. Loirat C, Ehrich JH, Geerlings W, et al: Report on management of renal failure in children in Europe, XXIII, 1992. Nephrol Dial Transplant 9:S26-S40, 1994 (suppl 1)
454. Mitsnefes M, Ho PL, McEnery PT: 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 14:2618–2622, 2003
455. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 114:S555-S576, 2004 (suppl 4)
456. He FJ, MacGregor GA: Importance of salt in determining blood pressure in children: Meta-analysis of controlled trials. Hypertension 48:861–869, 2006
457. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S: Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. Nephrol Dial Transplant 13:552–553, 1998
458. Maduell F, Navarro V: Dietary salt intake and blood pressure control in haemodialysis patients. Nephrol Dial Transplant 15:2063, 2000
459. Shaldon S: Dietary salt restriction and drug-free treatment of hypertension in ESRD patients: A largely abandoned therapy. Nephrol Dial Transplant 17:1163–1165, 2002
460. US Department of Health and Human Services and US Department of Agriculture: Dietary Guidelines for Americans. Washington, DC, US Government Printing Office, 2005, p 70
461. Garriguet D: Sodium consumption at all ages. Health Rep 18:47–52, 2007
462. Mattes RD, Donnelly D: Relative contributions of dietary sodium sources. J Am Coll Nutr 10:383–393, 1991
463. Sanders PW: Assessment and treatment of hypertension in dialysis: The case for salt restriction. Semin Dial 20:408–411, 2007
464. Tomson CR: Advising dialysis patients to restrict fluid intake without restricting sodium intake is not based on evidence and is a waste of time. Nephrol Dial Transplant 16:1538–1542, 2001
465. Biesecker R, Stuart N: Nutrition management of the adult hemodialysis patient, in Byham-Gray L, Wiesen K (eds): A Clinical Guide to Nutrition Care in Kidney Disease (ed 1). Chicago, IL, American Dietetic Association, 2004, pp 43–55
465. Falkenhein M, Hartman J, Hebert L: Nutritional management of water, sodium, potassium, chloride and magnesium in renal disease and renal failure, in Kopple JD, Massry SG (eds): Nutritional Management of Renal Disease (ed 1). Baltimore, MD, Williams & Wilkins, 1997, pp 371–394
467. Schiro-Harvey K: Renal Dietitians Dietetic Practice Group: National Renal Diet: Professional Guide. Chicago, IL, American Dietetic Association, 2002
468. Burrowes JD, Ramer NJ: Removal of potassium from tuberous root vegetables by leaching. J Ren Nutr 16:304–311, 2006
469. Louis CJ, Dolan EM: Removal of potassium in potatoes by leaching. J Am Diet Assoc 57:42–43, 1970
470. Doorenbos CJ, Vermeij CG: Danger of salt substitutes that contain potassium in patients with renal failure. BMJ 326:35–36, 2003
471. Smellie WS: Spurious hyperkalaemia. BMJ 334:693–695, 2007
472. Stover J: Non-dietary causes of hyperkalemia. Nephrol Nurs J 33:221–222, 2006
473. Bunchman TE, Wood EG, Schenck MH, Weaver KA, Klein BL, Lynch RE: Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. Pediatr Nephrol 5:29–32, 1991
474. Fassinger N, Dabbagh S, Mukhopadhyay S, Lee DY: Mineral content of infant formula after treatment with sodium polystyrene sulfonate or calcium polystyrene sulfonate. Adv Perit Dial 14:274–277, 1998
475. Gowrishankar M, Kerr L, Bamforth F, Yiu V, Spady D: Kayexalate treatment of infant formula reduces potassium content. J Am Soc Nephrol 14:467A, 2003
476. Rivard AL, Raup SM, Beilman GJ: Sodium polystyrene sulfonate used to reduce the potassium content of a high-protein enteral formula: A quantitative analysis. JPEN J Parenter Enteral Nutr 28:76–78, 2004
477. Schroder CH, van den Berg AM, Willems JL, Monnens LA: Reduction of potassium in drinks by pre-treatment with calcium polystyrene sulphonate. Eur J Pediatr 152:263–264, 1993
478. 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 23:167–169, 2007
479. Hodson E: The CARI guidelines. Sodium chloride and water intake in children. Nephrology (Carlton) 10:S211-S212, 2005 (suppl 5)
480. Voss D: The CARI guidelines. Potassium in predialysis patients. Nephrology (Carlton) 10:S188-S190, 2005 (suppl 5)
481. Reuter SE, Faull RJ, Evans AM: L-Carnitine supplementation in the dialysis population: Are Australian patients missing out? Nephrology (Carlton) 13:3–16, 2008
482. Belay B, Esteban-Cruciani N, Walsh CA, Kaskel FJ: The use of levo-carnitine in children with renal disease: A review and a call for future studies. Pediatr Nephrol 21:308–317, 2006

483. Evans AM, Fornasini G: Pharmacokinetics of L-carnitine. Clin Pharmacokinet 42:941–967, 2003
484. Evans A: Dialysis-related carnitine disorder and levocarnitine pharmacology. Am J Kidney Dis 41:S13-S26, 2003 (suppl 4)
485. Verrina E, Caruso U, Calevo MG, et al: Effect of carnitine supplementation on lipid profile and anemia in children on chronic dialysis. Pediatr Nephrol 22:727–733, 2007
486. 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 10:109–114, 1990
487. Eknoyan G, Latos DL, Lindberg J: Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. National Kidney Foundation Carnitine Consensus Conference. Am J Kidney Dis 41:868–876, 2003
488. Guarnieri G, Biolo G, Vinci P, Massolino B, Barazzoni R: Advances in carnitine in chronic uremia. J Ren Nutr 17:23–29, 2007
489. Kosan C, Sever L, Arisoy N, Caliskan S, Kasapcopur O: Carnitine supplementation improves apolipoprotein B levels in pediatric peritoneal dialysis patients. Pediatr Nephrol 18:1184–1188, 2003
490. Lilien MR, Duran M, Quak JM, Frankhuisen JJ, Schroder CH: Oral L-carnitine does not decrease erythropoietin requirement in pediatric dialysis. Pediatr Nephrol 15:17–20, 2000
491. National Kidney Foundation: KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 47:S11-S145, 2006 (suppl 3)
492. Simenhoff ML, Burke JF, Saukkonen JJ, Ordinario AT, Doty R: Biochemical profile of uremic breath. N Engl J Med 297:132–135, 1977
493. Schroder CH: The management of anemia in pediatric peritoneal dialysis patients. Guidelines by an ad hoc European committee. Pediatr Nephrol 18:805–809, 2003
494. Levey AS, Eckardt KU, Tsukamoto Y, et al: Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 67:2089–2100, 2005
495. Craig JC: Kidney transplantation in children: The preferred option but still no cure. Am J Kidney Dis 51:880–881, 2008
496. White CT, Schisler T, Er L, Djurdjev O, Matsuda-Abedini M: CKD following kidney transplantation in children and adolescents. Am J Kidney Dis 51:996–1004, 2008
497. McPartland KJ, Pomposelli JJ: Update on immunosuppressive drugs used in solid-organ transplantation and their nutrition implications. Nutr Clin Pract 22:467–473, 2007
498. Meier-Kriesche HU, Arndorfer JA, Kaplan B: The impact of body mass index on renal transplant outcomes: A significant independent risk factor for graft failure and patient death. Transplantation 73:70–74, 2002
499. National Kidney Foundation: Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: A report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 4:13–53, 2004
500. Milliner DS, Morgenstern BZ, Murphy M, Gonyea J, Sterioff S: Lipid levels following renal transplantation in pediatric recipients. Transplant Proc 26:112–114, 1994
501. Querfeld U, Lang M, Friedrich JB, Kohl B, Fiehn W, Scharer K: Lipoprotein(a) serum levels and apolipoprotein(a) phenotypes in children with chronic renal disease. Pediatr Res 34:772–776, 1993
502. Singh A, Tejani C, Benfield M, Tejani A: Sequential analysis of the lipid profile of children post-renal transplantation. Pediatr Transplant 2:216–223, 1998
503. Van Gool S, Van Damme-Lombaerts R, Cobbaert C, Proesmans W, Eggermont E: Lipid and lipoprotein abnormalities in children on hemodialysis and after renal transplantation. Transplant Proc 23:1375–1377, 1991
504. Bhakta N, Marik J, Malekzadeh M, Gjertson D, Ettenger R: Can pediatric steroid-free renal transplantation improve growth and metabolic complications? Pediatr Transplant 12:854–861, 2008
505. Sarwal MM, Vidhun JR, Alexander SR, Satterwhite T, Millan M, Salvatierra O Jr: Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. Transplantation 76:1331–1339, 2003
506. Sgambat K, He J, McCarter RJ, Moudgil A: Lipoprotein profile changes in children after renal transplantation in the modern immunosuppression era. Pediatr Transplant 12:796–803, 2008
507. Parekh RS, Carroll CE, Wolfe RA, Port FK: Cardiovascular mortality in children and young adults with end-stage kidney disease. J Pediatr 141:191–197, 2002
508. Ferraris JR, Ghezzi L, Waisman G, Krmar RT: Potential cardiovascular risk factors in paediatric renal transplant recipients. Pediatr Nephrol 21:119–125, 2006
509. Silverstein DM: Risk factors for cardiovascular disease in pediatric renal transplant recipients. Pediatr Transplant 8:386–393, 2004
510. Aldamiz-Echevarria L, Vallo A, Sanjurjo P, et al: Influence of diet on atherogenic risk in children with renal transplants. Pediatr Nephrol 19:1039–1045, 2004
511. Delucchi A, Marin V, Trabucco G, et al: Dyslipidemia and dietary modification in Chilean renal pediatric transplantation. Transplant Proc 33:1297–1301, 2001

512. Guida B, Trio R, Laccetti R, et al: Role of dietary intervention on metabolic abnormalities and nutritional status after renal transplantation. Nephrol Dial Transplant 22:3304–3310, 2007
513. Al-Uzri A, Stablein DM, A Cohn R: Posttransplant diabetes mellitus in pediatric renal transplant recipients: A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Transplantation 72:1020–1024, 2001
514. Levi M: Post-transplant hypophosphatemia. Kidney Int 59:2377–2387, 2001
515. Chan JC: Post-transplant metabolic bone complications and optimization of treatment. Pediatr Transplant 11:349–353, 2007
516. Saland JM, Goode ML, Haas DL, Romano TA, Seikaly MG: The prevalence of osteopenia in pediatric renal allograft recipients varies with the method of analysis. Am J Transplant 1:243–250, 2001
517. Leonard MB, Bachrach LK: Assessment of bone mineralization following renal transplantation in children: Limitations of DXA and the confounding effects of delayed growth and development. Am J Transplant 1:193–196, 2001
518. Canani RB, Cirillo P, Roggero P, et al: Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics 117:e817-e820, 2006
519. US Department of Agriculture: Food Safety for Transplant Recipients. A Need-to-Know Guide for Bone Marrow and Solid Organ Transplant Recipients. Washington, DC, US Department of Agriculture, Food Safety and Inspection Service, 2006, p 24
520. Cole TJ: The LMS method for constructing normalized growth standards. Eur J Clin Nutr 44:45–60, 1990
521. Secker D: Infancy, childhood and adolescence, in Byham-Gray LD, Burrowes JD, Chertow GM (eds): Nutrition in Kidney Disease. New York, NY, Humana, 2008, pp 431–467
522. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM: Standardized reporting of clinical practice guidelines: A proposal from the Conference on Guideline Standardization. Ann Intern Med 139:493–498, 2003
523. Schaefer F, Wuhl E, Feneberg R, Mehls O, Scharer K: Assessment of body composition in children with chronic renal failure. Pediatr Nephrol 14:673–678, 2000
524. Specker BL, Lichtenstein P, Mimouni F, Gormley C, Tsang RC: Calcium-regulating hormones and minerals from birth to 18 months of age. A cross-sectional study. II. Effects of sex, race, age, season, and diet on serum minerals, parathyroid hormone, and calcitonin. Pediatrics 77:891–896, 1986

Technical Aspects of Controlled Enteral Nutrition in Pediatric Dialysis

23

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Keywords
Controlled enteral nutrition • Pediatric dialysis • Children

Introduction

Concerns regarding the adequacy of nutritional intake among children with chronic renal failure are common, primarily due to the impact nutritional intake may have on growth and neurodevelopment. In some children, oral intake is insufficient to support normal growth and development, and must be supplemented with nasogastric (NG) or gastrostomy tube feedings, wherein nutrition is provided via a tube that delivers nutrients distal to the oral cavity. This chapter will review the rationale underlying the use of tube feeding, the existing evidence supporting the use of tube feeding in children with renal insufficiency, and the indications for tube feeding. In addition, we will consider the advantages and disadvantages of NG versus gastrostomy tube feeding, the practical details of tube feeding prescriptions, and the potential complications. The transition from tube to oral feedings will also be discussed.

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Rationale for Nutritional Supplementation in Pediatric Renal Insufficiency

Growth retardation is a common feature of pediatric chronic renal failure. One of the mechanisms underlying renal failure–related growth retardation is inadequate caloric intake. Calorie intake may be limited by anorexia, due to a combination of factors including altered taste, gastroesophageal reflux, delayed gastric emptying, and elevated levels of numerous cytokines, including leptin, IL-1, IL-6, and TNF-α [1, 2]. Children with polyuric chronic kidney disease (CKD) may have diminished appetite due to consumption of large volumes of water. Frequent vomiting may also impair calorie intake in CKD. Abdominal fullness due to the presence of dialysate may also compromise appetite among children on peritoneal dialysis.

Poor spontaneous calorie intake is particularly problematic among infants with CKD and routine calorie supplementation has been shown to improve growth [3–6]. In contrast, energy intakes

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for older children are usually normal relative to body size [7], and the role for nutritional supplements in improving growth is controversial; clear evidence that nutritional supplements improve growth in older children is lacking.

There is a sound theoretical basis for this age-dependent response to calorie supplementation in renal insufficiency. Normal postnatal growth can be divided into three phases, each primarily influenced by a different factor. The *infancy phase* of growth is driven primarily by nutrition, whereas the *childhood* and *pubertal* phases are dominated by growth hormone and sex hormones respectively [8]. Therefore, nutritional intake has the greatest influence during the infancy phase of growth [9, 10]. In healthy infants, the infancy phase of growth is replaced by the childhood phase between 6 and 12 months of age. However, in renal insufficiency, onset of the childhood phase is frequently delayed until 2–3 years of age, or interrupted by a transient resumption of the infancy pattern [8, 9, 11, 12]. Therefore, this chapter will focus primarily on infants and children under 3 years of age – in whom nutritional interventions are most likely to provide an important benefit. However, the evidence for nutritional intervention in older children will also be briefly considered.

Weight loss, or wasting, is another reason that nutritional supplements may be considered in children with renal insufficiency. Both children and adults with renal insufficiency have long been considered at high risk for "malnutrition" or wasting, defined as low weight for height [13]. However, outside infancy, the role of nutrient intake in maintaining normal body composition in renal insufficiency has been questioned recently [14–18]. Abnormalities in body composition may be better attributed to cachexia – a loss of lean mass resulting from multiple causes including systemic inflammation [19], acidosis-related disturbances in the ubiquitin–proteosome pathway [17, 20–22], and disturbed neuropeptide signaling [23]. Alterations to the growth hormone–insulin-like growth factor axis may also play a role in renal insufficiency–related cachexia [24]. Cachexia is often not remediable with increased calorie or protein intake [25]. Unless calorie intake is clearly below estimated needs, there is little evidence that increased calorie intake will normalize body composition.

The potential benefits of nutritional supplementation on neurodevelopment have never been rigorously studied in the setting of renal insufficiency. However, studies of otherwise healthy malnourished children have established an important role for nutrition in normal brain development. Malnourished infants have been repeatedly demonstrated to have intellectual deficits compared to their well-nourished counterparts [26, 27]. Observational data in children with renal insufficiency suggest that developmental outcomes are improved when adequate nutrition is provided during infancy [28]. Because brain growth is most rapid during the first 3 years of life, nutritional intervention has the most potential to have an impact during this interval [28, 29].

Evidence for Benefits of Tube Feeding: Infants

The majority of infants under 2 years of age with moderate to severe renal insufficiency will require tube feeding [30]. Spontaneous intake is poor, and gastroesophageal reflux and vomiting are common in this age group [30, 31]. Even infants with glomerular filtration rates as high as 70 mL/min/1.73 m^2 may show poor oral intake and associated poor growth [31].

Numerous studies have considered the impact of NG or gastrostomy tube feeding on growth in infants with renal insufficiency. Although not all studies have shown evidence of catch-up growth [31, 32], significant increases in growth velocity were observed after provision of adequate calories via NG or gastrostomy tube in numerous studies [3–5, 33, 34]. Interpretation of the literature in this area can be challenging. No randomized controlled trials have been done. Given that the degree of severity of renal insufficiency [10] and the intensity of dialysis [35] may each have an independent impact on growth, comparison of studies including individuals with different levels

of renal function and treated with different therapeutic modalities (from conservative therapy to intensive dialysis) is difficult. In addition, some studies included older children as well as infants; a poor growth response among older children may have masked a good response among infants. In most cases, when the outcomes of older children are separated from those of infants, growth benefits are evident among infants [5, 32, 36]. The balance of evidence supports the routine use of tube feedings in infants with renal insufficiency. Existing evidence for the growth benefits of tube feeding is summarized in Table 23.1.

A number of studies also emphasize the importance of providing sodium supplements to infants with polyuric renal insufficiency, in whom urinary sodium losses may be large [3, 4, 34]. Infants on peritoneal dialysis may also experience large sodium losses through the dialysate, necessitating the use of sodium supplements [10]. Chronic sodium losses impair linear growth [37]; severe volume depletion resulting from sodium and water losses may also result in neurologic injury [38]. The relatively large doses of sodium and large volumes of fluid required in infants with polyuric renal insufficiency can rarely be taken orally; tube feeding facilitates delivery of adequate sodium, fluid, and calories to these infants [34].

The International Pediatric Peritoneal Dialysis Network (IPPN) registry has begun to provide information on enteral feeding among infants treated with peritoneal dialysis, including the growth response to enteral feeds. Among 153 infants under 2 years of age entering the database between 2007 and 2009, 55% received enteral feeds (33% via NG tube and 22% via gastrostomy). Oral calorie supplements were provided to 22%, and 23% received no supplemental feeding at all. Both height and body mass index (BMI) standard deviation scores (SDS) were significantly higher in children receiving gastrostomy feeding compared with those receiving NG feeding or no enteral feeding. While BMI SDS increased during prospective follow-up in the children receiving enteral feeding, catch-up growth was restricted to gastrostomy fed infants (Rees et al., in press).

Indications for Tube Feeding: Infants

When considering dietary prescriptions for infants with chronic renal insufficiency, emphasis should be placed on prevention of growth retardation by early intervention. Even brief intervals of poor growth during infancy may result in substantial loss of height potential; fortunately, catch-up growth is also most likely during infancy [10]. However, height potential lost during infancy is extremely difficult to catch up later in childhood. One should not wait for evidence of stunting before intervening. Height outcomes are superior for children in whom tube feedings are started before important height deficits are noted [34]. Dietary intake should be regularly monitored in infants with chronic renal insufficiency, and supplemental tube feedings considered for any infant failing to meet energy or fluid requirements for normal growth [38].

Evidence for Benefits of Tube Feeding: Older Children

Controversy remains regarding the contribution of undernutrition to growth retardation in older children with renal insufficiency. As noted previously, growth is driven primarily by growth hormone and sex hormones during childhood and adolescence respectively [8, 9, 11, 12]. Although nutrition undoubtedly plays a role in growth during childhood, convincing evidence for the success of supplemental tube feeding in promoting growth in this older age group is lacking. Growth benefits of tube feeding were limited to infants and very young children in the majority of studies [5, 32, 36].

In fact, there is little evidence that older children with renal insufficiency are undernourished. In 2006, the mean BMI SDS at the time of transplant among children over 2 years of age recorded in the North American Pediatric Renal Trials and Collaborative Studies Registry was +0.45, indicating a prevalence of obesity greater than expected in a healthy pediatric population. Although older children with renal insufficiency do consume fewer calories than their healthy,

Table 23.1 Evidence for benefits of tube feeding

	Population studied	Study design	Intervention	Duration	Outcome
Abitbol et al. [31]	• n = 12 • Age <1 month at diagnosis • Estimated glomerular filtration rate (GFR): <70 mL/min/1.73 m^2	Case series	• ≥100% recommended dietary allowances (RDA) for calories • Progressive intervention: First concentrated formula for oral feeds, then tube feeding • 6/12 got enteral feeds starting at 4–16 months	24 months	• No catch-up growth • Weight velocity SDS positive after 12 months • Height velocity SDS remained negative, but did increase
Claris-Appiani et al. [3]	• n = 5 • Age: 0.2–3.8 years • Estimated GFR: 15.2 ± 6.8 mL/min/1.73 m^2	Case series	• ≥100% RDA for calories relative to height-age • Supplemental NaCl of 2–3 mEq/kg/day • All tube fed	12 months	• Weight for age SDS increased by a mean of 1.76 SD • Height for age SDS increased by a mean of 1.52 SD • Height velocity SDS increased by a mean of 5.38 SD
Coleman et al. [36]	• n = 22 • Median age 2.4 years (range 0.2–10.3) • Peritoneal dialysis: n = 20 • Hemodialysis: n = 2	Case series	• ≥100% estimated average requirement for calories • All tube fed	14.5 months (mean)	• Weight for age SDS increased by a mean of 0.16 SD • Height for age SDS increased by a mean of 1.06 SD
Ledermann et al. [5]	• n = 35 • Mean age: 1.6 years (range 0–4.9) • CKD stage 5: n = 29 • Peritoneal dialysis: n = 6	Case series	• ≥100% estimated average requirement for calories • All tube fed • Supplemental NaCl • Supplemental $NaHCO_3$	30.8 months (mean)	*≤2 years old* • Weight for age SDS increased by a mean of 1.4 SD at 1 year • Height for age SDS increased by a mean of 0.7 SD at 1 year *>2 years old* • Weight for age SDS increased by a mean of 0.9 SD at 1 year, Height for age SDS did not change by 1 year
Ramage et al. [32]	• n = 15 • Age: n = 8 ≤ 2.5 years n = 7 >2.5 years • Peritoneal dialysis	Case series	• ≥100% RDA for calories • Tube feeds started an average of 0.6 and 1.0 years after initiation of PD in those ≤2.5 years and > 2.5 years, respectively	12 months	• Of the three infants who achieved ≥100% RDA, height for age SDS increased by a mean of 1.63 SD, and weight for height increased by 14% at 1 year • Infants achieving <100% RDA, height for age SDS decreased by a mean of 0.3 SD • Those >2.5 years old had no increase in height for age SDS

Kari et al. [4]	• n = 81 • Median age 0.7 years (range: 0–4.5) • Estimated GFR < 20 n = 20 conservative therapy n = 25 preemptive transplant n = 36 dialysis	• Cohort • 66/81 enteral feeds • 15/81 oral	• ≥100% estimated average requirement for calories	1.9 years (median)	*Conservative therapy* • Height for age SDS increased by a mean of 0.41 SD at 2 years and by 0.97 SD at 5 years of age *Preemptive transplant (before transplant)* • Height for age SDS decreased by a mean of 0.26 SD at 2 years and increased by 0.14 SD at 5 years of age *Dialysis* • Height for age SDS increased by a mean of 0.95 SD at 2 years and by 1.92 SD at 5 years of age
Parekh et al. [34]	• n = 24 • Age not specified • Estimated GFR <65 mL/min/1.73 m^2	• Cohort with two different historical control groups 1. Abitbol, 1993 (n = 12) 2. USRDS Pediatric Growth Special Study (n = 42)	• ≥100% RDA for calories • 180–240 mL/kg/day • Supplemental NaCl of 2–4 mEq/kg/day • Fed orally or by tube	24 months	• Intervention group had a 1.37 SD greater increase in height for age SDS than USRDS controls at 1 year • Intervention group had a 1.83 SD greater increase in height for age SDS than Abitbol controls at 2 years
Waller et al. [73]	• n = 99 • Age 2.8 (0.25–8.9) • GFR < 41 (median 22) mL/min/1.73 m^2, conservative therapy	Case series	• Orally (n = 58) or tube fed (n = 41) • PTH within normal range • Phosphate below 50th percentile for age	Until 10 years of age, start of growth hormone or dialysis	• Height for age SDS increased by 0.3 SD over the study period (0.09 per year) • Increase in height for age SDS was independently negatively associated with age, GFR, and iPTH, and positively with the use of enteral feeds
Cansick et al. [74]	• n = 35 • Mean age 2.8 (0.25–8.9) • 17 infants less than 2 years of age • 14 PD, 4 HD, 17 PD and HD	Case series	• ≥100% RDA for calories • Use of NG or gastrostomy tube in 32 pts • PTH within normal range • Phosphate below 50th percentile for age	Until 10 years of age, start of growth hormone or transplant	• Infants showed catch-up growth in the first year on dialysis – median change in height for age SDS was +0.31 (−0.78–3.13) SD • No catch-up growth in older children

normally growing peers, they are smaller; intakes are usually normal relative to body size [39]. The possibility that poor intake is a consequence of the poor growth, rather than the cause, must be considered. Spontaneous calorie intake increased by almost 12% in a study of 33 children with renal insufficiency during treatment with recombinant human growth hormone [40].

We do not wish to suggest that older children will never benefit from supplemental tube feeding. Selected children, who are observed to have inadequate intake and are unable to tolerate oral supplements, may benefit. However, this represents the minority of older children with renal insufficiency. Prolonged trials of supplemental calories in an effort to improve growth should not delay the initiation of therapies of proven benefit [41], such as growth hormone.

Indications for Tube Feeding: Older Children

Dietary intake should be monitored at regular intervals in older children with chronic renal insufficiency [38]. When intake is discovered to be inadequate, efforts should be made to identify an underlying cause. Nausea, vomiting, or severe anorexia may signify progressive uremia requiring intensification of therapy: children being managed conservatively may require initiation of dialysis; children on dialysis may require a higher dose of dialysis [35]. Gastrointestinal and eating disorders must also be considered. Oral nutritional supplements should be the first-line intervention; these are usually adequate, particularly for children needing a brief interval of supplementation following an acute illness or surgery. Tube feedings should be reserved for children with progressive weight loss or growth failure who are unable to take adequate calories by the oral route.

Nasogastric Versus Gastrostomy Tube Feeding

There are two methods of delivering enteral feedings: NG or gastrostomy tube. The NG tube was the first means of nutritional support in children with CKD [42, 43]. More recently, gastrostomy feeding has been favored by many because of the cosmetic advantages (hidden under clothing) and because this approach avoids the negative oropharyngeal stimulation associated with chronic presence of and frequent replacement of a NG tube [44]. However, NG tube feeding remains a reasonable option, particularly for children expected to require tube feedings only for a short interval, and for families wishing to avoid a surgical procedure. A NG tube is also the method of choice in infants weighing less than 4 kg [44]. Each method will be considered separately.

Nasogastric tube feeding: A variety of soft, flexible NG tubes of varying external diameters, with or without a weighted tip, are commercially available. Most tubes are designed for a single use – so if the tube becomes dislodged, a new one must be inserted. The life-span of a NG tube depends on the type of NG tube used; polyvinyl chloride tubes need to be changed every 5–7 days, whereas silk tubes are designed to remain in place up to 4–6 weeks.

NG tubes are inserted through the nostril, and passed through the oropharynx and into the stomach. Correct placement in the stomach must be verified prior to commencing feeding. This may be done either by auscultation during infusion of a small volume of air, or by withdrawing a small amount of fluid, and testing a sample of it on blue (alkaline) litmus paper – which will turn red when acidic stomach secretions are present [45]. Once in place, a NG tube requires regular care to prevent tube blockage. NG tubes must be flushed before and after all tube use for feedings or medication administration, or at least every 8 h if not in use [45].

NG tube complications: The potential complications associated with NG tube feeding include pulmonary aspiration, sinusitis, otitis, and nasoseptal erosion. In some children, frequent vomiting results in a need for frequent replacement of the tube – which may be unpleasant. Repeated unpleasant stimulation of the oropharyx during NG tube placement, and irritation due to chronic presence of the tube may lead to oral feeding aversion and poor development of

oral-motor skills [44]. The presence of a NG tube may also exacerbate gastroesophageal reflux [44]. Finally, the psychological impact of an NG tube on caregivers should not be underestimated; the presence of NG tube may cause parental anxiety by identifying the child as "sick" to the rest of the world [46–48].

Gastrostomy tube feeding: Two main forms of gastrostomy tubes are available: larger gastrostomy tubes and low-profile gastrostomy button devices. In some centers, a larger gastrostomy tube is placed initially and subsequently replaced with a button device 4–12 weeks later. Alternatively, a button device may be placed immediately. The primary advantage of gastrostomy button devices is that they are small and discrete, and can be easily changed without surgical intervention.

Two kinds of button devices are commercially available. The first (manufactured by Bard or Ross laboratories) has a one-way valve that prevents gastric reflux and a silicone dome- or mushroom-shaped internal anchoring device. The second device has an external skin disk and an internal balloon that is inflated with water after it is placed in the stomach (e.g., the silicone MIC-KEY button manufactured by Medical Innovations Corp/Ballard). The Bard device has the advantage of lasting longer than the MIC device, whereas MIC buttons are easier to remove and insert, and can be changed without medical assistance. The use of button gastrostomies is not advised for children with cystinosis, because potassium supplements may cause balloon rupture [49].

Both gastrostomy tubes and button devices may be left in place for months to years. Gastrostomy tubes or button devices with a balloon need to be replaced every 3–6 months, whereas rigid button devices may remain in place up to 1–2 years [44]. The mean reported life-span of a gastrostomy button is 7.7 (range 2.6–16) months [36]; the most common reason for changing a button is leakage at the exit site [36].

Placement techniques: General anesthesia is typically required for the placement of any type of gastrostomy. There are two main categories of techniques used for gastrostomy placement: percutaneous or open. Percutaneous gastrostomy placement methods include percutaneous placement under endoscopy guidance (PEG), laparoscopic guidance, or radiologic guidance. Percutaneous methods have the advantage of shorter recovery time than an open surgical approach. The most popular open gastrostomy technique is the Stamm open gastrostomy. Technical details regarding percutaneous and open methods are available elsewhere [44].

The major difference between percutaneous and open techniques is that with the open technique, the stomach is brought anteriorly and sutured to the abdominal wall. These sutures prevent the leakage of small amounts of gastric contents into the peritoneal cavity, which occurs during and after a percutaneous procedure. Although the leakage is considered to be sterile, patients on acid-reducing therapy are at increased risk of bacterial and fungal colonization of the stomach, and may be at higher risk of infection. Therefore, some recommend discontinuation of H2-blockers and proton pump inhibitors a week before percutaneous gastrostomy placement [44].

Regardless of the surgical approach used, antibiotic prophylaxis is suggested in the perioperative period. A meta-analysis of randomized controlled trials showed that antibiotic prophylaxis with either amoxicillin–clavulanic acid or a cephalosporin prior to gastrostomy insertion is effective in reducing gastrostomy site wound infection [50]. In some cases, especially in children who have been on antibiotics prior to surgery, antifungal prophylaxis is also advisable [51].

The necessity for Nissen fundoplication at the time of gastrostomy placement is controversial [52]. Some advocate preoperative esophageal pH-monitoring studies, and recommend fundoplication if gastroesophageal reflux is present [53]. Others routinely perform fundoplication with open gastrostomy to prevent reflux and vomiting – two highly prevalent problems in pediatric CKD [54].

It is recommended that gastrostomies be left to drain freely for 24–48 h postoperatively, prior to use for feeding; oral feedings may be introduced 16–24 h after placement [45, 52].

Gastrostomies in peritoneal dialysis patients: Patients being treated with peritoneal dialysis, or those for whom peritoneal dialysis is planned, require special consideration with respect to choice of gastrostomy device and placement technique due to the risk of peritonitis. We strongly recommend open gastrostomy placement for all patients already on peritoneal dialysis [45, 49, 55, 56]. Percutaneous placement is not advised in children established on peritoneal dialysis due to the leak of stomach contents into peritoneal cavity described above; the high dextrose content of dialysate may promote growth of any bacteria present in the leaked fluid causing peritonitis. In one multicenter retrospective study of children undergoing peritoneal dialysis, percutaneous gastrostomy placement was associated with peritonitis within 7 days of the procedure in 37%, including fungal peritonitis in 26% [56]. Other small case series were also highly suggestive of a substantial risk of peritonitis following percutaneous gastrostomy placement among children on peritoneal dialysis [49, 55].

For patients in whom peritoneal dialysis is planned, some advocate a single surgical procedure, during which partial omentectomy, gastrostomy, and dialysis catheter placement are performed during the same intervention either via a single middle incision or by laparoscopy [36, 57]. This procedure is carried out under antibiotic prophylaxis, and requires delays in starting enteral feeding by 48 h, and peritoneal dialysis by at least 2 weeks, if possible [36, 58]. Others suggest that gastrostomy placement should precede peritoneal dialysis catheter placement [49, 52, 55]. To date, there is no evidence that the risk of peritonitis is increased in children commencing peritoneal dialysis with an established gastrostomy in place.

Exit site and gastrostomy care: As with NG tubes, gastrostomies must be flushed regularly to avoid obstruction. In addition, the exit site must be cared for to minimize infection risk. In the first 2 days following placement, the exit site should be cleaned with sterile saline. Thereafter, the site should be cleaned daily with mild soap and water, starting with the tube itself, and moving outward using circular motions. After cleaning the exit site should be dried thoroughly. The exit site should be monitored regularly for signs of infection, which include redness and irritation of the skin around exit site and discharge.

Gastrostomy feeding complications: The most common complications associated with gastrostomy feeding include tube blockage, balloon rupture, tube displacement, leakage around exit site, skin irritation and itching, exit site infection, and granulation at the exit site. All of those are usually mild in nature and may occur with either the percutaneous or open approach. Bacterial exit site infection can be treated with topical antibiotics such as neomycin or chloramphenicol, whereas a nystatin hydrocortisone cream can be used for candida infection [44, 45]. Granulation tissue may be treated with application of silver nitrate twice a week [1]. Complications specific to percutaneous gastrostomy placement include gastroenteric fistula and intra-abdominal leakage [44].

Major complications, defined as those requiring surgical or endoscopic intervention, non-prophylactic systemic antibiotics, blood transfusion, or leading to death occurred in 12–17% of children observed in four large series of children who underwent percutaneous gastrostomy placement [59–62]. Rare complications such as bowel obstruction, gastrocutaneous fistula, paraesophageal hernia of the peritoneal sac, and pneumoperitoneum have also been described [45, 48, 55, 63]. Risk factors for gastrostomy-related complications include age <1 year, mental retardation, scoliosis, constipation, hepatomegaly, upper abdominal surgery, ventriculoperitoneal shunt, esophageal stenosis, and coagulopathy [61, 62, 64–68].

Practical Aspects of Enteral Feeding

Enteral feeding can be used to provide all of a child's nutritional requirements, or to supplement insufficient oral intake. Infants, because of their reduced spontaneous intake, frequently need all calories to be given by tube, usually as an overnight continuous infusion with additional daytime boluses. A combination of daytime oral feedings with or without NG tube bolus "top-offs" and overnight continuous infusion is also an

Table 23.2 Suggested rates for initiating and advancing tube feedings Appendix 4 KDOQI 2008 nutrition guidelines

Age	Initial hourly infusion	Daily increases	Goal[a]
Continuous feedings			
0–1 year	10–20 mL/h or 1–2 mL/kg/h	5–10 mL/8 h or 1 mL/kg/h	21–54 mL/h or 6 mL/kg/h
1–6 years	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 years	30–40 mL/h or 1 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 years	50 mL/h or 0.5–1 mL/kg/h	25 mL/8 h or 0.4–0.5 mL/kg/h	125 mL/h
Bolus feedings			
0–1 year	60–80 mL q 4 h or 10–15 mL/kg/feed	20–40 mL q 4 h	80–240 mL q 4 h or 20–30 mL/kg/feed
1–6 years	80–120 mL q 4 h or 5–10 mL/kg/feed	40–60 mL q 4 h	280–375 mL q 4 h or 15–20 mL/kg/feed
6–14 years	120–160 mL q 4 h or 3–5 mL/kg/feed	60–80 mL q 4 h	430–520 mL q 4 h or 10–20 mL/kg/feed
>14 years	200 mL q 4 h or 3 mL/kg/feed	100 mL q 4 h	500 mL q 4 h or 10 mL/kg/feed

Calculating rates based on age and per kilogram bodyweight 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 density of feeding and therefore may be lower than expected maximum tolerance

option for infants. Older children who require tube feeding can usually be managed with supplemental overnight infusion only, and continue normal oral feeding during daytime.

To ensure feed tolerance, attention must be given to both hourly infusion rate and caloric density of delivered nutrients. Tolerance is evaluated based on the gastric residual volume and absence of gastrointestinal complications such as emesis and diarrhea. For infants, the initial hourly infusion speed may be as low as 1–2 mL/kg/h and the maximum tolerated amount will not exceed 6 mL/kg/h. It is also recommended that the maximum calorie concentration not exceed 1–2 kcal/mL, as higher caloric density may be associated with osmotic diarrhea.

Suggested rates for initiating and advancing tube feeding are given in Table 23.2. Although there are specific renal high energy, low potassium and phosphate formulas accessible, their usage may be limited because of hyperosmolarity and high fat content.

Gastrointestinal Disturbances in Children with CKD

One of the most common problems among infants and young children with CKD is recurrent vomiting. Impaired foregut motility and decreased gastric emptying may result from autonomic neuropathy and increased levels of polypeptides such as gastrin. Gastroesophageal reflux is also common, and may contribute. In the case of patients treated with peritoneal dialysis, the presence of dialysate in peritoneal cavity may also predispose to reflux or vomiting [69]. Vomiting may result from a too rapid rate of formula infusion via the feeding tube or may be associated with excessive caloric density [45].

In children who have undergone Nissen fundoplication, or in those who receive hyperosmolar feeds, a dumping syndrome may occur in which accelerated gastric emptying causes rapid delivery of undigested hyperosmolar feeds into the jejunum. This results in increased bowel blood flow, resulting in decreasing systemic circulating blood volume and activation of the renin-angiotensin-aldosterone axis. The clinical symptoms include abdominal pain, vasomotor symptoms, and tachycardia. Undigested chyme reaching the distal gut causes the release of various hormones resulting in diarrhea. Late dumping syndrome symptoms include diaphoresis, weakness, and lethargy associated with reactive hypoglycemia 1–4 h after feeding [70]. Possible causes of vomiting and diarrhea are summarized in Table 23.3 [45].

Impaired Oromotor Development

Long-term tube feeding in infancy is inevitably associated with impaired development of normal oromotor skills and coordination during feeding. Although this problem may occur with both NG

Table 23.3 Possible causes of vomiting and diarrhea

Feeding related	Non-feeding related
• Feed too concentrated, osmolarity too high	• Gastrointestinal reflux • Disturbances of gastric motility and decreased gastric emptying
• Volume of feed for pump assisted continuous feeding delivered via tube is set too high	• Infections, e.g, gastroenteritis, peritonitis
• Rate for feeding pump to deliver feed is set too high	• Abdominal fullness from the presence of dialysate
• Bolus delivered via tube is too large	• PD volumes – when increased
• Intolerance to feed, e.g., whole protein intolerance	• Inadequate fluid intake in CPD may accompany too great an ultrafiltration volume
• [a]Medications added to feed	• Coughing
• Feed contaminated	• Psychogenic/behavioral

[a]Antibiotics and medications, for example, oral iron, sodium, and potassium supplements

and gastrostomy feeding, the discomfort associated with NG tube use may result in greater difficulties. Children in whom NG tubes are used frequently develop oral hypersensitivity, characterized by a hyperactive gag reflex and immature bite-chew-swallow coordination. The unpleasant sensation associated with NG tube insertion enhances the child's perception that anything that comes toward the mouth is potentially painful or stressful, promoting hypersensitivity; chronic presence of the NG tube may impair normal swallowing [71]. These problems may be severe enough that the child refuses all oral feeding. Alternatively, the problem may be restricted to solid food. To prevent food-aversive behavior, forced feeding should be avoided, and the child should be allowed to play with food. It may also be helpful if the child participates in family meals, and is encouraged to continue to try enjoy food, even if it is not swallowed [44, 71].

Transition to Oral Feeding

Tube feeding is generally intended as a temporary support, until normal oral feeding can be established. For most infants, tube feeding will be required at least until successful renal transplantation. A significant proportion of children who were tube fed before transplant will continue to require tube feeding for some interval after successful renal transplantation [45]. Dello Strogolo reported persistent feeding dysfunction following transplantation in 8 out of 12 infants who were managed with NG tubes for more than 9 months pre-transplant [46]. In another series of 16 infants with normal cognitive development who were tube fed, 9 made the transition to oral feeding by 1 month post-transplant, 4 by 5 months, and 3 by 10 months. Among five infants with cognitive deficits, two made the transition at 3 and 8 months respectively, while three continued to rely on enteral feeds to provide most of their nutritional requirements [72]. Some authors advise assessment of dietary intake 4–6 weeks following transplant, with gradual withdrawal of tube feeding, as oral intake increases. The gastrostomy should be removed when nutrition, fluid intake, and growth rate are appropriate [44].

Summary

Enteral tube feeding is a key component of global care for infants with CKD. Ensuring adequate nutrition and fluid intake is the most important means of achieving normal growth and development in this population; frequently this can only be achieved with use of a tube. For children requiring long-term enteral feeding, a gastrostomy is likely the optimal choice.

References

1. 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.
2. Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. Kidney Int. 2006;69(5):794–7.
3. 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-Parenter Enter. 1995;19(3):175–8.
4. 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.
5. 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.
6. Warady BA. Growth retardation in children with chronic renal insufficiency. J Am Soc Nephrol. 1998;9(12 Suppl):S85–9.
7. 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.
8. Karlberg J. On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr Scand Suppl. 1989;356:26–37.
9. Karlberg J, Schaefer F, Rigden AM, Hennicke M, Wingen 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.
10. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702.
11. 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.
12. 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.
13. Waterlow JC. Classification and definition of protein-calorie malnutrition. Br Med J. 1972;3(826):566–9.
14. Mitch WE. Mechanisms causing loss of lean body mass in kidney disease. Am J Clin Nutr. 1998;67: 359–66.
15. Mitch WE. Insights into the abnormalities of chronic renal disease attributed to malnutrition. J Am Soc Nephrol. 2002;13(Suppl 1):S22–7.
16. Mitch WE. Malnutrition: a frequent misdiagnosis for hemodialysis patients. J Clin Invest. 2002;110(4):437–9.
17. Mitch WE. Proteolytic mechanisms, not malnutrition, cause loss of muscle mass in kidney failure. J Ren Nutr. 2006;16(3):208–11.
18. Mitch WE. Malnutrition is an unusual cause of decreased muscle mass in chronic kidney disease. J Ren Nutr. 2007;17(1):66–9.
19. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38(6):1251–63.
20. Kalantar-Zadeh K, Mehrotra R, Fouque D, Kopple JD. Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. Semin Dial. 2004;17(6):455–65.
21. Mak RH, Cheung W. Therapeutic strategy for cachexia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2007;16(6):542–6.
22. Mitch WE, Maroni BJ. Factors causing malnutrition in patients with chronic uremia. Am J Kidney Dis. 1999;33(1):176–9.
23. Mak RH, Cheung W. Cachexia in chronic kidney disease: role of inflammation and neuropeptide signaling. Curr Opin Nephrol Hypertens. 2007;16(1):27–31.
24. Mak RH, Cheung WW, Roberts Jr CT. The growth hormone-insulin-like growth factor-I axis in chronic kidney disease. Growth Horm IGF Res. 2008;18(1): 17–25.
25. Ahuja TS, Mitch WE. The evidence against malnutrition as a prominent problem for chronic dialysis patients. Semin Dial. 2004;17(6):427–31.
26. Evans D, Hansen JD, Moodie AD, van der Spuy HI. Intellectual development and nutrition. J Pediatr. 1980;97(3):358–63.
27. Sigman M, Neumann C, Baksh M, Bwibo N, McDonald MA. Relationship between nutrition and development in Kenyan toddlers. J Pediatr. 1989; 115(3):357–64.
28. 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.
29. 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.
30. Rees L. Management of the infant with end-stage renal failure. Nephrol Dial Transplant. 2002;17(9): 1564–7.
31. Abitbol CL, Zilleruelo G, Montane B, Strauss J. Growth of uremic infants on forced feeding regimens. Pediatr Nephrol. 1993;7(2):173–7.
32. 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.
33. 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.
34. 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(11):2418–26.

35. Tom A, McCauley L, Bell L, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134(4):464–71.
36. Coleman JE, Watson AR, Rance CH, Moore E. Gastrostomy buttons for nutritional support on chronic dialysis. Nephrol Dial Transplant. 1998;13(8):2041–6.
37. Wassner SJ, Kulin HE. Diminished linear growth associated with chronic salt depletion. Clin Pediatr (Phila). 1990;29(12):719–21.
38. K/DOQI. 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.
39. Foreman JW, Abitbol CL, Trachtman H, 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.
40. Zadik Z, Frishberg Y, Drukker A, 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.
41. 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.
42. Ellis EN, Yiu V, Harley F, 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.
43. Warady BA, Weis L, Johnson L. Nasogastric tube feeding in infants on peritoneal dialysis. Perit Dial Int. 1996;16(Suppl 1):S521–5.
44. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2009;25(4):699–704.
45. Coleman JE, Warady BA. Supplemental tube feeding. In: Warady BA, Schaefer F, Fine RN, Alexander SR, editors. Pediatric dialysis. Dordrecht: Kluwer Academic Publisher; 2004. p. 243–57.
46. Dello Strologo L, Principato F, Sinibaldi D, et al. Feeding dysfunction in infants with severe chronic renal failure after long-term nasogastric tube feeding. Pediatr Nephrol. 1997;11(1):84–6.
47. Kuizon BD, Nelson PA, Salusky IB. Tube feeding in children with end-stage renal disease. Miner Electrolyte Metab. 1997;23(3–6):306–10.
48. 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.
49. 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.
50. 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.
51. Wirth R, Bauer J, Sieber C. Necrotizing Candida infection after percutaneous endoscopic gastrostomy: a fatal and rare complication. JPEN-Parenter Enter. 2008;32(3):285–7.
52. Warady BA. Gastrostomy feedings in patients receiving peritoneal dialysis. Perit Dial Int. 1999;19(3): 204–6.
53. 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.
54. Humphrey GM, Najmaldin A. Laparoscopic gastrostomy in children. Pediatr Surg Int. 1997;12(7):501–4.
55. 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.
56. von Schnakenburg C, Feneberg R, Plank C, et al. Percutaneous endoscopic gastrostomy in children on peritoneal dialysis. Perit Dial Int. 2006;26(1):69–77.
57. Stringel G, McBride W, Weiss R. Laparoscopic placement of peritoneal dialysis catheters in children. J Pediatr Surg. 2008;43(5):857–60.
58. Watson AR. Gastrostomy feeding in children on chronic peritoneal dialysis. Perit Dial Int. 2006;26(1): 41–2.
59. Avitsland TL, Kristensen C, Emblem R, Veenstra M, Mala T, Bjornland K. Percutaneous endoscopic gastrostomy in children: a safe technique with major symptom relief and high parental satisfaction. J Pediatr Gastroenterol Nutr. 2006;43(5):624–8.
60. Gauderer MW. Percutaneous endoscopic gastrostomy: a 10-year experience with 220 children. J Pediatr Surg. 1991;26(3):288–92. discussion 92–4.
61. Khattak IU, Kimber C, Kiely EM, Spitz L. Percutaneous endoscopic gastrostomy in paediatric practice: complications and outcome. J Pediatr Surg. 1998;33(1):67–72.
62. Vervloessem D, van Leersum F, Boer D, 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.
63. Beres A, Bratu I, Laberge JM. Attention to small details: big deal for gastrostomies. Semin Pediatr Surg. 2009;18(2):87–92.
64. Beasley SW, Catto-Smith AG, Davidson PM. How to avoid complications during percutaneous endoscopic gastrostomy. J Pediatr Surg. 1995;30(5):671–3.
65. Goretsky MF, Johnson N, Farrell M, Ziegler MM. Alternative techniques of feeding gastrostomy in children: a critical analysis. J Am Coll Surg. 1996;182(3): 233–40.
66. Kimber C, Beasley S. Limitations of percutaneous endoscopic gastrostomy in facilitating enteral nutrition in children: review of the shortcomings of a new technique. J Paediatr Child Health. 1999;35(5): 427–31.

67. Schrag SP, Sharma R, Jaik NP, et al. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. J Gastr Liver Dis. 2007;16(4):407–18.
68. Stellato TA, Gauderer MW, Ponsky JL. Percutaneous endoscopic gastrostomy following previous abdominal surgery. Ann Surg. 1984;200(1):46–50.
69. Fallone CA, Mayrand S. Gastroesophageal reflux and hyperacidity in chronic renal failure. Perit Dial Int. 2001;21(Suppl 3):S295–9.
70. Bufler P, Ehringhaus C, Koletzko S. Dumping syndrome: a common problem following Nissen fundoplication in young children. Pediatr Surg Int. 2001; 17(5–6):351–5.
71. 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.
72. Pugh P, Watson AR. Transition from gastrostomy to oral feeding following renal transplantation. Adv Perit Dial. 2006;22:153–7.
73. 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.
74. 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.

Growth and Pubertal Development in Dialyzed Children and Adolescents

24

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Keywords
Dialyzed children • Pediatric dialysis • Adolescents • Pubertal development

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. 24.1), with nutrition being critical during infancy, the somatotropic hormone axis during mid-childhood, and the gonadotropic hormones during puberty [1].

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 [2, 3]. In this chapter, we will discuss the current knowledge on the phenotype and underlying pathophysiology of growth failure in children suffering from end-stage renal disease (ESRD) and line out the currently available therapeutic options.

Growth impairment and disproportionality is most obvious in early childhood when the growth of legs and arms is most affected, whereas trunk length is somewhat better preserved.

The introduction of dialysis therapies in the 1970s and 1980s raised initial hopes that this would improve growth. However, most reports on growth after initiation of dialysis are disappointing. 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. Beyond this, the degree of growth retardation and mortality are closely associated, suggesting that the growth rate is a sensitive marker of overall patient well-being [4, 5]. Thus, 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 growth in children on maintenance dialysis, it should be emphasized that early intervention is critical since measures such as the correction of malnutrition and renal osteodystrophy, and treatment with recombinant human growth hormone (rhGH) are considerably more effective when started before initiation of dialysis.

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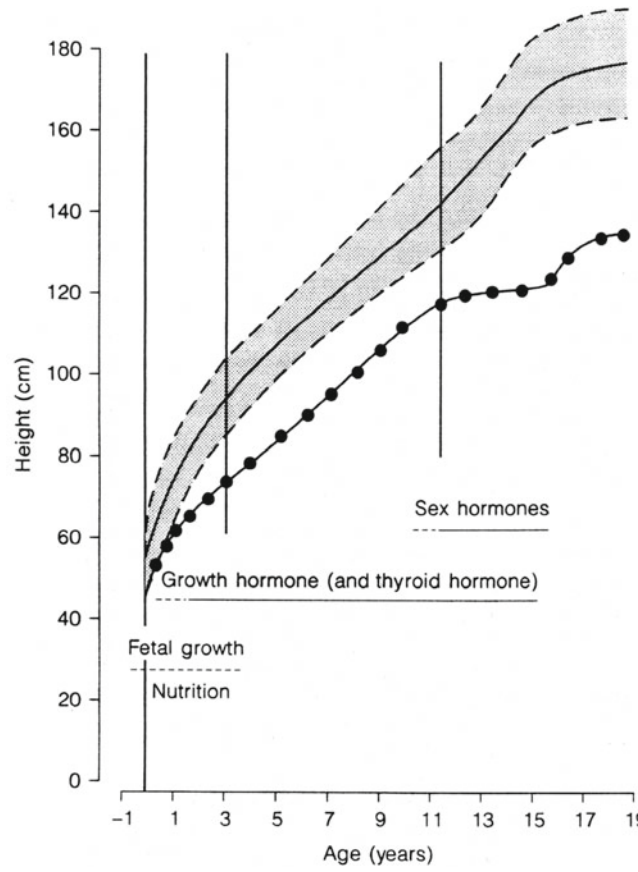


Fig. 24.1 Typical growth pattern in congenital chronic renal failure. Relative loss in the nutrient-dependent infantile and gonadal hormone–dependent puberty phases, and percentile-parallel growth in the mainly GH-dependent growth period in mid-childhood are shown. The *shaded area* represents the normal range, 3rd to 97th percentiles (Reproduced with permission of Schaefer and Mehls [22])

Final Height and Height Prediction

Reduced adult height has been reported in about 30% to 50% of pediatric CKD patients, although a trend toward improved final height was noted during the past decade [6–15]. Mean final height in CKD patients stage 3–5 ranged between −0.6 and −3.5 SDS. In general, patients receiving renal transplants or additional treatment with rhGH showed improved mean levels of final height compared to patients on long-term dialysis and those without concomitant rhGH therapy [16]. Young age at onset of ESRD, long duration of renal failure, male gender, and the presence of congenital nephropathies are the most relevant risk factors of attaining a poor final height. Among the different renal disease entities, patients suffering from nephropathic cystinosis or primary hyperoxaluria show most markedly compromised final heights [17, 18].

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, 14, 16]. Most likely, this reflects the complexity and thus unpredictability of growth and development under the condition of chronic uremia with 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 during the first 2 years of life. Growth during mid-childhood tends to be percentile parallel but height velocity

decreases disproportionately during the last 2–3 prepubertal years. Eventually, growth potential is irreversibly lost in the peripubertal period due to a delayed pubertal growth spurt of insufficient magnitude (Fig. 24.1).

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 [19, 20]. A recent 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, a time that is particularly dependent on nutrition, which may be very hard to maintain because of prematurity, poor feeding, vomiting, and episodes of fasting as a result of surgery or sepsis [21]. In addition, infants with comorbidities presented with much more severe growth failure than infants without comorbidities (Fig. 24.2). In infants with ESRD, i.e., those with severe congenital CKD, the decrease in mean standardized height can be as much as 0.6 SD per month [22]. At 3 years of age these children may have lost already 3 SD scores (SDS). According to the Infancy-Childhood-Puberty model approximately 1 SDS each is lost during 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 pattern. It has been suggested that the growth failure during fetal life and the first postnatal months reflects metabolic and/or nutritional influences, and the impaired growth 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 [21, 23].

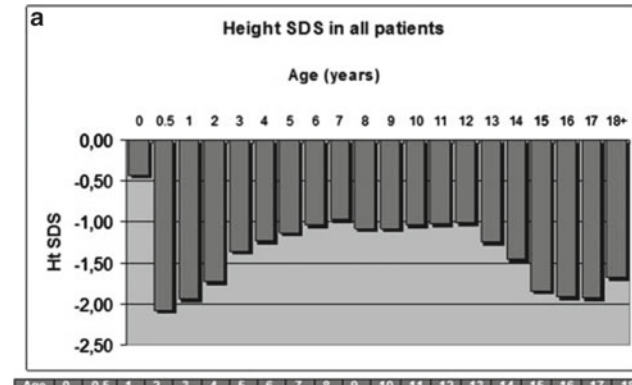
Growth During Mid-childhood

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 GFR remains above 25 mL/min/1.73 m² and tends to diverge from the percentiles below this level [24, 25]. A mean cumulative loss of 6 cm from predicted final height was observed in children with mean GFR below 25 mL/min/1.73 m² between early childhood and the age of 10 years [24]. Sequelae of CKD such as anemia, metabolic acidosis, and malnutrition seem to be less-important determinants of statural growth in mid-childhood.

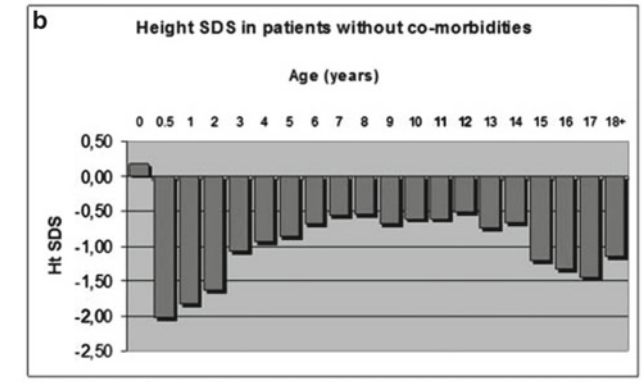
Pubertal Development

Clinical signs of puberty as well as the start of the pubertal growth spurt in children with CKD stage V appear with a delay of approximately 2 years. At least 50% of adolescents with ESRD achieve the pubertal milestones later than 95% of their healthy peers [26]. The "Cooperative Study for Pubertal Development in Chronic Renal Failure" showed that start of genital growth (Tanner stage G2) was delayed by 1.8 years in boys on dialysis and by 2.5 years in transplanted boys. Full genital maturation was achieved with a delay of 2.2 and 3.2 years, respectively. Likewise, the maturation of reproductive function is altered by the uremic state. Germ cell depletion in the testicular tubules of uremic boys was found in postmortem studies [27]. In patients exposed to chronic uremia before or during adolescence, i.e., during the period crucial for spermatogenesis, semen quality is severely and irreversibly affected [28, 29]. Several studies revealed reduced sperm cell count, erectile dysfunction, decreased libido, and decreased fertility in uremic patients on dialysis [30].

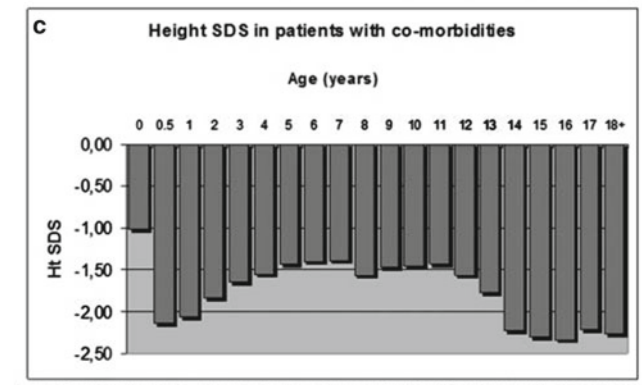
Menarche occurs in almost beyond the upper limit of the normal age range (i.e., 15 years) in



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	59	62	53	52	44	46	40	40	31	32
BMI	13	13	13	14	14	15	16	16	17	19	20	20	21	22	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. 24.2 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 comorbidites. (**c**) Height SDS and BMI values for patients with comorbidities. (Reproduced with permission of Mekahli et al. [21])

50% of girls with ESRD [31], and conception rates in adolescent girls and women with ESRD are diminished. In those who manage to get pregnant, intrauterine growth retardation and low birth weight are frequently noted [32].

Pubertal Growth

Total pubertal height gain is subnormal in ESRD patients [6, 12, 19, 33, 34], with an average 1 SD loss of standardized height. In the seminal study of Schaefer et al. pubertal growth in 29 CKD patients attaining ESRD before the age of 15 years was assessed [34]. In these patients the pubertal growth spurt started with a mean delay of 2.5 years and this delay was related to the duration of uremia. While an acceleration of height velocity comparable to that seen in healthy adolescents was observed, the mean height velocity at start of the pubertal growth spurt was reduced and its duration was shortened by approximately 1.5 years.

Etiology of Growth Failure in Chronic Kidney Disease

There is no single cause of growth failure in CKD (Table 24.1). 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. 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. Hence, growth in children with CKD is not only influenced by renal dysfunction but also by specific disease-related comorbidities and treatment modalities.

Table 24.1 Etiology of growth failure in children suffering from CKD

Genetic factors
Parent height
Gender
Syndromal disorders (with kidney involvement as a part)
Age at onset of CKD
Residual renal function
Treatment modalities for CKD
Energy malnutrition
Water and electrolyte disturbances
Metabolic acidosis
Renal anemia
Hormonal disturbances affecting the
Somatotropic hormone axis
Gonadotropic hormone axis
PTH-, FGF-23-, and vitamin D metabolism/action (renal osteodystrophy)
Other hormones

Underlying Renal Disease

Congenital anomalies of the kidneys and urinary tract (CAKUT), characterized by renal hypoplasia or dysplasia with and without refluxive or obstructive uropathy, are the most common cause of ESRD during infancy and childhood. Renal dysplasia is often associated with electrolyte and/or water losses, and both are likely to contribute to growth failure. Thus, it is important to compensate for these losses and to provide appropriate treatment of concomitant urinary tract infections.

In children suffering from *glomerulopathies* growth rates might decline even with rather mild renal insufficiency [35]. The nephrotic state per se and glucocorticoid treatment are known risk factors for growth delay [36, 37]. The *congenital nephrotic syndrome* is usually associated with severe early infantile growth failure, which may occur even with preserved global renal function and seems to be secondary to persistent edema, recurrent infections, losses of peptide and

protein-bound hormones, and/or protein-calorie malnutrition [38]. In Finnish-type nephrotic syndrome, aggressive nutritional support is vital and bilateral nephrectomy and initiation of peritoneal dialysis may be necessary to stabilize 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 stabilize growth and overall clinical condition [39, 40].

Nephropathic cystinosis results in complex tubular dysfunction and consecutive severe growth failure already during infancy when glomerular function is not yet compromised [41, 42]. Progressive growth failure is further sustained by generalized deposition of cystine crystals altering the function of growth plates, bone marrow, hypothalamus, pituitary gland, and thyroid gland. Early initiation of treatment with the cystine depleting agent cysteamine improves growth rates and has the potential to delay the development of chronic renal failure [43]. In patients with *primary hyperoxaluria* supplementary treatment with citrate and pyridoxine can protract progression of renal failure, and possibly improve longitudinal growth [42]. 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 [44].

In summary, every measure directed to preserve kidney function except glucocorticoid therapy has a beneficial impact on growth.

Consequences of Renal Disease

Protein-Calorie Malnutrition

Nutritional imbalances, particularly protein-energy malnutrition, are frequently seen in children suffering from CKD [45]. Particularly infants and young children are vulnerable to malnutrition because of low nutritional stores and high energy demands which are in turn necessary to allow high growth rates in this age group. Malnutrition is a crucial clinical issue since it is significantly associated with increased mortality in children suffering from CKD [4, 5]. Recently, the term "malnutrition-inflammation complex syndrome" (MICS) has been coined to describe the association between chronic inflammation and malnutrition in dialyzed children and adults [46]. Possible causes of MICS 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 is considered the main cause of erythropoietin hyporesponsiveness, early cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients, and may also be causative of growth hormone resistance and growth failure in children on dialysis [47–49]. Indeed, a recent in vitro study could demonstrate that uremia attenuates GH-stimulated IGF-I expression in the liver, which was further aggravated by inflammation [50].

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 [25]. In addition, protein synthesis is decreased in uremia and catabolism increased [51]. In CKD patients, spontaneous energy intake is correlated with growth rates if it is less than 80% of recommended dietary allowance [52]. However, a further augmentation of energy above this level translates in increasing obesity rather than additional length gain [52–54]. Other approaches to prevent MICS include the preferential use of biocompatible dialysis materials to minimize inflammatory responses and intensified dialysis protocols to increase cytokine clearance and improve the volume status. Preliminary results support the efficacy of these measures in improving growth hormone sensitivity and inducing catch-up growth (see below).

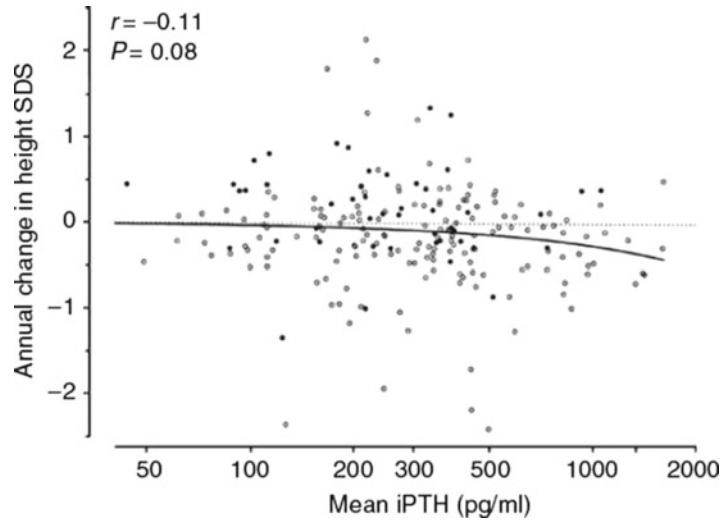


Fig. 24.3 Time-averaged mean plasma intact parathyroid hormone (iPTH) concentrations and change in standardized height in 214 pre- and early pubertal children on peritoneal dialysis followed prospectively for at least 12 months. *Full circles* indicate patients receiving recombinant growth hormone (Reproduced with permission of Borzych et al. [71])

Metabolic Acidosis

Metabolic acidosis usually occurs when GFR is below 50% of normal, although nutritional intake (protein and acid load), catabolism, and alterations in electrolyte balance contribute markedly. 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 [55–57]. Recent studies on metabolic acidosis in uremic animals revealed a complex pattern of interrelated pathophysiological reactions. An increased glucocorticoid production and protein degradation together with suppressed spontaneous pituitary GH secretion, decreased expression of the GH-receptor, and insulin-like growth factor I (IGF-I) receptor, and decreased IGF-I serum concentrations highlight the necessity for adequate control of metabolic acidosis [58–60].

Renal Osteodystrophy

Skeletal deformities due to renal osteodystrophy contribute to uremic growth failure [61]. 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 ($1,25(OH)_2D_3$) in principle should revert sHPT and thus preserve growth potential, clinical data are conflicting [62–64]. The situation gets even more complicated as 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, $1,25(OH)_2D_3$, and fibroblast growth factor-23, as well as numerous paracrine and autocrine signals [65–67].

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 induction of local IGF-I synthesis [68]. However, bones and growth plates are relatively resistant to PTH in chronic uremia [64]. Hence, low or normal PTH levels, which are indicative of low bone turnover in experimental uremia as well as in children with CKD, have been suspected to impair longitudinal growth [69]. However, direct histomorphometric assessment in children on dialysis showed no association of low bone turnover with statural growth [70]. Likewise, a recent study on longitudinal growth of a large cohort of children on peritoneal dialysis failed to show a relationship between growth and PTH levels between 50–400 pg/mL (Fig. 24.3). However, growth in patients with levels above approximately 400 pg/mL tended to be impaired [71].

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 allowed to investigate the impact of anemia on longitudinal growth. Whereas partial correction of anemia improved exercise capacity, and decreased heart rate and resting oxygen consumption, no persistent catch-up growth of EPO could be demonstrated in several multicenter clinical trials in dialyzed children [72, 73] despite anecdotal reports of short-term growth promoting effects [73, 74]. However, a recent retrospective study suggests an association between early initiation of erythropoietin treatment and growth in children with pre-dialytic CKD [75].

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.

Gonadotropic Hormone Axis

Gonadal Hormones

Adolescents and adults suffering from ESRD usually show low or low normal total and free testosterone (T) as well as dihydrotestosterone (DHT) plasma concentrations, which are thought to be due to decreased synthesis and/or increased metabolic clearance [76–80]. The reduced conversion of T to DHT secondary to diminished 5α-reductase activity might explain at least partially the delayed pubertal development in boys with advanced renal failure [81]. In addition, the probably uremia-related decreased clearance of the sex hormone–binding protein lowers the serum concentration of unbound T [76, 78]. Beyond this, the plasma concentration of inhibin, a gonadotropin feedback inhibitor produced by Sertoli cells, is increased in pubertal boys with CKD [82]. 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 [83, 84].

Gonadotropins

Increased plasma concentrations of LH and FSH in combination with decreased or low-normal gonadal hormones suggest a state of compensated hypergonadotropic hypogonadism in uremia [77, 78, 83, 85]. However, in CKD patients the usually inadequate degree of hypergonadotropism relative to the degree of hypogonadism is compatible with an additional defect of pituitary gonadotropin release, and the analysis of spontaneous pulsatile LH secretion has provided new insights into the underlying pathophysiology [86]. In CKD, mean LH plasma levels are elevated despite significantly reduced pituitary LH secretion, due to the markedly impaired renal metabolic clearance of LH [87–89]. When renal function is restored by kidney transplantation, pulsatile LH secretion normalizes [88].

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 due to a primary hypothalamic defect. Indeed, experimental evidence suggests reduced release of hypothalamic gonadotropin-releasing hormone (GnRH) due to uremia-related inhibitory factors and/or to an increased tone of the inhibitory neurotransmitter gamma-aminobutyric acid [89–92]. 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 [79, 88, 90, 93].

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 CKD. The neuroendocrine pathology resembles the regression of the gonadotropic hormone axis to the prepubertal state in patients with anorexia nervosa.

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 [94]. 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 ESRD [95, 96]. The prolonged plasma half-life of GH, rather than increased endogeneous 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 [97–99]. In addition, malnutrition and metabolic acidosis negatively impact GH secretion rates in children with CKD [58].

Growth Hormone Receptor and GH Signaling

Studies in experimental uremia have considerably advanced our understanding of uremic GH resistance. GH-induced hepatic IGF-I synthesis is diminished, due to either a decreased expression of the GH-receptor (GH-R) and/or a postreceptor signaling defect [100, 101]. Whereas reduced expression of the GH-R encoding mRNA in liver and growth plate chondrocytes was consistently seen, hepatic but not growth plate cartilage GH-R protein levels were comparable in uremic and non-uremic animals when corrected for uremia-associated anorexia by pair feeding [100–105]. Thus, while decreased GH-R abundance in growth plate cartilage is likely to contribute to uremic growth failure, a postreceptor GH signaling defect was identified as cause of the diminished hepatic IGF-I secretion upon GH stimulation. In fact, aberrant GH-dependent JAK/STAT signaling has been noted (Fig. 24.4). Activation of the JAK-STAT cascade by tyrosine phosphorylation upon binding of GH to its receptor leads to transcriptional activation of IGF-I synthesis but also of proteins of the suppressor of cytokine signaling (SOCS) family. The latter are responsible for dephosphorylation of the GH-activated cascade and as such provide a GH-regulated negative feedback loop. However, under the conditions of chronic uremia the equilibrium between GH-induced transcriptional activation of IGF-I and SOCS is shifted toward SOCS overstimulation. Preliminary evidence suggests that the micro-inflammatory state associated with uremia might contribute to GH resistance, as SOCS are also induced by inflammatory cytokines [100, 106].

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 pathomechanism, GHBP plasma levels in CKD patients are decreased and related to the residual renal function [107, 108].

Insulin-like Growth Factor Plasma Binding and Tissue Action

Apart from GH resistance, insensitivity to IGF-I is also found in the state of uremia [109–113]. While serum concentrations of IGF-I and IGF-II are usually within the normal range in children

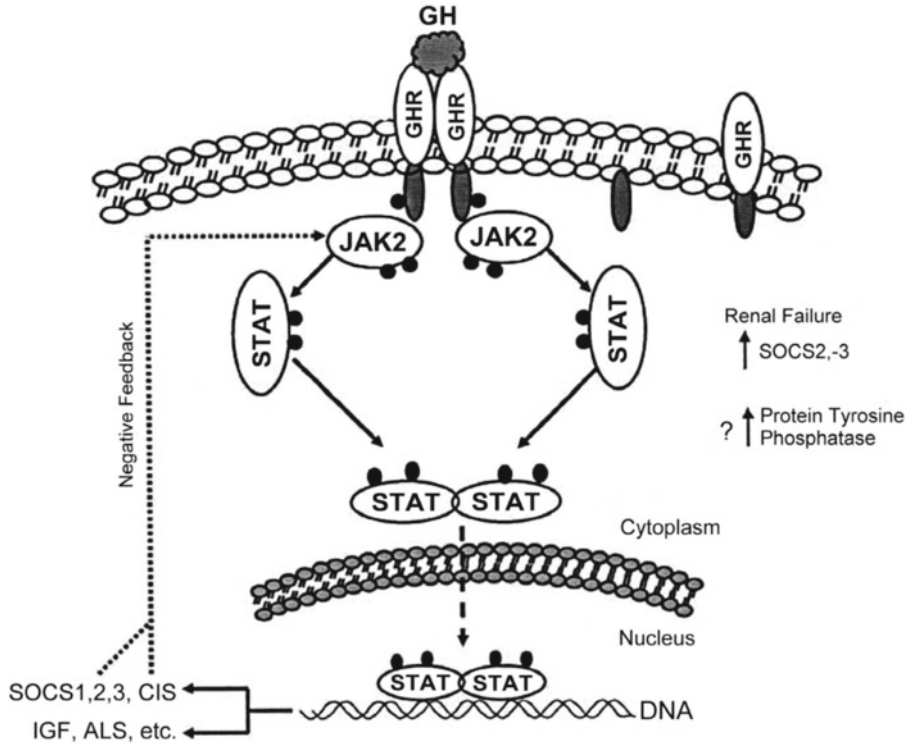


Fig. 24.4 Growth hormone (GH)-mediated JAK2/STAT signal transduction. GH activates several signaling pathways via Janus kinase2 (JAK2) including the JAK/STAT (signal transducer and activator of transcription) pathway. Binding of GH to its receptor (GHR) activates JAK2, which then self-phosphorylates followed by phosphorylation of the GHR 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-1 (IGF-1) 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 resistance may result in part from 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 Rabkin et al. [106])

with CKD, IGF-I levels are slightly reduced and those of IGF-II mildly increased in dialyzed patients [114]. In contrast to the unchanged total amount of circulating immunoreactive IGF, somatomedin bioavailability is reduced in uremia pointing to the existence of circulating inhibitors [115, 116]. A low-molecular weight somatomedin inhibitor (~1 kDa) was reported to circulate in uremic serum in an early study, but this has not been characterized further. Later studies focused on the accumulation of the 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 (Fig. 24.5). In particular, the concentrations of IGFBP-1, -2, -3, -4 and -6 increase as renal function declines and IGFBP-1, -2 and -6 have been shown to inhibit IGF-I bioactivity in vitro [114, 117–121]. By contrast, the serum concentrations of IGFBP-5 are normal and IGFBP-5 proteins undergo intense proteolytic cleavage in chronic uremia [120]. Likewise, the elevated level of IGFBP-3 is mostly due to the accumulation of proteolytic fragments whereas intact IGFBP-3 is markedly diminished [122, 123]. The molar excess of IGFBPs over

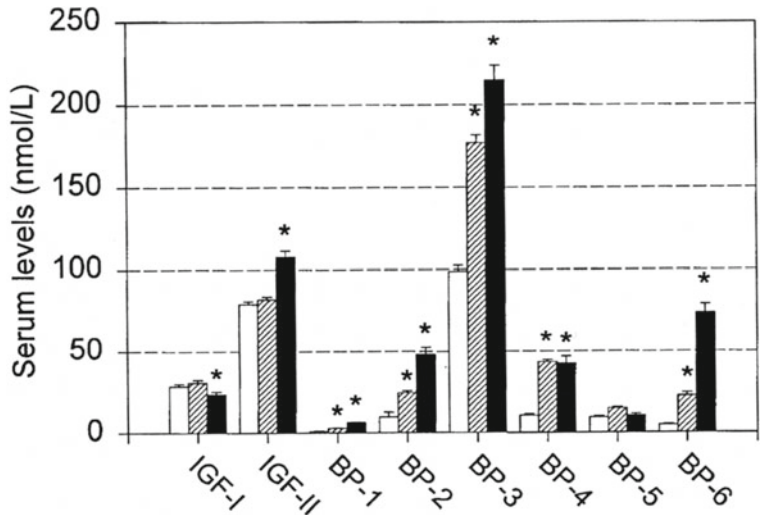


Fig. 24.5 Comparison of the molar serum concentrations of IGFs and IGFBPs in children with preterminal CRF (*hatched bars*) and children with ESRD (*filled bars*). The respective mean molar concentration in normal age-matched children is given in *open bars* for comparison. Data are means + SEM. *Significant ($P < 0.05$ by ANOVA) vs. control (Reproduced with permission of Ulinski et al. [120])

IGFs is approximately 150% in children with CKD and 200% in children on dialysis as compared to 25% in children with CKD. An inverse correlation between growth retardation and IGFBP-1, -2, and -4 serum concentrations has been described [109, 114, 120, 124]. Reduced IGF bioactivity can be returned to normal by removing unsaturated IGFBP [116]. 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 ESRD compared to pre-end-stage CKD patients contributes to the more severe growth failure and reduced response to rhGH therapy in these children. 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 [110, 125].

In summary, the markedly deficient IGF-I synthesis and the modest elevation of GH levels, which is due to decreased metabolic clearance, in the presence of increased IGF plasma–binding capacity strongly supports the concept of a multilevel homeostatic failure of the GH-IGF-I system in uremia.

Treatment of Growth Failure in Chronic Kidney Disease

General Measures

In infants and young children with CKD the most important measure to avoid uremic growth failure is the assurance of *adequate caloric intake*. This often necessitates supplementary feeding via a nasogastric tube or gastrostomy. In a recent retrospective analysis of growth in 101 infants and young children with severe CKD, it could be demonstrated that persistent catch-up growth can be achieved in the majority of patients when measures like tube feeding are commenced instantly if expected growth is not achieved (Fig. 24.2) [21]. In later childhood, adequate nutrition is permissive although catch-up growth is rarely achieved by dietary manipulations alone [45, 126]. In general, the targeted caloric intake should be between 80% and 100% of the recommended daily allowance (RDA) of healthy children [52, 127, 128]. Caloric intake should account for growth failure and be related to "height age" rather than to chronological age. Caloric intake in

excess of 100% of RDA does not induce catch-up growth but rather results in obesity and may thereby negatively contribute to long-term cardiovascular morbidity in CKD patients [52–54]. Protein intake should be 100% of RDA. In patients on peritoneal dialysis, a slightly higher intake (+0.2 g/kg/day) is recommended to compensate for dialytic protein losses. Higher protein intake should be avoided since, despite many attempts, anabolizing or growth promoting effects of high-protein diets have neither been demonstrated in animal models nor in children with CKD. On the contrary, high-protein diets may be detrimental by aggravating metabolic acidosis and augmenting the dietary phosphorus load.

Metabolic acidosis should be vigorously treated by alkaline supplementation. In addition, supplementation of water and electrolytes is essential in patients presenting with polyuria and/or salt losing nephropathies [127, 129]. 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 ultrafiltration.

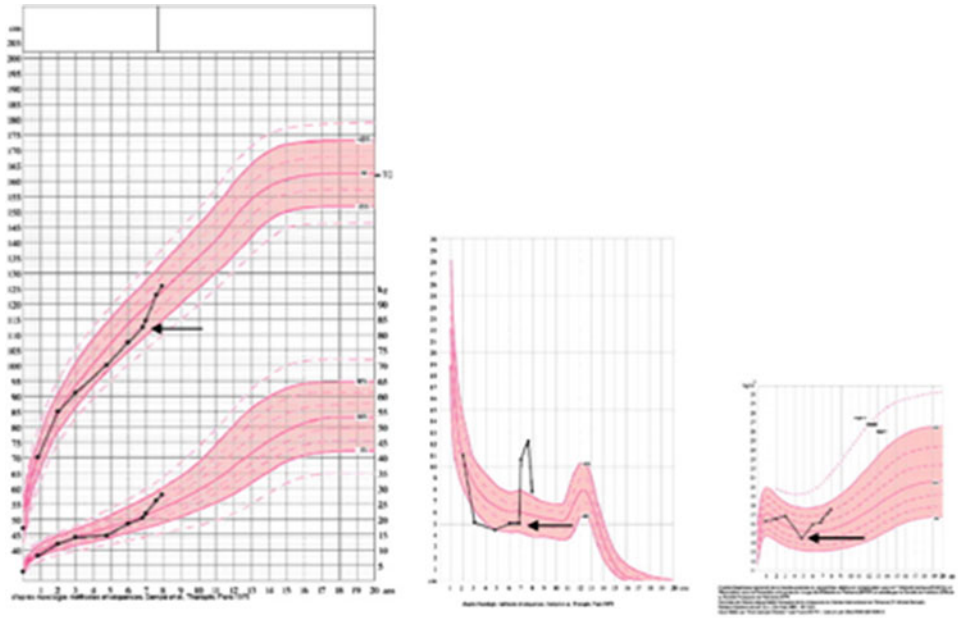
Dialysis and Intensified Dialysis

Although dialysis treatment attenuates the uremic state, longitudinal growth usually is not improved and long-term peritoneal or hemodialysis are associated with a gradual loss of standardized height in children and adolescents [15, 130–133]. In dialyzed infants, losses of up to 1 SD per year have been reported and even the utilization of high-flux hemodialysis and hemofiltration techniques does not improve the situation [22]. In fact, residual renal function appeared to be a better predictor of longitudinal growth than dialytic clearance [134, 135]. The same holds true for continuous peritoneal dialysis [134, 135]. Notably, a high peritoneal transporter status, a condition associated with increased morbidity and mortality in adults [136], is associated with poor longitudinal growth in children on chronic PD [134]. This might be due to the putative association of high peritoneal transport with micro-inflammation, which has been accused to suppress statural growth by interference with GH signaling (see above).

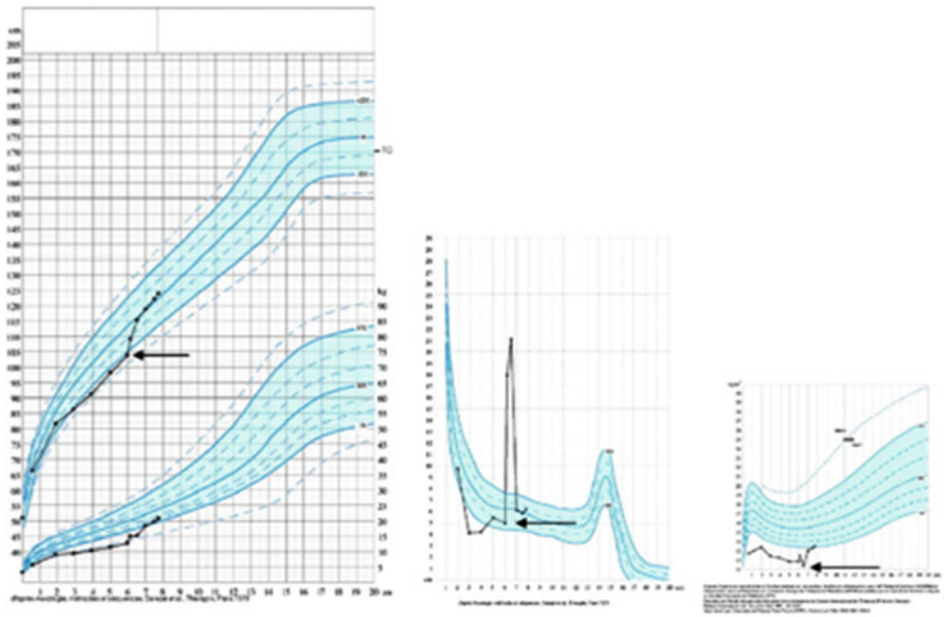
It has been suggested that intensified dialysis, achieved by either extended thrice weekly nocturnal or short daily sessions, might be able to induce catch-up growth [137–139]. According to a recent study, catch-up growth can be maximized when intensified hemodiafiltration (3 h, 6 times a week) and rhGH therapy are combined [140]. 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 (Fig. 24.6). 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 hemodiafiltration is a better substitute for physiological kidney function and may allow substantially better clearance of uremic toxins. As a result, micro-inflammation and metabolic acidosis may be abolished, leading to improved appetite and tissue anabolism. The improved removal of inflammatory cytokines might reverse growth hormone resistance and allow to exploit the full therapeutic potential of rhGH. However, the positive effects of this approach should be counterbalanced with the potential impact of intensified dialysis on psychosocial integration and augmented treatment costs. Prospective randomized trials appear required to provide definite proof to this promising concept.

Transplantation

Although many of the metabolic and endocrine disorders contributing to uremic growth failure are resolved by renal transplantation (RTx), post-transplant catch-up growth is usually restricted to young children and occurs far from regularly [9, 11–13, 141]. Beyond transplant function, age, and degree of stunting at time of transplantation, glucocorticoid dosage is inversely associated with longitudinal growth as well. While complete



Patient 14, a girl on daily on line hemodiafiltration
Protein diet intake(g/kg/d) : 2.4 ±0.4 ; protein nitrogen appearance(g/kg/d) : 1.3 ±0.14
Mean growth velocity (cm/year) : 9.6
Achieved height versus mid parental target height (SDS) : +0.3



Patient 1, a boy on daily on line hemodiafiltration.
Protein diet intake(g/kg/d) : 2.7±0.2 ; protein nitrogen appearance(g/kg/d) : 1.44 ±0.15
Mean growth velocity (cm/year) : 10.4
Achieved height versus mid parental target height (SDS) : +0.2

Fig. 24.6 Examples of growth charts (height and weight chart; growth velocity chart in centimeters per year; body mass under chart) of two patients on daily online hemodiafiltration (start indicated by bars) in addition to rhGH treatment. TC on height chart is the familial target height in centimeters (Reproduced with permission of Fischbach et al. [140])

steroid withdrawal was associated with unacceptably high rejection rates in children with azathioprine and/or cyclosporine A medication [142, 143], withdrawal appears much safer with the currently preferred immunosuppressants. In a recent randomized trial on late steroid withdrawal in patients on treatment with cyclosporine A, mycophenolate mofetil steroid-free patients showed improved growth compared to controls (i.e., change in height SDS; 0.6 ± 0.1 vs. -0.2 ± 0.1) within 27 months [144]. However, catch-up growth in pubertal patients was rather limited compared to that in prepubertal patients. Thus, efforts to avoid a height deficit before RTx, such as rhGH treatment, early (preemptive) RTx, and the use of efficacious immunosuppressive strategies for optimized graft function and early withdrawal or even complete avoidance of steroids are required to improve final height in children after RTx.

Endocrine Therapies

Calcitriol

Calcitriol deficiency is a major cause of sHPT and renal osteodystrophy. Although calcitriol supplementation reverses the biochemical, radiographic, and histological signs of high-turnover bone disease, neither experimental nor clinical studies provide consistent improvement of longitudinal height [145–147]. These conflicting results might be due to differences in the mode of administration and to the pleiotropic calcitriol-specific effects on growth plate chondrocytes. There is general concern that a low-turnover bone state induced by intense calcitriol therapy may compromise longitudinal growth. Therefore, plasma PTH levels should be kept at two–three times the upper normal range in patients with CKD stage 4–5, and within the upper limit of the normal range in CKD stages 1–3 [61]. Although not formally proven in prospective clinical trials, these target ranges are thought to allow sufficient control of sHPT and avoid adynamic bone disease, minimizing any interference of uremic bone and mineral disorder and its treatment with longitudinal growth [61, 148, 149].

Calcimimetics

Pilot studies have provided preliminary evidence that calcimimetics are an effective therapy of sHPT in pediatric dialysis patients [150, 151]. 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, calcimimetics (cinacalcet) was shown to improve food efficiency and body weight gain in uremic rats, but no effects on growth plate morphology and/or longitudinal growth were seen [152]. It is hoped that efficacy and safety will soon be further addressed in a carefully designed clinical trial.

Growth Hormone

The unraveling of the pathomechanisms by which chronic uremia impairs the action of endogenous GH paved the way for pharmacological treatment with recombinant human (rh)GH [153–155]. Administration of rhGH markedly stimulates IGF-I synthesis with only a modest effect on IGFBPs, thereby normalizing somatomedin bioactivity and promoting longitudinal growth (Fig. 24.7) [156, 157]. The efficacy and safety of long-term treatment with rhGH in children with CKD before and after renal transplantation have been established extensively.

Efficacy of rhGH in Prepubertal Children

In prepubertal children with pre-dialysis CKD, rhGH therapy typically doubles height velocity during the first treatment year [158–165]. Catch-up growth continues asymptotically during extended treatment. After 5–6 treatment years mean standardized height had increased from −2.6 to −0.7 SDS in North American, from −3.4 to −1.9 in German, and from −3.0 to −0.5 in Dutch patients [163–165]. In dialyzed children, the treatment response is significantly attenuated compared to children with pre-end-stage CKD (0.8 SD vs. 1.3 SD; [163]). RhGH responsiveness is similarly poor in children on peritoneal dialysis and standard hemodialysis, but can be markedly

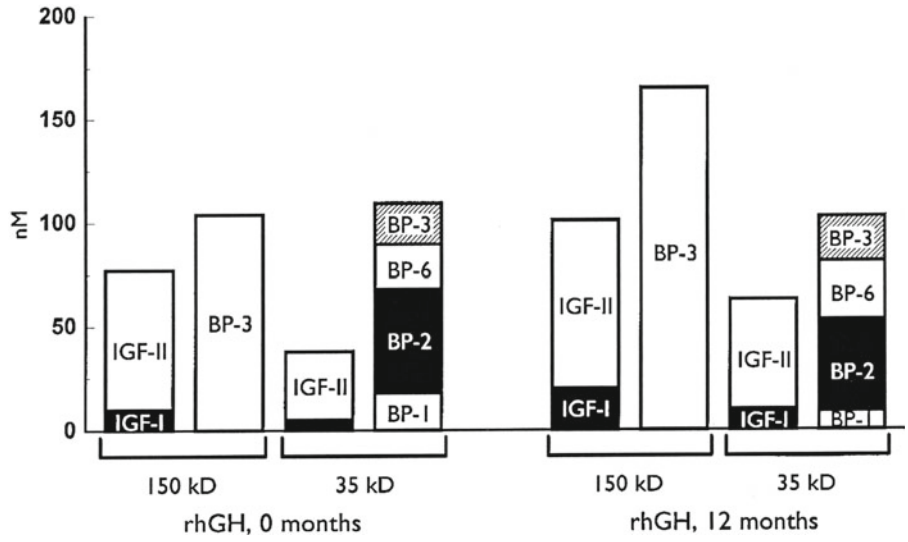


Fig. 24.7 Balance between IGFBPs and IGFs in serum of CRF children before and after rhGH treatment. Levels (nanomoles per L) of IGF-I, IGF-II, IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-6 in the 150- and 35-kDa fractions of CRF serum are presented. Protein levels were measured in whole serum of 30 CRF children before (0 months) and during (12 months) rhGH treatment. Mean IGFBP-1, IGFBP-2, and IGFBP-6 levels were assigned entirely to the 35 kDa serum fractions. The percentages of IGFBP-3 and IGFs at 150 kDa (fractions 23–27) and at 35 kDa (fractions 28–30) in sera from CRF children before and after 12 months of rhGH treatment were calculated; these percentages were then applied to the mean whole serum levels to calculate the amounts of each protein at 150 and 35 kDa. Both intact IGFBP-3 and IGFBP-329 were abundant in the 150-kDa fractions; IGFBP-329 was much more abundant than intact IGFBP-3 in the 35-kDa fractions (Reproduced with permission of Powell et al. [156])

improved when dialytic clearance is augmented by daily hemodialfiltration (vide supra) [163, 166–168].

Based on the current experience with rhGH in pediatric CKD patients, a model to predict growth response was developed very recently [169]. 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 (milligrams per kilogram per week) × 1.04] + [GFR (milliliters per minute × 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.

Effects of rhGH on Pubertal Growth and Final Height

The evaluation of pubertal growth in CKD patients is complicated by (i) the delayed and shortened pubertal growth spurt compared to healthy children and (ii) changes in treatment modalities, i.e., start of dialysis, renal transplantation, and initiation and cessation of rhGH therapy [34]. In a study following patients with CKD and ESRD from late prepubertal age to final height, the average height increment in rhGH-treated patients was twice that seen in a matched control group. The main benefit for total growth and final height was achieved before the onset of

the pubertal growth spurt whereas no overall effect on the pubertal height gain was observed [16] (Figs. 24.8 and 24.9). The final height results from several clinical trials are given in Table 24.2 [165, 170–179].

Recently the determinants of final height were analyzed in 240 rhGH-treated children on conservative treatment, dialysis, or after RTx reported to the KIGS registry (Fig. 24.10). In children with normal pubertal timing, the mean increase in standardized height from prepubertal age to final height was 1.3 SDS. Patients with delayed onset of puberty achieved a significantly lesser increase in standardized height (+0.9 SDS). However, the mean age at initiation of rhGH treatment in these patients was 14.5 years and the mean duration of rhGH therapy was only 2.0 years. The average cumulative increase in height SDS was significantly greater in CKD patients who remained on conservative treatment throughout puberty (+1.5 SDS) than in those on dialysis and in renal allograft recipients (both +1.1 SDS). Adult height was independently positively predicted by the height attained at start of rhGH and the duration of rhGH treatment, and inversely by the time spent on dialysis, the age at onset puberty, and the age at start of rhGH. Altogether these parameters explained 61% of the overall variability of adult height. Hence, rhGH improves final height in prepubertal and pubertal patients, but the growth response is diminished in patients with delayed onset of puberty and those on long-term dialysis [177].

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

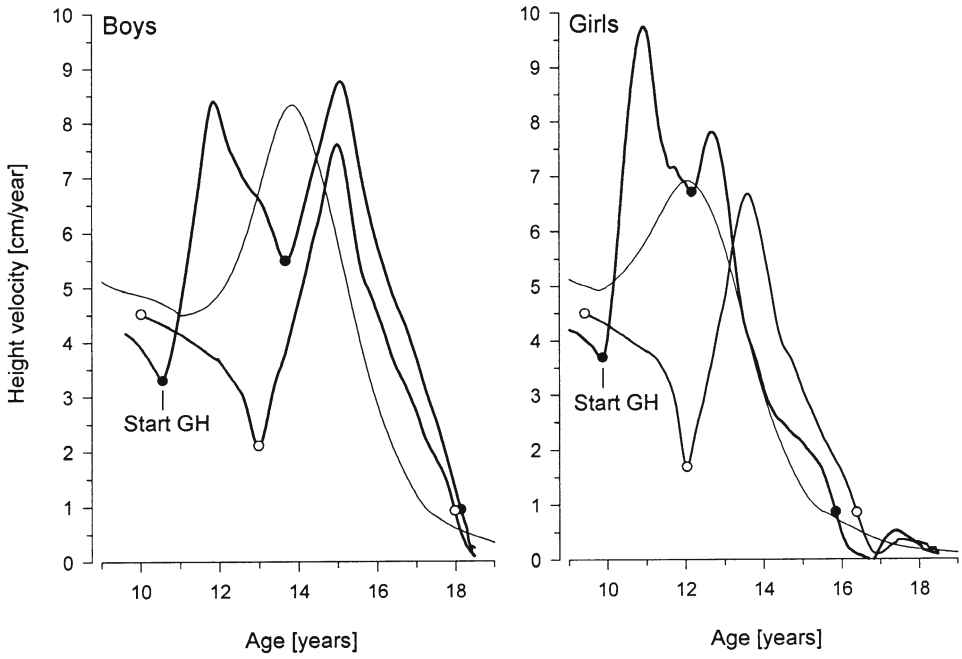


Fig. 24.8 Synchronized mean height velocity curves of 32 boys (*left panel*) and 6 girls (*right panel*) with CRF during rhGH treatment (*closed circles*), as compared with 50 children with CRF not treated with rhGH (*open circles*) and 232 normal children (*thin lines*). The *dots* indicate the time of the first observation, which corresponds to the start of rhGH treatment in the growth hormone–treated children, minimal pre-spurt height velocity, and the time of the end of the pubertal growth spurt (Reproduced with permission of Haffner et al. [16])

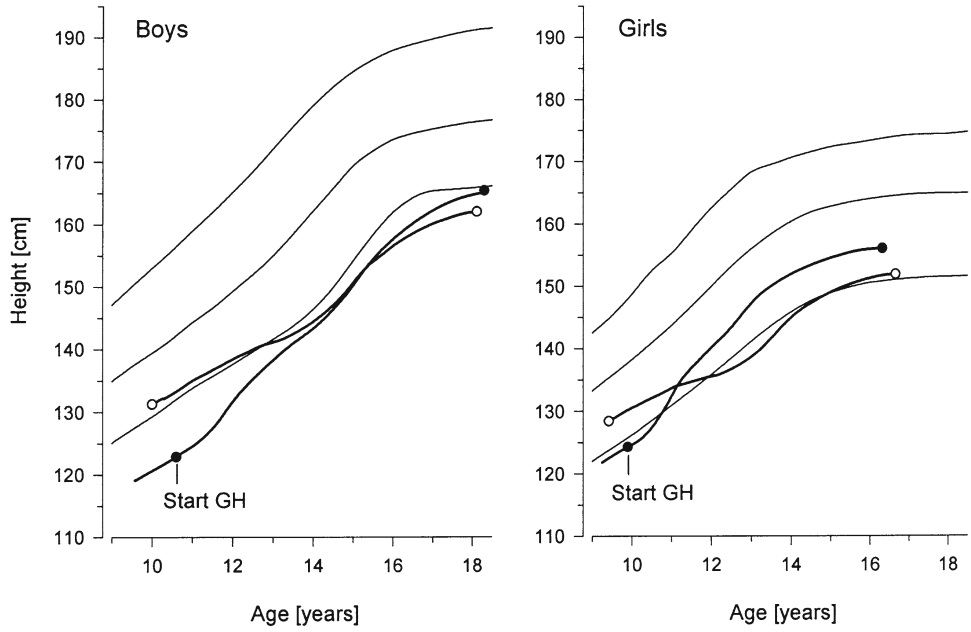


Fig. 24.9 Synchronized mean height curves of 32 boys (*left panel*) and 6 girls (*right panel*) with CRF during rhGH treatment (*closed circles*), as compared with 50 children with CRF not treated with rhGH (*open circles*). Normal values are indicated by the 3rd, 50th, and 97th percentiles. The *dots* 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 Haffner et al. [16])

of the nutritional status has been considered the primary and sufficient measure to restore normal growth in growth retarded infants, postponing the option of endocrine therapeutic intervention to beyond the second year of life. Recently, this concept has been challenged by several reports initiating rhGH in growth retarded infants with CKD [180–182]. A randomized controlled study involving 30 growth retarded infants (mean age 16 months) with moderate CKD (mean GFR 25 mL/min/1.73 m²) observed excellent catch-up growth from −3.0 to −1.1 SDS within 24 months, in contrast to no significant change in controls. Unfortunately, the caloric intake of the children was not reported [180]. Likewise, Maxwell and Rees reported an increase in height SDS −3.3 to 2.2 within 12 months in 8 infants with a mean age of 22 months and CKD stage III–IV [181]. Very recently, Mencarelli et al. reported on a cohort of 27 infants with early onset CKD receiving either standard therapy or additional rhGH treatment [182]. Children treated with rhGH, but not patients undergoing close nutritional management only showed significant increases in both weight and height SDS (Fig. 24.11). Notably, two thirds of the patients receiving rhGH were on dialysis treatment. Hence, the results of these studies lend further support to the previous observation that the relative efficacy and cost-efficiency of rhGH is actually best when initiated at young age, i.e., during infancy and early childhood [163]. While the provision of adequate nutrition is certainly vital to growth and development of infants with CKD, some children show growth failure despite adequate calorie supply. In these patients, any further increases of energy intake typically lead to fat deposition but not catch-up growth. Early growth hormone therapy appears as an attractive option to accelerate length and weight gain in such infants since it helps accomplishing the body size required for renal transplantation without delay. This concept, which

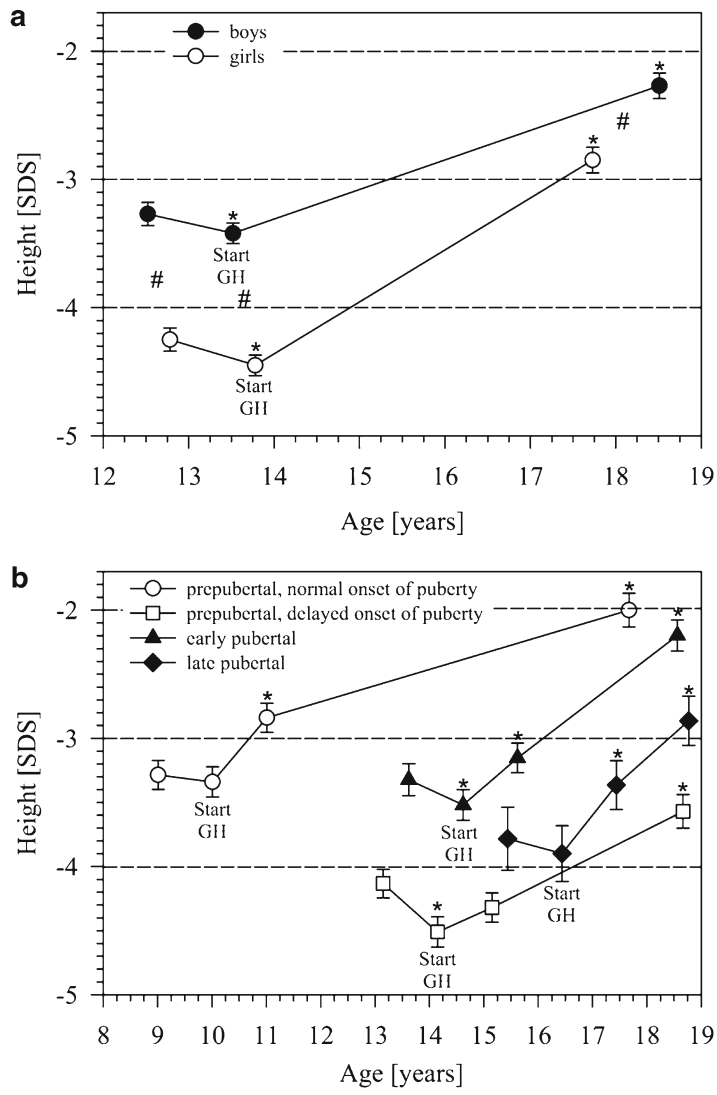


Fig. 24.10 (**a**) Mean height SDS of GH-treated boys (●; n = 193; aged 4.7–19.7 years) and girls (○; n = 47; aged 8.1–18.0 years) with CKD in the year before start of therapy until attainment of near-FH (data are given as mean ± SEM; #, P < 0.01 boys vs. girls; *, P < 0.01 vs. previous time point). (**b**) Mean height SDS of prepubertal CKD patients with normal (○, n = 68; aged 4.7–13.0 years) or delayed (□, n = 25; aged 10.1–17.1 years) onset of puberty and patients in early (▲, n = 112; aged 10.1–19.7 years) and late (◆, n = 35; aged 13.8–19.5 years) puberty in the year before start of GH therapy until attainment of near-FH (data are given as mean ± SEM; *, P < 0.003 vs. previous time point) (Reproduced with permission of Nissel et al. [177])

needs further elaboration in clinical trials, may include preemptive usage of rhGH in patients with still normal height but poor height velocity and downward crossing of percentiles.

General rhGH Treatment Strategies

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 with the age at start of treatment [163]. Daily dosing is more effective than three administrations per week and the optimal dose is 4 IU/m²/day (0.33 mg/kg/week) [183, 184]. 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 [174, 185]. Furthermore, although the absolute height gain achieved by rhGH is independent of age, the reference range increases

Table 24.2 Synopsis of studies reporting adult height data after rhGH treatment of growth failure in CKD patients

Study	No. of pts. studied	CRF treatment modalities	Age at start of rhGH (years)	Pubertal status at start of rhGH	Duration of follow-up (years)	Duration of rhGH (years)	Initial height SDS	Final height SDS	Change in height SDS
Dutch [175]	65	Cons Rx/ Dialysis	n.i.	Prepubertal	n.i.	5.8	−2.8.	−1.4	+1.4
KIGS [177]	108	Cons Rx	12.8	n.i.	4.9	>2.0	−3.2	−1.7	+1.5
	67	Dialysis	14.2	n.i.	4.0	>2.0	−4.0	−2.9	+1.1
	65	Transplant	13.7	n.i.	4.1	>2.0	−3.6	−2.5	+1.1
NAPRTCS [173]	9	Cons Rx	n.i.	n.i.	3.2	<3.2	−3.0	−2.2	+0.7
	22	Dialysis	n.i.	n.i.	4.1	<4.1	−3.6	−3.2	+0.4
	72	Transplant	n.i.	n.i.	3.7	<3.7	−3.0	−2.5	+0.5
German [16]	38	47% cons Rx 24% dialysis 29% transplant[a]	10.4	Prepubertal	7.6	5.3	−3.1	−1.6	+1.4
French [179]	35	Cons Rx	n.i.	n.i.	n.i.	n.i.	−3.0	−1.8	+1.2
	19	Dialysis	n.i.	n.i.	n.i.	n.i.	−4.1	−2.5	+1.6
	48	Transplant	n.i.	n.i.	n.i.	n.i.	−3.2	−2.2	+1.0
Belgian [171]	17	Transplant	n.i.	n.i.	n.i.	3.4	−3.0	−1.8	+1.2
Dutch [175]	18	Transplant	15.5	Pubertal	n.i.	n.i.	n.i.	n.i.	Total height gain 19 cm
NAPRTCS [176]	71	Transplant	n.i.	n.i.	n.i.	n.i.	−2.7	−1.8	+0.9

n.i. No information given

[a]Percentage distribution of patient years spent in each treatment category

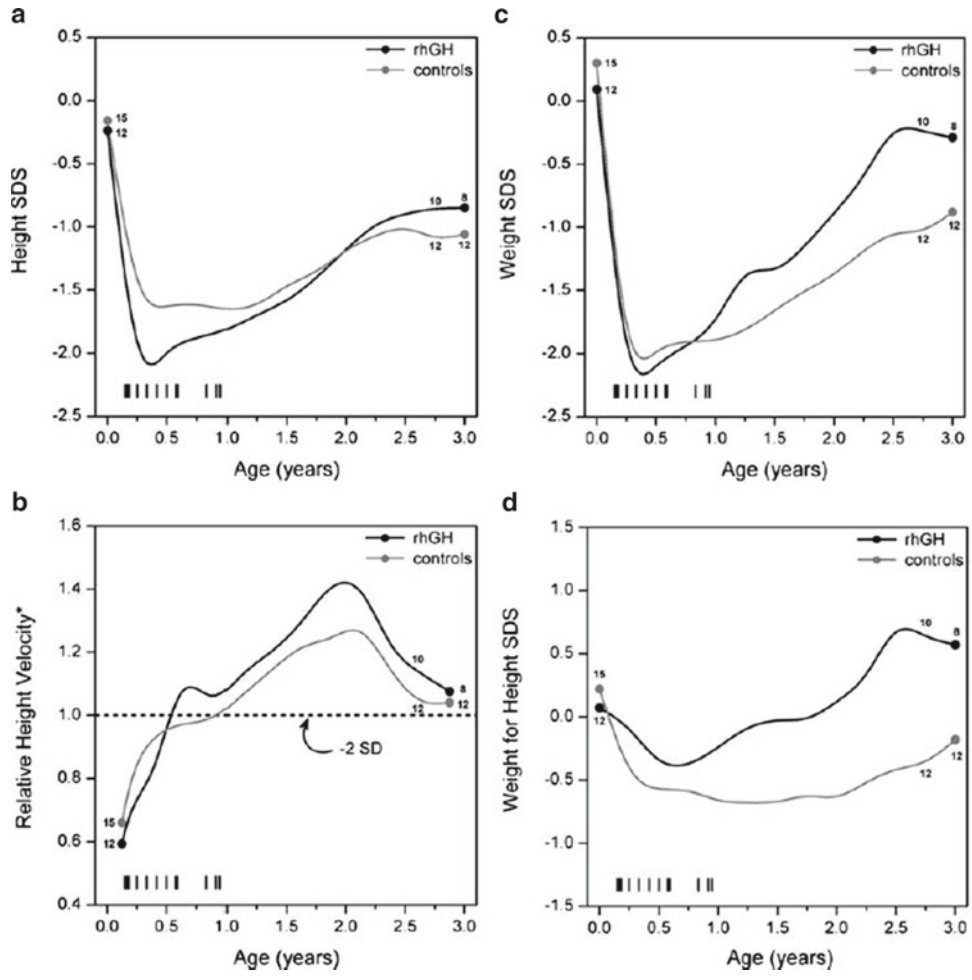


Fig. 24.11 Height and weight data. Recombinant human growth hormone (rhGH)-treated patients are shown in *black lines* and controls in *gray lines*. *Vertical bars* indicate the age at the beginning of rhGH therapy in individual patients. (**a**) Height standard deviation score (SDS), (**b**) growth velocity expressed as relative values to the −2 SDS channel for the normal population, (**c**) weight SDS, (**d**) weight for height SDS. Numbers indicate number of infants/children for which there were data at that time point (Reproduced with permission of Mencarelli et al. [182])

with age. Thus, rhGH treatment should be started as early as growth retardation becomes evident (i.e., height below 3rd percentile) (Fig. 24.12) [163]. It is still a matter of discussion whether a low growth rate (i.e., height velocity below the 5th percentile) is an indication to start rhGH even before height drops below the 3rd percentile. Such early, preventive therapy is probably more cost-effective than starting at a more advanced age when growth retardation has become evident and higher absolute rhGH doses are required.

Since rhGH is also effective in infants and young children with CKD, this treatment modality should not be withheld in this age group if malnutrition, metabolic acidosis, renal osteodystrophy, and electrolyte losses have been treated sufficiently [180–182]. The KDOQI guidelines for nutritional management in children with CKD suggest that rhGH should be initiated promptly if nutritional management has not induced catch-up growth within 3 months [128].

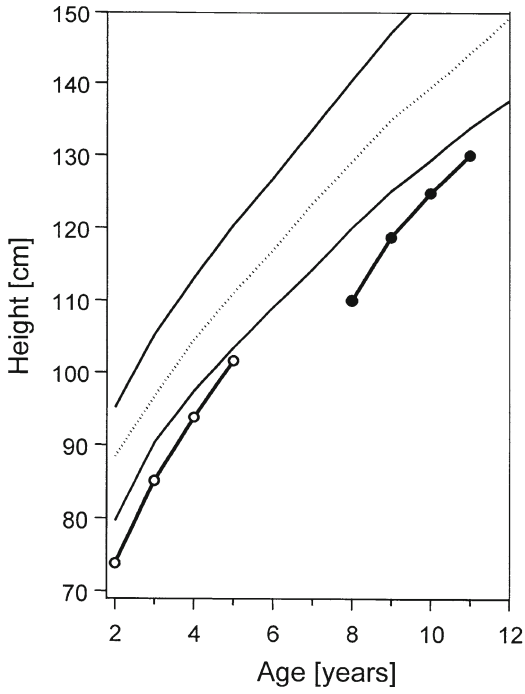


Fig. 24.12 Age-dependent efficacy of rhGH treatment exemplified by individual growth curves predicted for two patients of ages 2 and 8 years, started on rhGH at a basal height of −3.5 SD and a height velocity of −2.0 SD. The *dotted line* indicates the 50th percentile of a normal population, the *solid lines* bounding the *dotted line* denote the 3rd and 97th percentiles. Growth is accelerated over baseline height velocity in both patients by 4.5 cm in the first, 1.9 cm in the second, and 1.0 cm in the third years (empirical means of all patients on conservative treatment followed for 3 years). The young child reaches the third percentile within the third year, whereas the older child does not (Reproduced with permission of Haffner et al. [163])

The primary treatment target should be to return height into the patient's 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 initiation of dialysis; after renal transplantation rhGH should be stopped and spontaneous growth should be monitored for 12 months. If growth remains subnormal, weaning off glucocorticoids should be the first therapeutic consideration, and reinstitution of rhGH restricted to those patients with lacking or insufficient catch-up growth after steroid withdrawal or with a permanent need for maintenance glucocorticoid medication.

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. A comprehensive comparison on the incidence of adverse events in large cohorts of CKD patients on conservative treatment, on dialysis, and after renal transplantation with and without rhGH treatment revealed no significant association between utilization of rhGH and the incidence of malignancy, slipped capital femoral epiphysis, avascular necrosis, glucose intolerance, pancreatitis, progressive deterioration of renal function, acute allograft rejection, or fluid retention [186]. Intracranial hypertension (ICH) in 3 out of 1,376 CKD patients was the only adverse event significantly associated with rhGH therapy. However, in all 3 instances ICH occurred after discontinuation of rhGH. In another survey ICH was noted in 15 out of 1,670 CKD patients on rhGH treatment (0.9%) [187]. Although the clinical symptoms weaned off after cessation of rhGH treatment, two patients had persistent blindness. In four patients symptoms of ICH recurred after reinstitution of rhGH treatment. Due to the potentially slightly increased risk of ICH in CKD a baseline fundoscopy is recommended and the rhGH starting dose should be 50% of the expected maintenance rhGH dosage for the first few weeks of treatment. Furthermore, hydration should be carefully monitored in CKD patients receiving rhGH since overhydration seems to 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, dialysis, and after renal transplantation [188]. 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 [186].

An aggravation of secondary hyperparathyroidism has rarely been reported in CKD patients on rhGH treatment, but the underlying pathomechanisms remain to be elucidated [189, 190]. GH 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 and severe hyperparathyroidism and uremic bone disease should be treated before initiation of rhGH therapy in CKD patients. However, mild to moderate hyperparathyroidism should not be considered a reason to withhold rhGH from a poorly growing child.

Future Perspectives

Despite attention to nutrition and the availability of rhGH therapy, the problem of uremic growth failure has not been resolved in the majority of dialysis patients. The recently propagated concept of intensified hemodialysis combined with rhGH may be a promising option for patients suffering from growth retardation and GH resistance on conventional dialysis therapy [140] and deserves further investigation by controlled clinical trials. Another avenue of promising clinical research may be given by recombinant IGF-I administered as monotherapy or in combination with rhGH [191].

A particular challenge is given by the severely diminished pubertal height gain. 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. GnRH analogues arrest pubertal progress, but the potential growth benefit would come at the psychological disadvantage of delayed sexual maturation. In boys, aromatase inhibitors, which suppress the local conversion of testosterone to estradiol, might extend the growth phase without affecting pubertal development and thereby increase the time window for rhGH therapy. An initial proof of this concept has recently been provided in short male adolescents treated with rhGH combined with the aromatase inhibitor anastrozole [192]. It will be fascinating to study its efficacy in adolescents on long-term dialysis.

References

1. Haffner D, Nissel R. Growth and puberty in chronic kidney disease. In: Geary DF, Schaefer F, editors. Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008. p. 709–32.
2. de Graaff LC, Mulder PG, Hokken-Koelega AC. Body proportions before and during growth hormone therapy in children with chronic renal failure. Pediatr Nephrol. 2003;18(7):679–84.
3. Zivicnjak M, Franke D, Filler G, et al. Growth impairment shows an age-dependent pattern in boys with chronic kidney disease. Pediatr Nephrol. 2007;22(3):420–9.
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. Wong CS, Gipson DS, Gillen DL, et al. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis. 2000;36(4):811–9.
6. van Diemen-Steenvoorde R, Donckerwolcke RA, Brackel H, Wolff ED, de Jong MC. Growth and sexual maturation in children after kidney transplantation. J Pediatr. 1987;110(3):351–6.
7. Gilli G, Mehls O, Schärer K. Final height of children with chronic renal failure. Proc Eur Dial Transplant Assoc. 1984;21:830–6.
8. 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.
9. 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.
10. Fine RN, Ho M, Tejani A. The contribution of renal transplantation to final adult height: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Nephrol. 2001; 16(12):951–6.

11. 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.
12. Nissel R, Brazda I, Feneberg R, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. Kidney Int. 2004;66(2):792–800.
13. Offner G, Latta K, Hoyer PF, et al. Kidney transplanted children come of age. Kidney Int. 1999;55(4):1509–17.
14. Schaefer F, Gilli G, Schärer K. Pubertal growth and final height in chronic renal failure. In: Schärer K, editor. Growth and endocrine changes in children and adolescents with chronic renal failure. 22nd ed. Basel: Karger; 1989. p. 59–69.
15. 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.
16. 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.
17. Wühl E, Haffner D, Offner G, Broyer M, van't HW, Mehls O. Long-term treatment with growth hormone in short children with nephropathic cystinosis. J Pediatr. 2001;138(6):880–7.
18. Nissel R, Ucur E, Mehls O, Haffner D. Final height after long-term treatment with recombinant human growth hormone (rhGH) in children with uremic growth failure. Nephrol Dial Transplant. 2006;21(Suppl 4):367–8.
19. 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.
20. 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.
21. 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.
22. Schaefer F, Mehls O. Endocrine, metabolic and growth disorders. In: Holliday MA, Barratt TM, Avner ED, editors. Pediatric Nephrology. Baltimore: Williams & Wilkins; 1994. p. 1241–86.
23. 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.
24. 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.
25. 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.
26. Schärer 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.
27. 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.
28. Schaefer F, Walther U, Ruder H. Reduced spermaturia in adolescent and young adult patients after renal transplantation. Nephrol Dial Transplant. 1991;6:840.
29. Inci K, Duzova A, Aki FT, et al. Semen variables and hormone profiles after kidney transplantation during adolescence. Transplant Proc. 2006;38(2):541–2.
30. Palmer BF. Sexual dysfunction in uremia. J Am Soc Nephrol. 1999;10(6):1381–8.
31. Matuszkiewicz-Rowinska J, Skorzewska K, Radowicki S, et al. Endometrial morphology and pituitary-gonadal axis dysfunction in women of reproductive age undergoing chronic haemodialysis – a multicentre study. Nephrol Dial Transplant. 2004; 19(8):2074–7.
32. Hou S. Pregnancy in chronic renal insufficiency and end-stage renal disease. Am J Kidney Dis. 1999;33(2): 235–52.
33. Broyer M, Guest G. Growth after kidney transplantation - a single center experience. In: Schärer K, editor. Growth and endocrine changes in children and adolescents with chronic renal failure. 20th ed. Basel: Karger; 1989. p. 36–45.
34. Schaefer F, Seidel C, Binding A, et al. Pubertal growth in chronic renal failure. Pediatr Res. 1990;28(1): 5–10.
35. Hodson EM, Shaw PF, Evans RA, et al. Growth retardation and renal osteodystrophy in children with chronic renal failure. J Pediatr. 1983;103(5):735–40.
36. Schärer K, Essigmann HC, Schaefer F. Body growth of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 1999;13(9):828–34.
37. Rees L, Greene SA, Adlard P, et al. Growth and endocrine function in steroid sensitive nephrotic syndrome. Arch Dis Child. 1988;63(5):484–90.
38. Holtta TM, Ronnholm KA, Jalanko H, la-Houhala M, Antikainen M, Holmberg C. Peritoneal dialysis in children under 5 years of age. Perit Dial Int. 1997;17(6):573–80.
39. 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.
40. Kovacevic L, Reid CJ, Rigden SP. Management of congenital nephrotic syndrome. Pediatr Nephrol. 2003; 18(5):426–30.

41. Winkler L, Offner G, Krull F, Brodehl J. Growth and pubertal development in nephropathic cystinosis. Eur J Pediatr. 1993;152(3):244–9.
42. Leumann E, Hoppe B. The primary hyperoxalurias. J Am Soc Nephrol. 2001;12(9):1986–93.
43. Kimonis VE, Troendle J, Rose SR, Yang ML, Markello TC, Gahl WA. Effects of early cysteamine therapy on thyroid function and growth in nephropathic cystinosis. J Clin Endocrinol Metab. 1995;80(11):3257–61.
44. Nissel R, Latta K, Gagnadoux MF, et al. Body growth after combined liver-kidney transplantation in children with primary hyperoxaluria type 1. Transplantation. 2006;82(1):48–54.
45. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702.
46. Bamgbola FO, Kaskel FJ. Uremic malnutrition-inflammation syndrome in chronic renal disease: a pathobiologic entity. J Ren Nutr. 2003;13(4):250–8.
47. Chen Y, Sun D, Krishnamurthy VM, Rabkin R. Endotoxin attenuates growth hormone-induced hepatic insulin-like growth factor I expression by inhibiting JAK2/STAT5 signal transduction and STAT5b DNA binding. Am J Physiol Endocrinol Metab. 2007;292(6):E1856–62.
48. Chen Y, Sood S, Krishnamurthy VM, Rotwein P, Rabkin R. Endotoxin-induced growth hormone resistance in skeletal muscle. Endocrinology. 2009;150(8):3620–6.
49. Zheng Z, Sun DF, Tummala P, Rabkin R. Cardiac resistance to growth hormone in uremia. Kidney Int. 2005;67(3):858–66.
50. 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.
51. Mehls O, Ritz E, Gilli G, et al. Nitrogen metabolism and growth in experimental uremia. Int J Pediatr Nephrol. 1980;1(1):34–41.
52. Arnold WC, Danford D, Holliday MA. Effects of caloric supplementation on growth in children with uremia. Kidney Int. 1983;24(2):205–9.
53. Coleman JE, Watson AR. Gastrostomy buttons for nutritional support in children with cystinosis. Pediatr Nephrol. 2000;14(8–9):833–6.
54. 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.
55. May RC, Hara Y, Kelly RA, Block KP, Buse MG, Mitch WE. Branched-chain amino acid metabolism in rat muscle: abnormal regulation in acidosis. Am J Physiol. 1987;252(6 Pt 1):E712–8.
56. 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.
57. 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.
58. Challa A, Krieg Jr RJ, Thabet MA, Veldhuis JD, Chan JC. Metabolic acidosis inhibits growth hormone secretion in rats: mechanism of growth retardation. Am J Physiol. 1993;265(4 Pt 1):E547–53.
59. Challa A, Chan W, Krieg Jr RJ, 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.
60. 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.
61. Klaus G, Watson A, Edefonti A, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol. 2006;21(2):151–9.
62. Mehls O, Ritz E, Gilli G, Heinrich U. Role of hormonal disturbances in uremic growth failure. Contrib Nephrol. 1986;50:119–29.
63. 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.
64. 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 Invest. 1982;12(4):337–43.
65. Kiela PR, Ghishan FK. Recent advances in the renal-skeletal-gut axis that controls phosphate homeostasis. Lab Invest. 2009;89(1):7–14.
66. Rodriguez M, Felsenfeld AJ. PTH, FGF-23 and early CKD. Nephrol Dial Transplant. 2008;23(11):3391–3.
67. Wesseling-Perry K, Pereira RC, Wang H, et al. Relationship between plasma fibroblast growth factor-23 concentration and bone mineralization in children with renal failure on peritoneal dialysis. J Clin Endocrinol Metab. 2009;94(2):511–7.
68. 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.
69. Kuizon BD, Goodman WG, Juppner H, et al. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int. 1998;53(1):205–11.
70. 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.
71. Borzych D, Rees L, Ha IS, et al. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78(12):1295–304. Epub ahead of print.
72. Martin GR, Ongkingo JR, Turner ME, Skurow ES, Ruley EJ. Recombinant erythropoietin (Epogen)

improves cardiac exercise performance in children with end-stage renal disease. Pediatr Nephrol. 1993;7(3):276–80.
73. 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.
74. Jabs K. The effects of recombinant human erythropoietin on growth and nutritional status. Pediatr Nephrol. 1996;10(3):324–7.
75. Boehm M, Riesenhuber A, Winkelmayer WC, Arbeiter K, Mueller T, Aufricht C. Early erythropoietin therapy is associated with improved growth in children with chronic kidney disease. Pediatr Nephrol. 2007;22(8):1189–93.
76. 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.
77. Handelsman DJ. Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. Endocr Rev. 1985;6(2):151–82.
78. 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.
79. Schaefer F, Hamill G, Stanhope R, Preece MA, Scharer K. Pulsatile growth hormone secretion in peripubertal patients with chronic renal failure. Cooperative Study Group on Pubertal Development in Chronic Renal Failure. J Pediatr. 1991;119(4):568–77.
80. Schärer K, Broyer M, Vecsei P, Roger M, Arnold-Schwender E, Usberti J. Damage to testicular function in chronic renal failure of children. Proc Eur Dial Transplant Assoc. 1980;17:725–9.
81. 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 (Oxf). 1978;8(1):7–14.
82. 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 (Oxf). 1993;39(1):27–33.
83. 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 (Copenh). 1987;115(3): 289–96.
84. Schärer K, Schaefer F, Trott M. Pubertal development in children with chronic renal failure. In: Schärer K, editor. Growth and endocrine changes in children and adolescents with chronic renal failure. Basel: Karger; 1989. p. 151–68.
85. 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.
86. Veldhuis JD, Carlson ML, Johnson ML. The pituitary gland secretes in bursts: appraising the nature of glandular secretory impulses by simultaneous multiple-parameter deconvolution of plasma hormone concentrations. Proc Natl Acad Sci USA. 1987;84(21): 7686–90.
87. Dong QH, Handelsman DJ. Regulation of pulsatile luteinizing hormone secretion in experimental uremia. Endocrinology. 1991;128(3):1218–22.
88. 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.
89. 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.
90. Wibullaksanakul S, Handelsman DJ. Regulation of hypothalamic gonadotropin-releasing hormone secretion in experimental uremia: in vitro studies. Neuroendocrinology. 1991;54(4):353–8.
91. 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.
92. Daschner M, Philippin B, Nguyen T, et al. Circulating inhibitor of gonadotropin releasing hormone secretion by hypothalamic neurons in uremia. Kidney Int. 2002;62(5):1582–90.
93. 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 (Oxf). 1994;41(1):65–73.
94. Johnson V, Maack T. Renal extraction, filtration, absorption, and catabolism of growth hormone. Am J Physiol. 1977;233(3):F185–96.
95. 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.
96. Schaefer F, Baumann G, Haffner D, 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.
97. Tönshoff 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.
98. Veldhuis JD, Iranmanesh A, Wilkowski MJ, Samojlik E. Neuroendocrine alterations in the somatotropic and lactotropic axes in uremic men. Eur J Endocrinol. 1994;131(5):489–98.
99. 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.
100. 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.
101. Chan W, Valerie KC, Chan JC. Expression of insulin-like growth factor-1 in uremic rats: growth hormone resistance and nutritional intake. Kidney Int. 1993;43(4):790–5.
102. 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.
103. Martinez V, Balbin M, Ordonez FA, et al. Hepatic expression of growth hormone receptor/binding protein and insulin-like growth factor I genes in uremic rats. Influence of nutritional deficit. Growth Horm IGF Res. 1999;9(1):61–8.
104. Tönshoff B, Eden S, Weiser E, et al. Reduced hepatic growth hormone (GH) receptor gene expression and increased plasma GH binding protein in experimental uremia. Kidney Int. 1994;45(4):1085–92.
105. Villares SM, Goujon L, Maniar S, et al. Reduced food intake is the main cause of low growth hormone receptor expression in uremic rats. Mol Cell Endocrinol. 1994;106(1–2):51–6.
106. 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.
107. Postel-Vinay MC, Tar A, Crosnier H, et al. Plasma growth hormone-binding activity is low in uraemic children. Pediatr Nephrol. 1991;5(4):545–7.
108. Tönshoff B, Cronin MJ, Reichert M, 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.
109. Powell DR, Liu F, Baker BK, 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.
110. 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 post-receptor defect. J Clin Invest. 1996;97(4):1064–75.
111. Phillips LS, Kopple JD. Circulating somatomedin activity and sulfate levels in adults with normal and impaired kidney function. Metabolism. 1981;30(11):1091–5.
112. Fouque D. Insulin-like growth factor 1 resistance in chronic renal failure. Miner Electrolyte Metab. 1996;22(1–3):133–7.
113. Fouque D, Peng SC, Kopple JD. Impaired metabolic response to recombinant insulin-like growth factor-1 in dialysis patients. Kidney Int. 1995;47(3):876–83.
114. Tönshoff 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.
115. Phillips LS, Fusco AC, Unterman TG, del GF. Somatomedin inhibitor in uremia. J Clin Endocrinol Metab. 1984;59(4):764–72.
116. 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.
117. Blum WF, Ranke MB, Kietzmann K. Excess of IGF-binding proteins in chronic renal failure: evidence for relative GH resistance and inhibition of somatomedin activity. In: Drop SLS, Hintz RL, editors. Insulin-like growth factor binding proteins. Amsterdam: Elsevier Science Publishers; 1989. p. 93–9.
118. Powell DR, Durham SK, Brewer ED, et al. Effects of chronic renal failure and growth hormone on serum levels of insulin-like growth factor-binding protein-4 (IGFBP-4) and IGFBP-5 in children: a report of the Southwest Pediatric Nephrology Study Group. J Clin Endocrinol Metab. 1999;84(2):596–601.
119. Powell DR, Liu F, Baker BK, 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.
120. Ulinski T, Mohan S, Kiepe D, 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.
121. 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.

122. 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.
123. Liu F, Powell DR, Hintz RL. Characterization of insulin-like growth factor-binding proteins in human serum from patients with chronic renal failure. J Clin Endocrinol Metab. 1990;70(3):620–8.
124. Tönshoff 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.
125. 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.
126. 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.
127. Van Dyck M, Bilem N, Proesmans W. Conservative treatment for chronic renal failure from birth: a 3-year follow-up study. Pediatr Nephrol. 1999;13(9):865–9.
128. Foundation NK. KDOQI Clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53(3):S11–104.
129. 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(11):2418–26.
130. Trachtman H, Hackney P, Tejani A. Pediatric hemodialysis: a decade's (1974–1984) perspective. Kidney Int Suppl. 1986;19:S15–22.
131. Fennell III RS, Orak JK, Hudson T, et al. Growth in children with various therapies for end-stage renal disease. Am J Dis Child. 1984;138(1):28–31.
132. Neu AM, Bedinger M, Fivush BA, 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.
133. 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.
134. 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.
135. 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.
136. Heaf J. High transport and malnutrition-inflammation-atherosclerosis (MIA) syndrome. Perit Dial Int. 2003;23(2):109–10.
137. Tom A, McCauley L, Bell L, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134(4):464–71.
138. Katz A, Bock GH, Mauer M. Improved growth velocity with intensive dialysis. Consequence or coincidence? Pediatr Nephrol. 2000;14(8–9):710–2.
139. Fischbach M, Terzic J, Laugel V, et al. Daily on-line haemodiafiltration: a pilot trial in children. Nephrol Dial Transplant. 2004;19(9):2360–7.
140. 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.
141. Tejani A, Cortes L, Sullivan EK. A longitudinal study of the natural history of growth post-transplantation. Kidney Int Suppl. 1996;53:103–8.
142. Ingulli E, Tejani AH. Steroid withdrawal after renal transplantation. In: Tejani AH, Fine RN, editors. Pediatric renal transplantation. New York: Wiley Liss; 2006. p. 221–38.
143. Tönshoff B, Hocker B, Weber LT. Steroid withdrawal in pediatric and adult renal transplant recipients. Pediatr Nephrol. 2005;20(3):409–17.
144. Hoecker B, Weber LT, Feneberg R, 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.
145. 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.
146. 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.
147. 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.
148. Waller S, Ledermann S, Trompeter R, van't HW, Ridout D, Rees L. Catch-up growth with normal parathyroid hormone levels in chronic renal failure. Pediatr Nephrol. 2003;18(12):1236–41.
149. 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.
150. 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.
151. Platt C, Inward C, McGraw M, et al. Middle-term use of Cinacalcet in paediatric dialysis patients. Pediatr Nephrol. 2010;25(1):143–8.
152. Nakagawa K, Perez EC, Oh J, et al. Cinacalcet does not affect longitudinal growth but increases body weight gain in experimental uraemia. Nephrol Dial Transplant. 2008;23(9):2761–7.
153. Mehls O, Ritz E. Skeletal growth in experimental uremia. Kidney Int Suppl. 1983;15:S53–62.

154. 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.
155. Kovacs G, Fine RN, Worgall S, et al. Growth hormone prevents steroid-induced growth depression in health and uremia. Kidney Int. 1991;40(6):1032–40.
156. Powell DR, Durham SK, Liu F, 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.
157. Bereket A, Lang CH, Blethen SL, Kaskel FJ, Stewart C, Wilson TA. Growth hormone treatment in growth retarded children with end stage renal failure: effect on free/dissociable IGF-I levels. J Pediatr Endocrinol Metab. 1997;10(2):197–202.
158. 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.
159. Rees L, Rigden SP, Ward G, Preece MA. Treatment of short stature in renal disease with recombinant human growth hormone. Arch Dis Child. 1990;65(8): 856–60.
160. Tönshoff B, Dietz M, Haffner D, Tonshoff C, Stover B, Mehls O. Effects of two years of growth hormone treatment in short children with renal disease. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Acta Paediatr Scand Suppl. 1991;379:33–41.
161. Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, et al. Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in prepubertal children with chronic renal failure. Lancet. 1991;338(8767):585–90.
162. Fine RN, Kohaut EC, Brown D, Perlman AJ. Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. J Pediatr. 1994;124(3):374–82.
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 AC, 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. Wühl 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. Berard E, Crosnier H, Six-Beneton A, Chevallier T, Cochat P, Broyer M. Recombinant human growth hormone treatment of children on hemodialysis. French Society of Pediatric Nephrology. Pediatr Nephrol. 1998;12(4):304–10.
168. Schaefer F, Wuhl E, Haffner D, Mehls O. Stimulation of growth by recombinant human growth hormone in children undergoing peritoneal or hemodialysis treatment. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Adv Perit Dial. 1994;10:321–6.
169. 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.
170. Hokken-Koelega AC, Stijnen T, de Jong RC, et al. A placebo-controlled, double-blind trial of growth hormone treatment in prepubertal children after renal transplant. Kidney Int Suppl. 1996;53:S128–34.
171. Janssen F, Van Damme-Lombaerts R, Van Dyck M, et al. Impact of growth hormone treatment on a Belgian population of short children with renal allografts. Pediatr Transplant. 1997;1(2):190–6.
172. Mehls O, Berg U, Broyer M, Rizzoni G. Chronic renal failure and growth hormone treatment: review of the literature and experience in KIGS. In: Ranke MB, Wilton P, editors. Growth hormone therapy in KIGS: 10 years experience. Heidelberg: Barth; 1999. p. 327–40.
173. Fine RN, Sullivan EK, Tejani A. The impact of recombinant human growth hormone treatment on final adult height. Pediatr Nephrol. 2000;14(7):679–81.
174. Rees L, Ward G, Rigden SP. Growth over 10 years following a 1-year trial of growth hormone therapy. Pediatr Nephrol. 2000;14(4):309–14.
175. Hokken-Koelega AC, Nauta J, Lilien M, Ploos van Amstel J, Levcenko N. Long-term growth hormone treatment in children with chronic renal failure. Pediatr Nephrol. 2004;19:C38 (S04.33).
176. Fine RN, Stablein D. Long-term use of recombinant human growth hormone in pediatric allograft recipients: a report of the NAPRTCS Transplant Registry. Pediatr Nephrol. 2005;20(3):404–8.
177. Nissel R, Lindberg A, Mehls O, Haffner D. 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.
178. Harambat J, Cochat P. Growth after renal transplantation. Pediatr Nephrol. 2009;24(7):1297–306.
179. Berard E, Andre JL, Guest G, et al. Long-term results of rhGH treatment in children with renal failure: experience of the French Society of Pediatric Nephrology. Pediatr Nephrol. 2008;23(11):2031–8.

180. 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.
181. Maxwell H, Rees L. Recombinant human growth hormone treatment in infants with chronic renal failure. Arch Dis Child. 1996;74(1):40–3.
182. 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.
183. Fine RN, Pyke-Grimm K, Nelson PA, et al. Recombinant human growth hormone treatment of children with chronic renal failure: long-term (1- to 3-year) outcome. Pediatr Nephrol. 1991;5(4):477–81.
184. Hokken-Koelega AC, Stijnen T, de Jong MC, et al. Double blind trial comparing the effects of two doses of growth hormone in prepubertal patients with chronic renal insufficiency. J Clin Endocrinol Metab. 1994;79(4):1185–90.
185. 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.
186. 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.
187. Koller EA, Stadel BV, Malozowski SN. Papilledema in 15 renally compromised patients treated with growth hormone. Pediatr Nephrol. 1997;11(4):451–4.
188. Haffner D, Nissel R, Wuhl E, et al. Metabolic effects of long-term growth hormone treatment in prepubertal children with chronic renal failure and after kidney transplantation. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Pediatr Res. 1998;43(2):209–15.
189. Kaufman DB. Growth hormone and renal osteodystrophy: a case report. Pediatr Nephrol. 1998;12(2):157–9.
190. Picca S, Cappa M, Rizzoni G. Hyperparathyroidism during growth hormone treatment: a role for puberty? Pediatr Nephrol. 2000;14(1):56–8.
191. Kovács GT, Oh J, Kovács J, et al. Growth promoting effects of growth hormone and IGF-I are additive in experimental uremia. Kidney Int. 1996;49(5):1413–21.
192. Mauras N, Gonzalez de Pijem L, Hsiang HY, 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.

Diagnosis and Management of Renal Osteodystrophy in Children

25

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Keywords

Renal osteodystrophy • Metabolic bone disease children • Slipped epiphyses • Skeletal deformities • Bone turnover • Bone mineralization • Bone volume • Growth • Bone strength and structure

Introduction

The kidney plays a major role in bone and mineral homeostasis by regulating calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and calcitriol (1,25 dihydroxyvitamin D_3, $1,25(OH)_2$ D_3) metabolism. Disordered regulation of mineral metabolism occurs early in the course of chronic kidney disease (CKD) and results in alterations in bone modeling, remodeling, and growth. These alterations have been a focus of CKD management in children for decades. However, a growing awareness that cardiovascular calcifications accompany CKD, that cardiovascular disease is the leading cause of mortality in both adults and children with kidney disease, and that therapies designed to treat the skeletal consequences of CKD affect the progression of vascular pathology, has led to a reclassification of the mineral, skeletal, and vascular complications associated with progressive kidney disease. Together, these alterations are termed "CKD Mineral and Bone Disorder" ("CKD-MBD") [1], and the management of bone disease must consider effects on the cardiovascular system as well as on overall mortality in the pediatric CKD population. "Renal osteodystrophy" is the specific term used to describe the bone pathology that occurs as a complication of CKD and is therefore one aspect of the CKD-MBD. Traditionally, such lesions have been defined according to alterations in bone turnover, ranging from high bone turnover (secondary hyperparathyroidism, osteitis fibrosa) to lesions of low bone turnover (adynamic bone disease and osteomalacia). However, alterations in skeletal mineralization and volume are also common in patients with CKD [1] and may contribute to outcomes such as fractures, skeletal deformities, and poor growth which persist despite normalization of bone turnover [2].

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Pathogenesis of Disordered Mineral Metabolism in CKD-MBD

Through signals between the kidney, parathyroid gland, and bone, alterations in kidney function lead to changes in serum biochemical values that accompany progressive skeletal disease. Due to alterations in calcium, phosphorus, FGF-23, and $1,25(OH)_2 D_3$ metabolism, PTH levels increase as CKD progresses, thus contributing to the development of secondary hyperparathyroidism (2^oHPT). In early stages of CKD, levels of FGF-23 rise in order to enhance urinary phosphate excretion. These rising levels suppress $1,25(OH)_2$vitamin D values and as a result, increase PTH levels. In advanced CKD, rising PTH levels cause a release of calcium and phosphorus from bone and, when compensatory mechanisms fail, severely impaired glomerular filtration rate (GFR) results in phosphate retention which itself directly suppresses 1α-hydroxylase activity [3]. At this stage, hypocalcemia (from decreased intestinal calcium absorption mediated by declining calcitriol levels), hyperphosphatemia, and low circulating 1,25 dihydroxyvitamin D_3 values all combine to stimulate PTH secretion, thus contributing to the development of secondary hyperparathyroidism [4].

As early as stage 2 CKD, circulating levels of FGF-23 begin to rise [5]. FGF-23 levels are upregulated by chronic increases in phosphorus intake [3, 6] and levels rise as CKD progresses, likely due to a combination of decreased renal excretion of FGF-23 and increased phosphate load from declining GFR. The effects of increasing FGF-23 on mineral metabolism are multiple, and include the induction of renal phosphate excretion through inhibition of renal phosphate cotransporters, NaPi2a and NaPi2c, and the suppression of renal 1α-hydroxylase activity [7]. As CKD progresses, serum values of FGF-23 increase, becoming markedly elevated in individuals with end-stage kidney disease [8]. Simultaneously, $1,25(OH)_2 D_3$ levels decline; indeed, values are inversely related to levels of circulating FGF-23 [5]. Recent evidence suggests that FGF-23 may also regulate PTH secretion; *in vitro* experiments indicate that increased FGF-23 levels also directly suppress PTH release, independent of the action of FGF-23 on vitamin D metabolism [9, 10].

In CKD, reduced circulating $1,25(OH)_2D_3$ contributes to secondary hyperparathyroidism and parathyroid gland hyperplasia in a number of ways: through decreased intestinal calcium absorption, decreased binding to the vitamin D receptor (VDR), reduced calcium sensing receptor (CaSR) expression, and decreased VDR expression. Indeed, $1,25(OH)_2D_3$ has been shown to suppress PTH gene transcription, both *in vitro* (bovine parathyroid cell culture) and *in vivo* (intact rats). In conjunction with the VDR, $1,25(OH)_2D_3$ binds negative vitamin D response elements in the parathyroid glands which inhibit pre-proPTH gene transcription [11, 12]. In a positive feedback loop, $1,25(OH)_2D_3$ itself increases VDR gene expression in the parathyroid glands, further suppressing PTH gene transcription. $1,25(OH)_2D_3$ also increases the expression of the CaSR, the expression of which is reduced in hyperplastic parathyroid tissues obtained from patients with 2^oHPT [13]. Vitamin D deficiency in animals is associated with decreased expression of CaSR mRNA in parathyroid tissue, while $1,25(OH)_2D_3$ therapy increases CaSR mRNA levels in a dose-dependent manner [14].

25(OH)vitamin D (25(OH)D) deficiency is prevalent in patients with CKD and low levels of this form of the hormone also contribute to the development of 2^oHPT – both directly and through limiting substrate for the formation of $1,25(OH)_2D$. Vitamin D is either made in the skin or ingested from the diet [15, 16]. UVB (290–315 nm) photons penetrate the skin and are absorbed by 7-dehydrocholesterol to form previtamin D_3 which then spontaneously converts to vitamin D_3. Vitamin D (both D_2 and D_3) undergoes hydroxylation by the liver, forming 25(OH)D [17], and is subsequently taken up by the renal tubular cells, and undergoes a second hydroxylation, facilitated by renal 1α-hydroxylase, to $1,25(OH)_2 D_3$, a more potent stimulator of intestinal calcium absorption [18, 19]. Although conversion of 25(OH)D to $1,25(OH)_2 D_3$ is, in the general population, a substrate-independent process, it becomes a substrate-dependent process in

patients with CKD [20]. Apart from its conversion to $1,25(OH)_2D_3$, 25(OH)D may have its own effect on tissues. Indeed, supplementation with ergocalciferol has been shown to decrease serum PTH levels in patients with CKD [21, 22]. Recent evidence demonstrates that 1α-hydroxylase is present in the parathyroid glands; thus, 25(OH)D is converted inside the gland to $1,25(OH)_2D_3$, suppressing PTH [23]. Furthermore, 25(OH)D administration suppresses PTH synthesis even when parathyroid gland 1α-hydroxylase is inhibited, indicating that 25(OH)D may contribute to PTH suppression, independent of its conversion to $1,25(OH)_2D_3$ [23]. Thus, low levels of the precursor 25(OH)D may exacerbate $1,25(OH)_2D_3$ deficiency in the context of CKD. Several studies have documented a high prevalence of 25(OH)D deficiency in the general population [24] and this prevalence increases as renal function declines [25, 26]. Indeed, the vast majority of patients treated with maintenance dialysis display insufficient vitamin D storage [27, 28]. Patients with advanced CKD are at increased risk of vitamin D deficiency for several reasons: many are chronically ill with little outdoor (sunlight) exposure; CKD dietary restrictions, particularly of dairy products, curtail the intake of vitamin D rich food and lead to decreased dietary calcium intake [29], and patients with CKD (particularly those with darker skin pigment) display decreased skin synthesis of vitamin D_3 in response to sunlight compared with individuals with normal kidney function [30, 31]. Proteinuric diseases further exacerbate D deficiency in the CKD population, as 25(OH)D in combination with vitamin D binding protein, is lost in the urine [32, 33].

Phosphorus retention and hyperphosphatemia are also important factors in the pathogenesis of secondary hyperparathyroidism in the late stages of CKD. The development of secondary hyperparathyroidism is prevented in experimental animals with CKD when dietary phosphorus intake is lowered in proportion to the GFR [34]. Dietary phosphate restriction can also reduce previously elevated serum PTH levels in patients with moderate renal failure [3, 35]. Phosphorus retention and hyperphosphatemia indirectly promote the secretion of PTH in several ways. Hyperphosphatemia lowers blood ionized calcium levels as free calcium ions complex with excess inorganic phosphate; the ensuing hypocalcemia stimulates PTH release. Phosphorus also enhance the secretion of FGF-23 [5], thereby impairing renal 1α-hydroxylase activity, which diminishes the conversion of 25(OH)D to $1,25(OH)_2D_3$ [3]. Finally, phosphorus can directly enhance PTH synthesis by the parathyroid cell by interrupting the normal CaSR signal cascade. High serum phosphorous levels decrease cytosolic phospholipase A2 (normally increased by CaSR activation), leading to a decrease in arachidonic acid production with a subsequent increase in PTH secretion [36]. Hypophosphatemia also decreases PTH mRNA transcript stability *in vitro* [37], suggesting that phosphorous itself affects serum PTH levels, probably by increasing the stability of the PTH mRNA transcript.

Finally, alterations in parathyroid gland CaSR expression also occur in secondary hyperparathyroidism and may, in turn, contribute to parathyroid gland hyperplasia. The CaSR is a seven transmembrane G protein-coupled receptor with a large extracellular N-terminus, which binds acidic amino acids and divalent cations [38]. Low extracellular calcium levels result in decreased calcium binding to the receptor, a conformational relaxation of the receptor and a resultant increase in PTH secretion [39], while activation of the receptor by high levels of serum calcium decrease PTH secretion [40, 41]. The expression of the CaSR is reduced by 30–70% as judged by immunohistochemical methods in hyperplastic parathyroid tissue obtained from human subjects with renal failure [13, 42]. CaSR gene transcription is regulated by vitamin D through two distinct vitamin D response elements in the gene's promoter region [43]; thus, alterations in vitamin D metabolism in renal failure could account for changes in calcium sensing by the parathyroid glands and vitamin D may act upstream of the CaSR in preventing parathyroid cell hyperplasia [44]. Decreased expression and activity of CaSR has been linked to decreased responsiveness in PTH secretion due to altered calcium levels [45]. This decreased expression of the CaSR results in an insensitivity to serum calcium levels with subsequent uncontrolled secretion of PTH. Increased stimulation of the

CaSR by calcimimetics has been shown to decrease PTH cell proliferation, implicating the CaSR as a regulator of cell proliferation as well as PTH secretion [46].

Spectrum of Renal Osteodystrophy

Abnormalities in Bone Turnover, Mineralization, Volume, Linear Growth, or Strength

Since calcium and phosphorus, in the form of hydroxyapatite, are the building blocks of bone, it is not surprising that disordered mineral metabolism is tightly linked to bone disease in the context of CKD. Aside from basic calcium and phosphorus homeostasis, other hormones play critical roles in the structure and function of bone; alterations in these hormones, as occur in CKD, thus contribute to abnormal bone turnover, mineralization, volume, linear growth, and strength which, together, define Renal Osteodystrophy.

Bone Turnover

Traditionally, renal osteodystrophy has been classified primarily by alterations in bone turnover. The primary lesion of renal osteodystrophy in children is one of high bone turnover, also termed "secondary hyperparathyroidism." Since PTH activates the PTH/PTHrP receptor on osteocytes and osteoblasts, increasing cellular activity of both osteoblasts and osteoclasts [47, 48], excessive levels of circulating PTH result in increased bone turnover [49]. Serum PTH levels are inversely correlated with GFR, and the majority of patients with a GFR less than 50 mL/min have increased serum PTH levels and high-turnover bone disease [50–52]. These findings are nearly universal in untreated children at the initiation of dialysis [2]. Hyperparathyroid bone disease is marked by an increased numbers of osteoblasts and osteoclasts. Excess osteoclastic activity leads to increased resorption of mineral and matrix along both the trabecular surface and within the haversian canals of cortical bone. Osteitis fibrosa cystica, the advanced lesion of secondary hyperparathyroidism, is also associated with peritrabecular fibrosis [53].

A state of low-turnover bone disease (adynamic renal osteodystrophy) also occurs in children treated with maintenance dialysis, although it has not been demonstrated in children with earlier stages of CKD [51]. Adynamic renal osteodystrophy is associated with disorders such as age-related or postmenopausal osteoporosis (in adults), steroid-induced osteoporosis, hypoparathyroidism (idiopathic or surgically induced), and diabetes mellitus. Reversible causes of adynamic renal osteodystrophy include aluminum toxicity, subtotal parathyroidectomy, prolonged treatment with calcium-containing phosphate-binding medications, use of high dialysate calcium concentrations, and aggressive vitamin D sterol therapy [54]. The prevalence of adynamic lesions of bone is less than 20% in children and adolescents with end-stage renal disease who are treated with daily doses of calcitriol, although adynamic bone is present in as many as 33% of pediatric patients treated with high dose intermittent calcitriol therapy and calcium-based binders for the control of secondary hyperparathyroidism [55]. Due to a direct suppressive effect of these agents on bone turnover, adynamic bone often develops in these patients despite markedly elevated serum PTH levels [55].

On bone histomorphometric analysis, adynamic bone is characterized by normal osteoid volume, an absence of fibrosis, and a reduced bone formation rate, as indicated by a reduced or absent double tetracycline label [55, 56]. A paucity of osteoblasts and osteoclasts are present [49]. Adynamic bone is associated with low PTH levels, low alkaline phosphatase levels, high serum calcium levels, hypercalcemic episodes, and a propensity for increased vascular calcification [57, 58]. In addition to the increased risk for fractures that is observed in adults with adynamic bone, dialyzed children with low bone turnover display an increased severity of growth retardation [59, 60].

Bone Mineralization

Although renal osteodystrophy has traditionally been defined by lesions in bone turnover, alterations

in skeletal mineralization are also prevalent in children with CKD [61]. While the ramifications of defective mineralization remain to be established, increased fracture rates, bone deformities, and growth retardation are prevalent in patients with CKD despite adequate control of bone turnover and may be due, at least in part to alterations in skeletal mineralization.

Increases in unmineralized bone (osteoid) in conjunction with delayed rates of mineral deposition are common [53, 61]. Defective mineralization that is associated with high-turnover bone disease is termed "mixed lesion"; when associated with low to normal bone turnover, it is referred to as "osteomalacia" [1]. In children with CKD, osteomalacia may result from inadequate dietary intake of calcium, phosphorus, or vitamin D, particularly during periods of rapid growth, when the skeletal demand for these nutrients is high. During previous decades, aluminum toxicity from the use of aluminum based phosphate binders resulted in low bone turnover and poor skeletal mineralization in many patients.

The skeletal histology of the "mixed lesion of renal osteodystrophy" has features of both osteitis fibrosa and osteomalacia [62]. Patients with this lesion often display high serum PTH and alkaline phosphatase levels. Mixed lesions are seen with high-turnover bone disease in patients who are developing aluminum toxicity or in patients with low-turnover aluminum-related bone disease during DFO therapy [63]. In these cases, mixed lesion represents a transitional stage between high-turnover and low-turnover bone disease.

Although the mechanisms of skeletal mineralization are incompletely understood, other factors, including 25(OH)D deficiency and alterations in skeletal dentrin matrix protein 1 (DMP1) and FGF-23 metabolism [64], have been implicated in the pathogenesis of osteoid accumulation in the CKD population. In the general population, nutritional 25(OH)D deficiency results in osteomalacia and a similar phenotype may occur in children with CKD. FGF-23 may also play a role; both overexpression [65–67] and ablation of FGF-23 [68, 69] in mice are associated with abnormal mineralization of osteoid, although by different mechanisms. The phosphaturic effect of increased FGF-23 may cause rickets and osteomalacia through an insufficiency of mineral substrate. The mechanisms leading to impaired mineralization in FGF-23-null animals, which have severe hyperphosphatemia and normal or elevated serum calcium levels, remain uncertain; however, osteomalacia in these animals suggests that FGF-23 may play a direct role in skeletal mineral deposition. Moreover, defects in DMP1, a protein which regulates FGF-23 expression, result in a similar phenotype in the context of normal kidney function [70]. Interestingly, skeletal expression of both FGF-23 and DMP1 are altered as early as stage 2 CKD in pediatric patients with CKD [64] and skeletal expression of both proteins are related to skeletal indices of mineralization [64].

Bone Volume

Since PTH is an anabolic steroid at the level of trabecular bone, high levels of serum PTH are typically associated with increases in bone volume, trabecular volume, and trabecular width [61, 71–73]. Thus, children with CKD typically have normal or high bone volume as assessed by bone histomorphometry. Those treated with corticosteroids, however, may display loss of bone volume, termed "osteoporosis." The impact of osteoporosis in childhood may not always be immediately apparent; however, suboptimal peak bone mass accretion in adolescence is associated with an increased risk of osteoporosis, hip fractures, and mortality in adulthood [74].

Growth

Growth retardation is the hallmark of CKD in children. Indeed, the average height of children with even mild CKD (GFR 50–70 mL/min/1.73 m^2) is 1 standard deviation (SDS) below the average for healthy children. Moderate CKD (GFR 25–49 mL/min/1.73 m^2) is associated with a height SDS of −1.5, and, at the time of initiation of dialysis, the mean height SDS is −1.8. Boys, younger patients, and those with prior renal transplants are at greatest risk for growth failure [75]. While protein and calorie malnutrition and metabolic acidosis contribute to growth retardation, growth hormone resistance at the level of

bone, calcitriol deficiency, and renal bone disease also contribute [76]. For an in-depth discussion of growth retardation in CKD, see Chap. 24.

Bone Strength and Structure

Symptoms: Bone Pain and Muscle Weakness

Early in the course of renal osteodystrophy, bone pain is nonspecific and difficult to distinguish from common aches and pains, and a great variability in clinical presentation occurs among patients. Pain often localizes to the lower back and to weight-bearing joints, including hips, knees, and ankles. Symptoms worsen with pressure and changes in posture. Limping requires prompt and thorough evaluation in a previously ambulatory child with secondary hyperparathyroidism due to the increased prevalence of fracture and slipped epiphysis in this population [41].

Myopathy in children with CKD may be progressive and the diagnosis is clinical; no specific tests are available. Initially, patients may complain of nonspecific aches and pains; subsequently they report limited ability to perform activities of daily living. These symptoms may go undiagnosed by the clinician, as patients may self-restrict physical activity, limiting their quality of life and social development. Similar to the proximal muscle weakness seen in patients with nutritional vitamin D deficiency, children with CKD may develop a characteristic waddling gait [77, 78]. The mechanism behind this proximal myopathy is not well understood, although secondary hyperparathyroidism, phosphate depletion, aluminum bone disease, and disorders of vitamin D metabolism may contribute [79]. No specific treatment is available, although an improvement in muscle strength in both proximal and distal muscles has been shown after treatment with vitamin D [80].

Slipped Epiphyses

Slipped epiphyses are one of the most severe and physically incapacitating manifestations of bone disease in children with CKD. In preschool children, the upper and lower femoral epiphyses are often affected, while the upper femur and the radial/ulnar epiphyses are involved in older children. The distal radius and metacarpal and metatarsal heads may also be affected [41]. The clinical presentation may include limping, waddling gait, limited range of motion, and inability to ambulate. Severe osteitis fibrosa with marked endosteal fibrosis is present on bone biopsy. A dense fibrous tissue develops between the growth plate cartilage and the adjacent metaphysis, where the plane of slippage may occur [81]. The diagnosis is usually established by roentgenograms. Total joint replacement is often required when the proximal femur is involved.

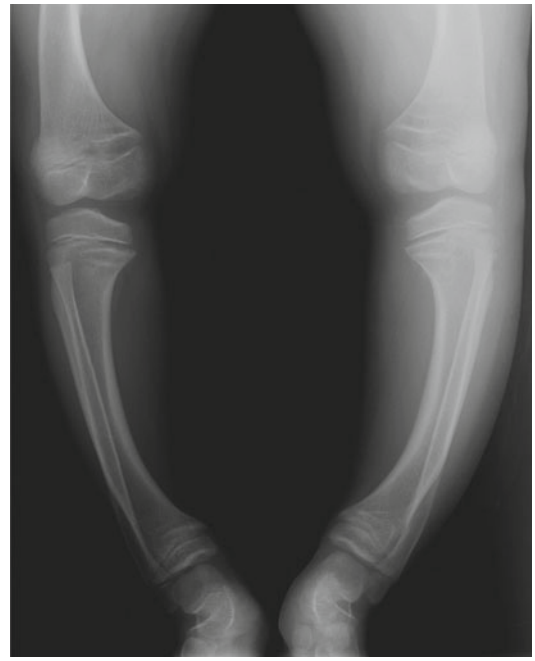

Fig. 25.1 Plane film demonstrating the skeletal deformity of genu varum in a young child

Skeletal Deformities

Bone deformities are also common in uremic children due to altered skeletal remodeling and, due to their increased growth velocity, are most evident in children younger than 10 years. The pattern of bone deformities varies with the child's age. Patients younger than 4 years have skeletal abnormalities similar to those due to vitamin D-deficient rickets, including rachitic rosary, metaphyseal widening (leading to wrist and ankle enlargement), craniotabes, and frontal bossing. Slipped epiphyses, genu valgum, and femoral and wrist deformities are most common in preadolescent children with long-standing CKD (Fig. 25.1) [2, 81]. Avascular necrosis of the femoral head

and pathologic fractures of the extremities and chest wall due to osteoporosis and bone deformities may occur with minimal trauma. In addition, vertebral crush fractures contribute to significant morbidity in this population. Patients may also present with ulnar deviation, pes varus, pseudoclubbing, and dental abnormalities. The initial management of skeletal deformities requires the normalization of serum calcium, phosphorus, and PTH levels. Surgical correction is often also necessary but should be performed only after correction of biochemical abnormalities [82].

Relationship Between Mineral, Bone, and Vascular Disease

Visceral, tumoral or periarticular, and vascular calcifications may develop in patients with CKD. Indeed, the mortality rate in adults and children with CKD is markedly higher than that of the general population, and cardiovascular disease is the leading cause of death in both children and adults treated with maintenance dialysis [83, 84]. In contrast to the calcifications of atherosclerotic plaques that develop with age in the vascular intima of individuals with normal kidney function, vascular calcification in the uremic milieu develops primarily in the tunica media. The etiology of cardiovascular disease in CKD is multifactorial and is addressed in more detail in Chap. 26. However, cardiovascular changes are associated with increased mortality rates have their origins in childhood [83, 85, 86] and are associated with mineral and bone metabolism in the CKD population. Hypercalcemia, hyperphosphatemia, excessive calcium intake, increased circulating FGF-23 levels, and adynamic bone disease have all been associated with the development of cardiovascular calcification in patients treated with maintenance dialysis [82, 83, 87–90].

Although traditional therapies such as lipid lowering agents are useful in decreasing mortality in adults with pre-dialysis CKD [91] and in those with stable renal allografts [92], these agents have not been shown to benefit patients treated with dialysis [93]. By contrast, moderating calcium intake and avoiding the development of adynamic bone disease are efficacious in halting the progression of vascular calcification [82, 83, 87, 88]. Paradoxically, although vitamin D sterols increase circulating FGF-23 levels, which have been associated with increased mortality in the adult dialysis population [89], the use of vitamin D therapy (in both 25(OH)vitamin D and $1,25(OH)_2$vitamin D forms) has also been associated with decreased mortality rates, likely through ameliorating cardiovascular disease, in the adult dialysis population [94–96].

Diagnosis of Renal Osteodystrophy

Calcium and Phosphorus Levels

Serum calcium levels are typically maintained within the normal range until late (stages 4 and 5) CKD, when serum calcium levels drop. Hypocalcemia often resolves during treatment with calcium-containing phosphate binders, vitamin D sterols, and with initiation of dialysis. Typical dialysis solutions containing 2.5 mEq/l calcium concentrations are generally adequate to maintain serum calcium within acceptable limits. Recurrent or persistent hypercalcemia in patients with CKD is uncommon yet may occur with severe secondary hyperparathyroidism, aluminum-related bone disease, adynamic bone, prolonged use of high dose vitamin D sterols, large amounts of calcium-containing phosphate-binding agents, and prolonged immobilization [56, 97, 98]. Malignancy and extrarenal production of calcitriol in disorders such as sarcoidosis or tuberculosis result in hypercalcemia, but these conditions are uncommon in the pediatric age group. Patients with adynamic bone lesion without evidence of aluminum toxicity are prone to develop hypercalcemic episodes, which are related to the skeleton's inability to incorporate an acute calcium load [99].

Serum phosphorus levels are often maintained within normal limits in early CKD. However, when the GFR falls below 30 mL/min/1.73 m^2 (stage 4 CKD), increases in FGF-23 and PTH fail to compensate for decreasing renal mass and hyperphosphatemia ensues [100]. Current recommendations suggest that serum phosphorus levels be maintained as close to normal as possible [101].

Alkaline Phosphatase

Serum total alkaline phosphatase is a biochemical marker of osteoblastic activity. Values generally correspond to the histologic severity of osteitis fibrosa, and serial measurements may be helpful in the follow-up of children with renal osteodystrophy; however, precise therapeutic guidelines have not been established. During intermittent calcitriol therapy, suppressed serum alkaline phosphatase levels have been found to be good predictors of adynamic renal osteodystrophy [60]. Bone-specific alkaline phosphatase activity may be useful in predicting the histologic lesion of renal osteodystrophy, but whether these values are superior to total alkaline phosphatase levels remains to be demonstrated.

Parathyroid Hormone Levels

Accurate measurements of the concentration of PTH in serum or plasma are essential for the proper assessment of renal osteodystrophy [61, 102–105]. Indeed, PTH levels are used as surrogates for bone turnover, although bone histology remains the most reliable method by which to establish the diagnosis of renal osteodystrophy [62, 71, 106]. Serum PTH levels are usually normal in early CKD and rise in patients with moderate and severe CKD [3, 35]. Increasing skeletal resistance to the actions of PTH necessitate that serum PTH levels be maintained at higher ranges in more severe renal failure.

Because PTH and its fragments are cleared by the kidneys, active and inactive fragments of the molecule accumulate as renal failure progresses. Different PTH assays measure these fragments to different degrees. The first-generation PTH-IMA (1st PTH-IMA) measures both the intact PTH(1–84) molecule and amino-terminally truncated fragments up to and including PTH(7–84) [107–109]. Although first PTH-IMAs overestimate the true concentration of PTH(1–84) in circulation, these assay have, over the past decades, proven to be reasonable predictors of the different subtypes of renal osteodystrophy and have also performed well in assessing the therapeutic response to active vitamin D sterols in patients with renal failure [61, 102, 105]. Second-generation PTH-IMAs (2nd PTH-IMAs), which use detection antibodies raised against the first four amino-terminal amino acids of human PTH, recognize only PTH(1–84) and not amino-terminally truncated fragments, such as PTH(7–84) [39, 110]. Although second PTH-IMAs are more specific for the concentrations of the full-length, active molecule, current data demonstrate that measurements of PTH using either first or second PTH-IMAs are highly correlated and provide similar accuracy for predicting bone turnover in pediatric patients undergoing maintenance peritoneal dialysis [72, 111]. Therefore, current recommendations for therapy with active vitamin D sterols are based on the relationship between indices of bone formation and PTH levels determined by first-generation immunometric assays.

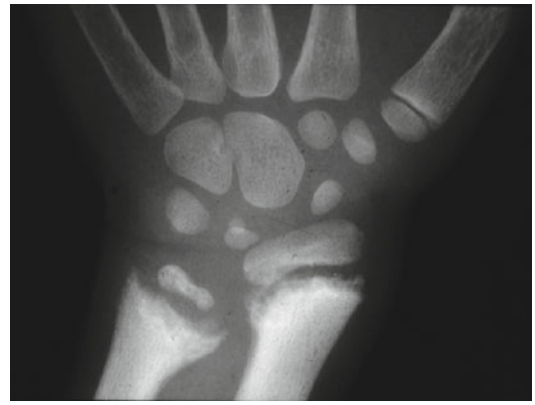

Fig. 25.2 Plane film demonstrating skeletal erosions ("rickets-like" lesions) in the hand

Radiography

Radiographic features of secondary hyperparathyroidism resemble those of nutritional rickets. Subperiosteal resorption may occur at the distal ends of the clavicles, ischial and pubic surfaces, sacroiliac joints, junction of the metaphysis and diaphysis of long bone, and in the phalanges [112, 113]. A diffuse ground-glass appearance, generalized mottling, focal radiolucencies, and sclerotic areas may be evident in the skull. Metaphyseal changes, called growth zone lesions or rickets-like lesions, are best demonstrated in hand radiographs (Fig. 25.2). Although subperiosteal erosions are a

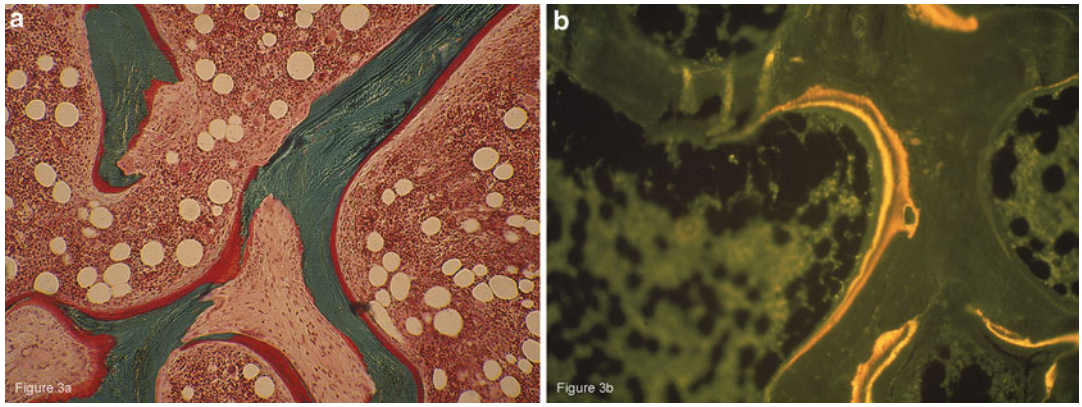

Fig. 25.3 Bone biopsy specimen demonstrating the skeletal lesion of osteitis fibrosa. (**a**) Under light microscopy, an increase in cellular activity, osteoid accumulation, erosion, and fibrosis are visible. (**b**) An increase in double tetracycline labeling signifies an increase in bone turnover rate

hallmark of secondary hyperparathyroidism, these lesions can also be seen in patients with aluminum-related bone disease, which may represent unhealed lesions from a previous state of secondary hyperparathyroidism [114]. To enhance the sensitivity of hand radiographs, the use of fine-grain films and magnification by hand lens has been recommended [113].

The radiographic features of osteomalacia are less evident, particularly in older children and adolescents. In young children, widening of the epiphyseal growth plate and other deformities of the growth plate cartilage are evident, whereas pseudofractures and Looser zones, which appear as straight, wide radiolucent bands within the cortex, may be the only findings in older children and adults. The radiographic density of bone on conventional skeletal radiographs is reduced in many patients with renal osteodystrophy, but osteosclerotic changes or localized increases in bone density are a prominent finding in children with chronic renal failure.

Bone Scintigraphy

Bone scans using the technetium-99-labeled diphosphonate are helpful in estimating the severity of bone disease and differentiating between high-turnover lesions of osteitis fibrosa and low-turnover lesions of osteomalacia [115]. Uptake is usually diffuse and symmetric in patients with severe secondary hyperparathyroidism, whereas patients with osteomalacia exhibit a less intense uptake [115]. Calcifications may also be demonstrated in various organs, including the lungs and heart, using the bone scan.

Bone Biopsy

Iliac crest bone biopsy provides the most valuable diagnostic information of the skeletal lesions of renal osteodystrophy (Fig. 25.3a, b). The procedure is safe and well tolerated in children and is done in an outpatient setting [71]. Bone biopsy provides information about the histologic appearance and dynamics of bone formation and mineralization. Although not routinely performed in the clinical setting, a bone biopsy should be considered in all patients with CKD who have fractures with minimal trauma (pathological fractures), suspected aluminum bone disease, or persistent hypercalcemia despite serum PTH levels between 400 and 600 pg/mL [82]. In order to assess bone formation rate, the bone is labeled prior to biopsy. A 2-day course of tetracycline is administered at 15 mg/kg/day (divided in twice or thrice daily doses). Fourteen days later, the 2-day course is repeated. During each 2-day course, tetracycline is deposited at the front of mineralization; thus, a measurement of the

distance between the two labels gives an estimate of the amount of bone formed in a 2 week period. For children younger than 8 years, the tetracycline dosage is usually kept below 10 mg/kg/day to avoid toxicity. Histochemical staining procedures may also be performed in the bone biopsy specimen in order to demonstrate the deposition of abnormal components within bone such as iron, aluminum, and oxalate [71, 79].

Treatment of Renal Osteodystrophy

In order to minimize complications on the growing skeleton and to prevent extraskeletal calcifications, particular attention must be made to the alterations of bone and mineral metabolism in children with CKD.

Dietary Manipulation

Evaluation of dietary intake and growth must be performed at regular intervals to maximize the growth potential of children with CKD. Nutritional requirements are based on the recommended dietary allowances for energy and protein. Nutritional supplements, which may be given orally or through a nasogastric or gastrostomy tube, are necessary when recommended dietary allowances for energy and protein are not achieved by food intake alone or when there is impaired linear growth and/or weight gain, particularly during the first few years of life.

Normal values for phosphorus are higher in infants and decline to adult values by late adolescence. During the first 3 months of life, values range from 4.8 to 7.4 mg/dL (mean: 6.2 mg/dL), levels decrease to 4.5–5.8 mg/dL (mean: 5.0 mg/dL) at age 1–2 years, and 3.5–5.5 mg/dL (mean: 4.4 mg/dL) during childhood [83]. Phosphorus is present in nearly all foods and with the highest concentration in meat and dairy products and approximately 60–70% is absorbed. The average phosphorus intake of children in the United States is higher than the dietary reference intake (DRI) established by the Food and Nutrition Board [116] (approximately 1500–2000 mg/day) [82]. In dialysis patients, phosphorus removal by peritoneal dialysis (240–440 mg/day) or hemodialysis (600 mg during a 4 h session) is inadequate to maintain target phosphorus levels [117]; therefore, dietary phosphorus restriction is usually required. More frequent hemodialysis, however, such as nocturnal hemodialysis, which is performed six to seven nights per week for 8–10 h at home, has been shown to remove twice as much phosphate per week compared to conventional hemodialysis [118, 119]. As a result, patients undergoing nocturnal hemodialysis do not require phosphate binders and are able to ingest higher dietary phosphate and protein intake, and may even require the addition of phosphorus to the dialysate [118–121].

Serum phosphorus levels should be measured routinely after starting the phosphorus-restricted diet in order to prevent hypophosphatemia, particularly in those who are also given large doses of phosphate-binding agents. Infants are particularly at risk for hypophosphatemia due to the use of low phosphorus-containing formulas, aggressive use of phosphate binders, and increased peritoneal dialysis phosphate removal (due to a higher peritoneal surface area to body area ratio than in older children) [122]. Patients with severe and persistent hypophosphatemia have been reported to develop bone disease such as osteomalacia and rickets, proximal myopathy, rhabdomyolysis, and congestive heart failure [122, 123].

Dietary phosphorus restriction is recommended in the majority of patients with advanced CKD; however, protein requirements for growth and the unpalatable taste of low phosphorous diets make long-term compliance with such restrictions difficult. Accordingly, the use of phosphate-binding agents is integral to the treatment of these children. Since calcitriol enhances intestinal phosphorus absorption, vitamin D sterol therapy may complicate the management of hyperphosphatemia and higher dosages of phosphate-binding agents are often required [124].

In order to attain peak bone mass and reduce risks of osteoporosis and fractures later in life, the DRI of calcium intake and regular exercise are strongly recommended throughout childhood

and adolescence, even in patients with CKD. The main source of calcium is milk and dairy products, although various foods such orange juice and cereals are fortified with calcium. Calcium supplementation is recommended when the DRI is not met by dietary intake. To limit the development of cardiovascular calcifications, however, calcium intake from both diet and calcium-containing phosphate binders should be limited to no more than 2,500 mg/day in children treated with maintenance dialysis [82].

Phosphate-Binding Agents

Phosphate-binding agents are recommended in patients with persistent hyperphosphatemia despite dietary phosphorus restriction. These agents form poorly soluble complexes with phosphorus in the intestinal tract, thereby decreasing phosphorus absorption. Calcium-containing phosphate binders are widely used as the initial agent for the management of hyperphosphatemia. They also provide an additional source of calcium. Several calcium-containing salts, including calcium carbonate, calcium acetate, and calcium citrate, are commercially available. Since citrate increases intestinal absorption of aluminum, calcium citrate should not be administered to patients with CKD who are also receiving aluminum-containing phosphate binders [125].

Calcium carbonate is the most widely prescribed calcium salt, and its effectiveness in reducing serum phosphorus levels has been reported in adult and pediatric patients [56, 126]. Calcium carbonate therapy has also been shown to decrease serum intact PTH levels in adult patients with secondary hyperparathyroidism [127–129]. The dose of calcium-based phosphate binders varies widely among children and should be adjusted to maintain normal calcium levels and age-appropriate serum phosphorus levels. Hypercalcemia is a major complication associated with the long-term use of high doses of calcium-based phosphate-binding agents, particularly in patients treated with vitamin D or those with adynamic bone lesions [130, 131]. Hypercalcemia usually resolves with lowering doses of vitamin D and calcium-based binders. Furthermore, bedtime administration of vitamin D may decrease intestinal calcium absorption and limit hypercalcemia.

The use of calcium-containing binders has been linked to the development of vascular calcifications in adult and pediatric patients treated with maintenance dialysis [83] as well as in adults with stage 4 CKD [132]. Furthermore, there is substantial evidence that hypercalcemia, hyperphosphatemia, and elevated calcium-phosphorus ion product are associated with the development of soft tissue and vascular calcifications [83, 85, 86]. Although it is difficult to differentiate between the effects of calcium intake and vitamin D sterols on the development of hypercalcemia, intake of calcium-containing phosphate binders may play a role in the development of accelerated cardiovascular disease that occurs in patients treated with dialysis [83, 85].

Alternative phosphate binders have therefore been developed to limit the risks of hypercalcemia and vascular calcification associated with the use of calcium salts. When used with active vitamin D sterols, sevelamer hydrochloride (Renagel^{R}), a calcium- and aluminum-free hydrogel of cross-linked poly(allylamine-hydrochloride), effectively lowers serum phosphorus, PTH, and bone formation rate without inducing hypercalcemia in pediatric patients with ESRD [73, 133–137]. Furthermore, treatment with sevelamer hydrochloride, when compared to calcium-containing binders, halts the progression of vascular calcification and reduces mortality in adult patients with CKD stages 4 and 5 [87, 88]. Serum total cholesterol and low-density lipoprotein cholesterol levels also decrease, high-density lipoprotein values increase, and FGF-23 values decline during sevelamer treatment [136, 138]. These effects may offer additional benefits in reducing cardiovascular complications in patients with ESRD. Sevelamer carbonate (Renvela^{R}) has recently been introduced and is also an effective phosphate binder. The carbonate in its composition may decrease the incidence of mild acidosis that sometimes accompanies the use of sevelamer hydrochloride [139].

Additional phosphate binders include magnesium, iron, and lanthanum compounds. Magnesium carbonate reduces serum phosphorus levels, but predisposes dialysis patients to developing hypermagnesemia and diarrhea. Iron compounds, such as stabilized polynuclear iron hydroxide and ferric polymaltose complex, are also effective in short-term studies in adults with CKD [140]. Lanthanum carbonate is also an effective phosphate binder that does not induce changes in serum calcium levels [141]; its role in the process of vascular calcification has not been defined. Lanthanum is a heavy metal that accumulates in liver and bone in rats with renal failure [142]. In dialysis patients, lanthanum has been shown to persist in bone as long as 2 years after discontinuation of the drug [143]. Due to the accumulation of lanthanum in tissues, this medication is not recommended for routine use in children.

Aluminum-containing gels are also effective phosphate-binding agents and may be used to acutely treat severe hyperphosphatemia. Due to their toxicities (encephalopathy and bone disease), the lowest possible dose should be used for a limited period (4–6 weeks), and plasma aluminum levels should be followed closely. Since citrate enhances aluminum absorption by altering tight junctions in the intestinal epithelium, simultaneous use of citrate (found in such medications as calcium citrate, Alka-Seltzer, Shohl's solution, and sodium citrate (Bicitra/Polycitra), as well as in citrus fruits) with aluminum should be avoided [125].

Vitamin D Therapy

Despite control of serum phosphorus levels, secondary hyperparathyroidism is present in the majority of pediatric patients treated with maintenance dialysis; vitamin D sterols are therefore used to control serum PTH levels. Optimal target values for PTH in children in all stages of CKD remain controversial. In children with moderate CKD, some data indicate that normal growth velocity is achieved when PTH levels are maintained within the normal range [144] while others have demonstrated a linear correlation between growth and PTH levels in the same patient population – those with the highest PTH values maintaining the highest rates of growth [145]. In children treated with maintenance dialysis, adynamic bone disease and growth failure have been associated with PTH levels around 100 pg/mL (first-generation assay), causing many experts to recommend target PTH levels three to five times the normal range in advanced CKD [60]. Data from the European community, however, have demonstrated that optimal growth velocity in this population may be associated with PTH levels of two to three times the normal range [146]. As a result, optimal PTH targets remain controversial and recommendations vary between experts.

Despite controversy as to optimal PTH target ranges, data clearly indicate that the presence of CKD markedly attenuates the effect of PTH on bone [147, 148]. The precise mechanisms are poorly understood; however, uremic animals and humans display decreased PTH/PTH-related protein receptor mRNA expression in bone and growth plate [149, 150] and circulating amino-terminally truncated PTH fragments may play a role in the skeletal resistance to the full-length PTH molecule. Indeed, PTH(7–84) blunts the calcemic response to PTH(1–84) and PTH(1–34) in parathyroidectomized rats with normal kidney function [110, 151, 152] while increased circulating levels of PTH(7–84) in dialysis patients is associated with a decreased response to the calcemic actions of PTH(1–34) in humans [153]. Moreover, PTH(7–84) has biological activity at the level of bone *in vitro*, inhibiting bone resorption and thus antagonizing the effects of PTH(1–84) and PTH(1–34) [154]. Hyperphosphatemia and alterations in vitamin D metabolism have also been implicated in these changes and calcitriol administration has been shown to partially restore the calcemic response to PTH in both experimental animals and in patients with moderate CKD [155].

Vitamin D therapy inhibits PTH release by two mechanisms: directly, by inhibiting pre-pro-PTH gene transcription, and indirectly, by increasing intestinal calcium absorption and increasing serum calcium levels. Active vitamin D sterol therapy is indicated when PTH

levels are above the target range despite repletion of 25(OH)vitamin D stores [82]. It is important to ensure that serum phosphorus levels are within the normal range for age before starting vitamin D sterol therapy. Calcitriol or alfacalcidol are started at a daily dose of 0.25–0.5 μg, and the dose is gradually titrated in 0.25–0.5 μg increments to achieve 1st PTH-IMA levels within the normal range for stage of CKD. In patients with CKD stage 5 or those requiring regular dialysis, vitamin D therapy is recommended when 1st PTH-IMA levels exceed 300 pg/mL and serum phosphorus concentrations are at age-appropriate levels [82]. Similar to patients with moderate CKD, daily calcitriol or alfacalcidol therapy may be initiated in patients treated with maintenance dialysis at a dose of 0.25–0.5 μg, with gradual dosage increases of 0.25–0.5 μg in order to achieve 1st PTH-IMA levels between 200 and 300 pg/mL. Paricalcitol and doxercalciferol therapy is typically initiated at 2.5–5 μg and titrated upward in 2.5 μg increments. Serum levels of calcium, phosphorus, and 1st PTH-IMA should be monitored at regular intervals after start of therapy [82].

Intermittent (thrice weekly) doses of vitamin D sterols (administered either orally or intravenously) may be considered when serum PTH levels are greater than 500 or 600 pg/mL in dialysis patients. Intravenous vitamin D sterols given in a thrice weekly dosing regimen are also effective at reducing serum PTH levels in children treated with maintenance dialysis; starting doses depend on serum PTH levels and, for calcitriol, are typically between 0.5 and 1.5 mcg/kg. Paricalcitol is also effective at starting doses of 0.04–0.08 μg/kg [156, 157]. Vitamin D should be titrated to maintain serum calcium levels less than 10.2 mg/dL, serum phosphorus levels within the age-appropriate range, and PTH levels between 300 and 400 pg/mL, since PTH levels in this range have been associated with normal rates of bone formation during intermittent vitamin D sterol therapy [73].

Hypercalcemia and hyperphosphatemia are undesired consequences of active vitamin D therapy. Hypercalcemia is a particular problem when active D sterols are administered in conjunction with calcium-based phosphate binders and have been associated with the progression of vascular calcification in the CKD population [87, 88], calling into question the safety of this form of therapy. Thus, newer active vitamin D sterols, with lower calcemic activity, have been developed. In the United States, 19-nor-1,25-$(OH)_2D_2$ (paricalcitol) and $1\alpha(OH)D_2$ (doxercalciferol) have been introduced, while 22-oxa-$1,25(OH)_2D_3$ (maxacalcitol) is used in Japan. These sterols offer the potential for reduced episodes of hypercalcemia [158, 159], though their superiority over calcitriol has not been consistently demonstrated in controlled trials in humans [73]. When active vitamin D sterols are used with sevelamer, the skeletal and biochemical features of secondary hyperparathyroidism are markedly improved without inducing changes in serum calcium levels. Thus, the use of calcium-free phosphate binders may enhance the margin of safety during therapy with active vitamin D sterols. This is of particular importance since hypercalcemia has been linked to adynamic bone disease and progressive vascular calcification in adults treated with maintenance dialysis [58], while vitamin D therapy has been associated with improved survival rates in adult dialysis patients [94, 95, 160]. Thus, treatment with vitamin D sterols while preventing hypercalcemia may maintain both cardiac and bone function in dialyzed patients. However, vitamin D sterol therapy increases circulating FGF-23 levels, which themselves have been linked to increased rates of mortality in the dialysis population [89]; thus further prospective studies are warranted to evaluate the long-term benefits of these different therapies.

Current observations suggest a role for 25(OH) vitamin D therapy (given as either ergocalciferol, the plant-based form, or cholecalciferol, the animal-based form) in improving bone disease, and potentially also survival, in patients treated with maintenance dialysis [96]. Supplementation with ergocalciferol in patients with all stages of CKD increases both 25(OH)D and $1,25(OH)_2D$ levels while suppressing PTH values [21, 27, 161]. Furthermore, dialysis patients require lower doses of epogen and active vitamin D sterols during ergocalciferol supplementation [27]. However,

the long-term effect of this form of therapy in patients with CKD remains to be carefully evaluated and the effects of combined therapy with active vitamin D sterol administration on target organs remain to be more completely defined.

Calcimimetic Agents

Cinacalcet, an allosteric activator of the calcium sensing receptor, is now available for the treatment of hyperparathyroidism. This small organic molecule reduces serum PTH levels and has also been shown to decrease the calcium–phosphorous ion product in adult patients treated with maintenance dialysis [46, 162]. Experiments in uremic rats have demonstrated that calcimimetics are able to halt the progression of parathyroid cell hyperplasia [46]; the antiproliferative effect of this agent shows promise for use of the molecule as a "medical parathyroidectomy." Studies in animals also suggest that the use of calcimimetic agents may play a role in reversing the process of vascular calcification [163]; however, such effects need to be further evaluated in humans. Although calcimimetics are effective in reducing PTH, calcium, and phosphorus in children, the calcium sensing receptor is expressed on growth plate cartilage and long-term effects on growth in this population remain unknown [164–166].

Parathyroidectomy

Parathyroid gland hyperplasia, which is characterized by serum PTH elevations and osteitis fibrosa on bone biopsy, is a result of poorly controlled secondary hyperparathyroidism. Calcitriol resistance may develop in the presence of an enlarged nodular hyperplastic parathyroid gland because of the decrease in the number of VDRs and the presence of monoclonal proliferation in nodular areas [167, 168]. When vitamin D therapy fails to correct the signs of secondary hyperparathyroidism, parathyroidectomy must be considered. Urgent indications for parathyroidectomy include persistent or recurrent hypercalcemia (particularly when associated with intractable pruritus not responding to intensive dialysis), progressive extraskeletal calcifications, bone pain, multiple and recurrent fractures, and the appearance of calciphylaxis [85]. However, prior to parathyroidectomy, care must be taken to ensure that these symptoms are attributable to secondary hyperparathyroidism and high-turnover renal osteodystrophy, since all may also be associated with adynamic bone disease [169].

Hypocalcemia may develop after parathyroidectomy in patients with severe secondary hyperparathyroidism. This condition, called "hungry bone syndrome," is caused by a high rate of skeletal calcium uptake, which may continue for some time after serum PTH levels are lowered by parathyroidectomy. Treatment of "hungry bone syndrome" consists of large daily doses of active vitamin D along with calcium (initially administered as a calcium gluconate drip and later as large daily doses of calcium carbonate). Hypophosphatemia may also develop postoperatively, but supplemental phosphorus may aggravate hypocalcemia and should be avoided unless serum levels of phosphorus are below 2.0 mg/dL.

References

1. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G. Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2006;69:1945–53.
2. 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.
3. Portale AA, Booth BE, Halloran BP, Morris Jr RC. 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;73:1580–9.
4. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL. 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;71:31–8.

5. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Jüppner H, Wolf M. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005;16:2205–15.
6. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. J Clin Endocrinol Metab. 2006;91:3144–9.
7. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004;19:429–35.
8. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int. 2003;64:2272–9.
9. Krajisnik T, Bjorklund P, Marsell R, Ljunggren O, Akerstrom G, Jonsson KB, Westin G, Larsson TE. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. J Endocrinol. 2007;195:125–31.
10. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro O, Mohammadi M, Sirkis R, Naveh-Many T, Silver J. The parathyroid is a target organ for FGF23 in rats. J Clin Invest. 2007;117:4003–8.
11. Silver J, Russell J, Sherwood LM. Regulation by vitamin D metabolites of messenger ribonucleic acid for preproparathyroid hormone in isolated bovine parathyroid cells. Proc Natl Acad Sci USA. 1985;82:4270–3.
12. Silver J, Naveh-Many T, Mayer H, Schmelzer HJ, Popovtzer MM. Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. J Clin Invest. 1986;78:1296–301.
13. Kifor O, Moore Jr FD, Wang P, Goldstein M, Vassilev P, Kifor I, Hebert SC, Brown EM. Reduced immunostaining for the extracellular Ca^{2+}-sensing receptor in primary and uremic secondary hyperparathyroidism. J Clin Endocrinol Metab. 1996;81:1598–606.
14. Brown AJ, Zhong M, Finch J, Ritter C, McCracken R, Morrissey J, Slatopolsky E. Rat calcium-sensing receptor is regulated by vitamin D but not by calcium. Am J Physiol. 1996;270:F454–60.
15. Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed. Washington, DC: American Society for Bone and Mineral Research; 2006. p. 129–37.
16. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 2004;80S:1689S–96S.
17. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
18. Nykjaer A, Dragun D, Walther D, Vorum H, Jacobsen C, Herz J, Melsen F, Christensen EI, Willnow TE. An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. Cell. 1999;96:507–15.
19. Leheste JR, Melsen F, Wellner M, Jansen P, Schlichting U, Renner-Muller I, Andreassen TT, Wolf E, Bachmann S, Nykjaer A, Willnow TE. Hypocalcemia and osteopathy in mice with kidney-specific megalin gene defect. FASEB J. 2003; 17:247–9.
20. Zehnder D, Landray MJ, Wheeler DC, Fraser W, Blackwell L, Nuttall S, Hughes SV, Townend J, Ferro C, Baigent C, Hewison M. Cross-sectional analysis of abnormalities of mineral homeostasis, vitamin D and parathyroid hormone in a cohort of pre-dialysis patients. The chronic renal impairment in Birmingham (CRIB) study. Nephron Clin Pract. 2007;107:c109–16.
21. Zisman AL, Hristova M, Ho LT, Sprague SM. Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. Am J Nephrol. 2007;27: 36–43.
22. Chandra P, Binongo JN, Ziegler TR, Schlanger LE, Wang W, Someren JT, Tangpricha V. Cholecalciferol (vitamin D3) therapy and vitamin D insufficiency in patients with chronic kidney disease: a randomized controlled pilot study. Endocr Pract. 2008;14: 10–17.
23. Ritter CS, Armbrecht HJ, Slatopolsky E, Brown AJ. 25-Hydroxyvitamin D(3) suppresses PTH synthesis and secretion by bovine parathyroid cells. Kidney Int. 2006;70:654–9.
24. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998;338:777–83.
25. Stavroulopoulos A, Porter CJ, Roe SD, Hosking DJ, Cassidy MJ. Relationship between vitamin D status, parathyroid hormone levels and bone mineral density in patients with chronic kidney disease stages 3 and 4. Nephrology (Carlton). 2008;13:63–7.
26. Reichel H, Deibert B, Schmidt-Gayk H, Ritz E. Calcium metabolism in early chronic renal failure: implications for the pathogenesis of hyperparathyroidism. Nephrol Dial Transplant. 1991;6:162–9.
27. Saab G, Young DO, Gincherman Y, Giles K, Norwood K, Coyne DW. Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. Nephron Clin Pract. 2007;105:c132–8.
28. Mucsi I, Almasi C, Deak G, Marton A, Ambrus C, Berta K, Lakatos P, Szabo A, Horvath C. Serum 25(OH)-vitamin D levels and bone metabolism in patients on maintenance hemodialysis. Clin Nephrol. 2005;64:288–94.
29. Coburn JW, Koppel MH, Brickman AS, Massry SG. Study of intestinal absorption of calcium in patients with renal failure. Kidney Int. 1973;3:264–72.

30. Holick MF. Vitamin D and the kidney. Kidney Int. 1987;32:912–29.
31. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet. 1982;1:74–6.
32. Koenig KG, Lindberg JS, Zerwekh JE, Padalino PK, Cushner HM, Copley JB. Free and total 1,25-dihydroxyvitamin D levels in subjects with renal disease. Kidney Int. 1992;41:161–5.
33. Saha H. Calcium and vitamin D homeostasis in patients with heavy proteinuria. Clin Nephrol. 1994;41:290–6.
34. Slatopolsky E, Caglar S, Pennell JP, Taggart DD, Canterbury JM, Reiss E, Bricker NS. On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog. J Clin Invest. 1971;50:492–9.
35. Llach F, Massry SG. On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. J Clin Endocrinol Metab. 1985;61:601–6.
36. Almaden Y, Canalejo A, Ballesteros E, Anon G, Canadillas S, Rodriguez M. Regulation of arachidonic acid production by intracellular calcium in parathyroid cells: effect of extracellular phosphate. J Am Soc Nephrol. 2002;13:693–8.
37. Silver J, Kilav R, Sela-Brown A, Naveh-Many T. Molecular mechanisms of secondary hyperparathyroidism. Pediatr Nephrol. 2000;14:626–8.
38. Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O, Sun A, Hediger MA, Lytton J, Hebert SC. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. Nature. 1993;366:575–80.
39. John MR, Goodman WG, Gao P, Cantor TL, Salusky IB, Jüppner H. A novel immunoradiometric assay detects full-length human PTH but not amino-terminally truncated fragments: implications for PTH measurements in renal failure. J Clin Endocrinol Metab. 1999;84:4287–90.
40. Freichel M, Zink-Lorenz A, Holloschi A, Hafner M, Flockerzi V, Raue F. Expression of a calcium-sensing receptor in a human medullary thyroid carcinoma cell line and its contribution to calcitonin secretion. Endocrinology. 1996;137:3842–8.
41. Kirkwood JR, Ozonoff MB, Steinbach HL. Epiphyseal displacement after metaphyseal fracture in renal osteodystrophy. Am J Roentgenol Radium Ther Nucl Med. 1972;115:547–54.
42. Martin-Salvago M, Villar-Rodriguez JL, Palma-Alvarez A, Beato-Moreno A, Galera-Davidson H. Decreased expression of calcium receptor in parathyroid tissue in patients with hyperparathyroidism secondary to chronic renal failure. Endocr Pathol. 2003;14:61–70.
43. Canaff L, Hendy GN. Human calcium-sensing receptor gene. Vitamin D response elements in promoters P1 and P2 confer transcriptional responsiveness to 1,25-dihydroxyvitamin D. J Biol Chem. 2002;277:30337–50.
44. Li YC, Pirro AE, Amling M, Delling G, Baron R, Bronson R, Demay MB. Targeted ablation of the vitamin D receptor: an animal model of vitamin D-dependent rickets type II with alopecia. Proc Natl Acad Sci USA. 1997;94:9831–5.
45. Brown AJ, Zhong M, Ritter C, Brown EM, Slatopolsky E. Loss of calcium responsiveness in cultured bovine parathyroid cells is associated with decreased calcium receptor expression. Biochem Biophys Res Commun. 1995;212:861–7.
46. Wada M, Furuya Y, Sakiyama J, Kobayashi N, Miyata S, Ishii H, Nagano N. The calcimimetic compound NPS R-568 suppresses parathyroid cell proliferation in rats with renal insufficiency. Control of parathyroid cell growth via a calcium receptor. J Clin Invest. 1997;100:2977–83.
47. Atkins D, Peacock M. A comparison of the effects of the calcitonins, steroid hormones and thyroid hormones on the response of bone to parathyroid hormone in tissue culture. J Endocrinol. 1975;64:573–83.
48. Lee K, Deeds JD, Bond AT, Jüppner H, Abou-Samra AB, Segre GV. In situ localization of PTH/PTHrP receptor mRNA in the bone of fetal and young rats. Bone. 1993;14:341–5.
49. Sherrard DJ. Renal osteodystrophy. Semin Nephrol. 1986;6:56–67.
50. Malluche HH, Ritz E, Lange HP, Schoeppe W. Changes of bone histology during maintenance hemodialysis at various levels of dialyzate Ca concentration. Clin Nephrol. 1976;6:440–7.
51. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, Josse S, Meyrier A, Lins RL, Fairey IT. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. BMJ. 1995;310:358–63.
52. Norman ME, Mazur AT, Borden S, Gruskin A, Anast C, Baron R, Rasmussen H. Early diagnosis of juvenile renal osteodystrophy. J Pediatr. 1980;97:226–32.
53. Malluche H, Faugere MC. Renal bone disease 1990: an unmet challenge for the nephrologist. Kidney Int. 1990;38:193–211.
54. Cohen-Solal ME, Sebert JL, Boudailliez B, Westeel PF, Moriniere PH, Marie A, Garabedian M, Fournier A. Non-aluminic adynamic bone disease in non-dialyzed uremic patients: a new type of osteopathy due to overtreatment? Bone. 1992;13:1–5.
55. Goodman WG, Ramirez JA, Belin TR, Chon Y, Gales B, Segre GV, Salusky IB. Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. Kidney Int. 1994;46:1160–6.
56. Salusky IB, Coburn JW, Foley J, Nelson P, Fine RN. Effects of oral calcium carbonate on control of serum phosphorus and changes in plasma aluminum levels after discontinuation of aluminum-containing gels in children receiving dialysis. J Pediatr. 1986;108:767–70.

57. Ott SM, Maloney NA, Klein GL, Alfrey AC, Ament ME, Coburn JW, Sherrard DJ. Aluminum is associated with low bone formation in patients receiving chronic parenteral nutrition. Ann Intern Med. 1983;98:910–14.
58. 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;15:1943–51.
59. Kuizon BD, Salusky IB. Intermittent calcitriol therapy and growth in children with chronic renal failure. Miner Electrolyte Metab. 1998;24:290–5.
60. Kuizon BD, Goodman WG, Jüppner H, Boechat I, Nelson P, Gales B, Salusky IB. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int. 1998;53:205–11.
61. Salusky IB, Ramirez JA, Oppenheim W, Gales B, Segre GV, Goodman WG. Biochemical markers of renal osteodystrophy in pediatric patients undergoing CAPD/CCPD. Kidney Int. 1994;45:253–8.
62. Sherrard DJ, Baylink DJ, Wergedal JE, Maloney NA. Quantitative histological studies on the pathogenesis of uremic bone disease. J Clin Endocrinol Metab. 1974;39:119–35.
63. NIDDK. USRDS 1994 Annual Report, 2008.
64. Pereira RC, Juppner H, Azucena-Serrano CE, Yadin O, Salusky IB, Wesseling-Perry K. Patterns of FGF-23, DMP1, and MEPE expression in patients with chronic kidney disease. Bone. 2009;45:1161–8.
65. De Beur SM, Finnegan RB, Vassiliadis J, Cook B, Barberio D, Estes S, Manavalan P, Petroziello J, Madden SL, Cho JY, Kumar R, Levine MA, Schiavi SC. Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. J Bone Miner Res. 2002;17:1102–10.
66. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, Yamamoto T, Hampson G, Koshiyama H, Ljunggren O, Oba K, Yang IM, Miyauchi A, Econs MJ, Lavigne J, Jüppner H. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med. 2003;348:1656–63.
67. Nelson AE, Bligh RC, Mirams M, Gill A, Au A, Clarkson A, Jüppner H, Ruff S, Stalley P, Scolyer RA, Robinson BG, Mason RS, Bligh PC. Clinical case seminar: fibroblast growth factor 23: a new clinical marker for oncogenic osteomalacia. J Clin Endocrinol Metab. 2003;88:4088–94.
68. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113:561–8.
69. Sitara D, Razzaque MS, Hesse M, Yoganathan S, Taguchi T, Erben RG, Jüppner H, Lanske B. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. Matrix Biol. 2004;23:421–32.
70. Lorenz-Depiereux B, Bastepe M, Benet-Pages A, Amyere M, Wagenstaller J, Muller-Barth U, Badenhoop K, Kaiser SM, Rittmaster RS, Shlossberg AH, Olivares JL, Loris C, Ramos FJ, Glorieux F, Vikkula M, Juppner H, Strom TM. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. Nat Genet. 2006;38:1248–50.
71. Salusky IB, Coburn JW, Brill J, Foley J, Slatopolsky E, Fine RN, Goodman WG. Bone disease in pediatric patients undergoing dialysis with CAPD or CCPD. Kidney Int. 1988;33:975–82.
72. Salusky IB, Goodman WG, Kuizon BD, Lavigne JR, Zahranik RJ, Gales B, Wang HJ, Elashoff RM, Juppner H. Similar predictive value of bone turnover using first- and second-generation immunometric PTH assays in pediatric patients treated with peritoneal dialysis. Kidney Int. 2003;63:1801–8.
73. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, Elashoff RM, Juppner H. 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;16:2501–8.
74. Ho AY, Kung AW. Determinants of peak bone mineral density and bone area in young women. J Bone Miner Metab. 2005;23:470–5.
75. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2006 Annual Report, 2006 https://web.emmes.com/study/ped/.
76. Tonshoff B, Schaefer F, Mehls O. Disturbance of growth hormone–insulin-like growth factor axis in uraemia. Implications for recombinant human growth hormone treatment. Pediatr Nephrol. 1990;4:654–62.
77. Schott GD, Wills MR. Muscle weakness in osteomalacia. Lancet. 1976;1:626–9.
78. Smith R, Stern G. Myopathy, osteomalacia and hyperparathyroidism. Brain. 1967;90:593–602.
79. Mallette LE, Patten BM, Engel WK. Neuromuscular disease in secondary hyperparathyroidism. Ann Intern Med. 1975;82:474–83.
80. Henderson RG, Russell RG, Ledingham JG, Smith R, Oliver DO, Walton RJ, Small DG, Preston C, Warner GT. Effects of 1,25-dihydroxycholecalciferol on calcium absorption, muscle weakness, and bone disease in chronic renal failure. Lancet. 1974;1:379–84.
81. Mehls O, Ritz E, Krempien B, Gilli G, Link K, Willich E, Scharer K. Slipped epiphyses in renal osteodystrophy. Arch Dis Child. 1975;50:545–54.
82. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J Kidney Dis. 2005;46:S1–121.
83. 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.
84. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62:648–53.
85. Milliner DS, Zinsmeister AR, Lieberman E, Landing B. Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int. 1990;38:931–6.
86. 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.
87. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005;68:1815–24.
88. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int. 2007;71:438–41.
89. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359:584–92.
90. Jean G, Bresson E, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, Chazot C. Peripheral vascular calcification in long-haemodialysis patients: associated factors and survival consequences. Nephrol Dial Transplant. 2009;24:948–55.
91. Tonelli M, Keech A, Shepherd J, Sacks F, Tonkin A, Packard C, Pfeffer M, Simes J, Isles C, Furberg C, West M, Craven T, Curhan G. Effect of pravastatin in people with diabetes and chronic kidney disease. J Am Soc Nephrol. 2005;16:3748–54.
92. Holdaas H, Fellstrom B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Gronhagen-Riska C, Neumayer HH, Maes B, Ambuhl P, Hartmann A, Staffler B, Jardine AG. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant. 2005;5:2929–36.
93. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
94. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo Jr CA, Thadhani R. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol. 2005;16: 1115–25.
95. 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;349:446–56.
96. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo Jr CA, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72:1004–13.
97. Brown EM, Wilson RE, Eastman RC, Pallotta J, Marynick SP. Abnormal regulation of parathyroid hormone release by calcium in secondary hyperparathyroidism due to chronic renal failure. J Clin Endocrinol Metab. 1982;54:172–9.
98. Salusky IB, Fine RN, Kangarloo H, Gold R, Paunier L, Goodman WG, Brill JE, Gilli G, Slatopolsky E, Coburn JW. "High-dose" calcitriol for control of renal osteodystrophy in children on CAPD. Kidney Int. 1987;32:89–95.
99. Kurz P, Monier-Faugere MC, Bognar B, Werner E, Roth P, Vlachojannis J, Malluche HH. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. Kidney Int. 1994;46:855–61.
100. Goldman R, Bassett SH. Phosphorus excretion in renal failure. J Clin Invest. 1954;33:1623–8.
101. KDIGO 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. 2009;76:s1–130.
102. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV. The spectrum of bone disease in end-stage renal failure–an evolving disorder. Kidney Int. 1993; 43:436–42.
103. Cohen-Solal ME, Shih MS, Lundy MW, Parfitt AM. A new method for measuring cancellous bone erosion depth: application to the cellular mechanisms of bone loss in postmenopausal osteoporosis. J Bone Miner Res. 1991;6:1331–8.
104. Quarles LD, Lobaugh B, Murphy G. Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. J Clin Endocrinol Metab. 1992;75:145–50.
105. Mathias R, Salusky I, Harman W, Paredes A, Emans J, Segre G, Goodman W. Renal bone disease in pediatric and young adult patients on hemodialysis in a children's hospital. J Am Soc Nephrol. 1993;3:1938–46.
106. Malluche HH, Monier-Faugere MC. The role of bone biopsy in the management of patients with renal osteodystrophy. J Am Soc Nephrol. 1994;4: 1631–42.
107. Brossard JH, Cloutier M, Roy L, Lepage R, Gascon-Barre M, D'Amour P. Accumulation of a non-(1–84) molecular form of parathyroid hormone (PTH) detected by intact PTH assay in renal failure: importance in the interpretation of PTH values. J Clin Endocrinol Metab. 1996;81:3923–9.
108. Lepage R, Roy L, Brossard JH, Rousseau L, Dorais C, Lazure C, D'Amour P. A non-(1–84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples. Clin Chem. 1998; 44:805–9.
109. Brossard JH, Yamamoto LN, D'Amour P. Parathyroid hormone metabolites in renal failure: bioactivity and clinical implications. Semin Dial. 2002;15:196–201.

110. Slatopolsky E, Finch J, Clay P, Martin D, Sicard G, Singer G, Gao P, Cantor T, Dusso A. A novel mechanism for skeletal resistance in uremia. Kidney Int. 2000;58:753–61.
111. Coen G, Bonucci E, Ballanti P, Balducci A, Calabria S, Nicolai GA, Fischer MS, Lifrieri F, Manni M, Morosetti M, Moscaritolo E, Sardella D. PTH 1–84 and PTH "7-84" in the noninvasive diagnosis of renal bone disease. Am J Kidney Dis. 2002;40: 348–54.
112. Dent CE, Hodson CJ. Radiological changes associated with certain metabolic bone diseases. Br J Radiol. 1954;27:605–18.
113. Meema HE, Rabinovich S, Meema S, Lloyd GJ, Oreopoulos DG. Improved radiological diagnosis of azotemic osteodystrophy. Radiology. 1972;102:1–10.
114. Mehls O, Krempien B, Ritz E, Scharer K, Schuler HW. Renal osteodystrophy in children on maintenance haemodialysis. Proc Eur Dial Transplant Assoc. 1973;10:197–201.
115. Olgaard K, Heerfordt J, Madsen S. Scintigraphic skeletal changes in uremic patients on regular hemodialysis. Nephron. 1976;17:325–34.
116. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington: National Academy Press; 1997. Ref Type: Report.
117. Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW. Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. Kidney Int. 1982;21:849–61.
118. Pierratos A. Daily hemodialysis: why the renewed interest? Am J Kidney Dis. 1998;32:S76–82.
119. 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;21:835–41.
120. 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.
121. Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A. Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int. 1998;53:1399–404.
122. Roodhooft AM, Van Hoeck KJ, Van Acker KJ. Hypophosphatemia in infants on continuous ambulatory peritoneal dialysis. Clin Nephrol. 1990;34: 131–5.
123. Tejeda A, Saffarian N, Uday K, Dave M. Hypophosphatemia in end stage renal disease. Nephron. 1996;73:674–8.
124. Brickman AS, Coburn JW, Massry SG, Norman AW. 1,25 Dihydroxy-vitamin D3 in normal man and patients with renal failure. Ann Intern Med. 1974; 80:161–8.
125. Coburn JW, Mischel MG, Goodman WG, Salusky IB. Calcium citrate markedly enhances aluminum absorption from aluminum hydroxide. Am J Kidney Dis. 1991;17:708–11.
126. Alon U, Davidai G, Bentur L, Berant M, Better OS. Oral calcium carbonate as phosphate-binder in infants and children with chronic renal failure. Miner Electrolyte Metab. 1986;12:320–5.
127. Tsukamoto Y, Moriya R, Nagaba Y, Morishita T, Izumida I, Okubo M. Effect of administering calcium carbonate to treat secondary hyperparathyroidism in nondialyzed patients with chronic renal failure. Am J Kidney Dis. 1995;25:879–86.
128. Indridason OS, Quarles LD. Comparison of treatments for mild secondary hyperparathyroidism in hemodialysis patients. Durham Renal Osteodystrophy Study Group. Kidney Int. 2000;57:282–92.
129. Tamanaha K, Mak RH, Rigden SP, Turner C, Start KM, Haycock GB, Chantler C. Long-term suppression of hyperparathyroidism by phosphate binders in uremic children. Pediatr Nephrol. 1987;1:145–9.
130. Slatopolsky E, Weerts C, Lopez-Hilker S, Norwood K, Zink M, Windus D, Delmez J. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. N Engl J Med. 1986;315:157–61.
131. Fournier A, Moriniere P, Sebert JL, Dkhissi H, Atik A, Leflon P, Renaud H, Gueris J, Gregoire I, Idrissi A. Calcium carbonate, an aluminum-free agent for control of hyperphosphatemia, hypocalcemia, and hyperparathyroidism in uremia. Kidney Int Suppl. 1986;18:S114–19.
132. Caglar K, Yilmaz MI, Saglam M, Cakir E, Acikel C, Eyileten T, Yenicesu M, Oguz Y, Vural A, Carrero JJ, Axelsson J, Lindholm B, Stenvinkel P. Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. Clin J Am Soc Nephrol. 2008;3:61–8.
133. Slatopolsky EA, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. The RenaGel Study Group. Kidney Int. 1999;55:299–307.
134. Bleyer AJ, Burke SK, Dillon M, Garrett B, Kant KS, Lynch D, Rahman SN, Schoenfeld P, Teitelbaum I, Zeig S, Slatopolsky E. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis. 1999;33:694–701.
135. Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB. Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. Pediatr Nephrol. 2003;18:1260–4.
136. Chertow GM, Dillon M, Burke SK, Steg M, Bleyer AJ, Garrett BN, Domoto DT, Wilkes BM, Wombolt DG, Slatopolsky E. A randomized trial of sevelamer hydrochloride (RenaGel) with and without supplemental calcium. Strategies for the control of hyperphosphatemia and hyperparathyroidism in hemodialysis patients. Clin Nephrol. 1999;51: 18–26.

137. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62:245–52.
138. Oliveira RB, Cancela AL, Graciolli FG, dos Reis LM, Draibe SA, Cuppari L, Carvalho AB, Jorgetti V, Canziani ME, Moyses RM. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? Clin J Am Soc Nephrol. 2010;5(2):286–91.
139. Delmez J, Block G, Robertson J, Chasan-Taber S, Blair A, Dillon M, Bleyer AJ. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. Clin Nephrol. 2007;68:386–91.
140. Hergesell O, Ritz E. Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients. Nephrol Dial Transplant. 1999;14: 863–7.
141. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, Backs W, Jamar R, Vosskuhler A. Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. Nephron Clin Pract. 2006;102:c61–71.
142. Slatopolsky E, Liapis H, Finch J. Progressive accumulation of lanthanum in the liver of normal and uremic rats. Kidney Int. 2005;68:2809–13.
143. Spasovski GB, Sikole A, Gelev S, Masin-Spasovska J, Freemont T, Webster I, Gill M, Jones C, De Broe ME, D'Haese PC. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. Nephrol Dial Transplant. 2006;21:2217–24.
144. Waller SC, Ridout D, Cantor T, Rees L. Parathyroid hormone and growth in children with chronic renal failure. Kidney Int. 2005;67:2338–45.
145. 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;18:440–4.
146. Klaus G, Watson A, Edefonti A, Fischbach M, Ronnholm K, Schaefer F, Simkova E, Stefanidis CJ, Strazdins V, Vande WJ, Schroder C, Zurowska A, Ekim M. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol. 2006;21: 151–9.
147. Massry SG, Friedler RM, Coburn JW. Excretion of phosphate and calcium. Physiology of their renal handling and relation to clinical medicine. Arch Intern Med. 1973;131:828–59.
148. Galceran T, Martin KJ, Morrissey JJ, Slatopolsky E. Role of 1,25-dihydroxyvitamin D on the skeletal resistance to parathyroid hormone. Kidney Int. 1987; 32:801–7.
149. Urena P, Ferreira A, Morieux C, Drueke T, de Vernejoul MC. PTH/PTHrP receptor mRNA is down-regulated in epiphyseal cartilage growth plate of uraemic rats. Nephrol Dial Transplant. 1996;11: 2008–16.
150. Sanchez CP, Salusky IB, Kuizon BD, Abdella P, Jüppner H, Goodman WG. Growth of long bones in renal failure: roles of hyperparathyroidism, growth hormone and calcitriol. Kidney Int. 1998;54: 1879–87.
151. Nguyen-Yamamoto L, Rousseau L, Brossard JH, Lepage R, D'Amour P. Synthetic carboxyl-terminal fragments of parathyroid hormone (PTH) decrease ionized calcium concentration in rats by acting on a receptor different from the PTH/PTH-related peptide receptor. Endocrinology. 2001;142:1386–92.
152. Langub MC, Monier-Faugere MC, Wang G, Williams JP, Koszewski NJ, Malluche HH. Administration of PTH-(7–84) antagonizes the effects of PTH-(1–84) on bone in rats with moderate renal failure. Endocrinology. 2003;144:1135–8.
153. Wesseling-Perry K, Harkins GC, Wang H, Elashoff RM, Gales B, Horwitz MJ, Stewart AF, Jüppner H, Salusky IB. The calcemic response to continuous PTH(1–34) infusion in end-stage kidney disease varies according to bone turnover: a potential role for PTH(7–84). J Clin Endocrinol Metab. 2010;95(6):2772–80.
154. Divieti P, John MR, Jüppner H, Bringhurst FR. Human PTH-(7–84) inhibits bone resorption *in vitro* via actions independent of the type 1 PTH/PTHrP receptor. Endocrinology. 2002;143:171–6.
155. Massry SG, Stein R, Garty J, Arieff AI, Coburn JW, Norman AW, Friedler RM. Skeletal resistance to the calcemic action of parathyroid hormone in uremia: role of 1,25 (OH)2 D3. Kidney Int. 1976;9:467–74.
156. Greenbaum LA, Grenda R, Qiu P, Restaino I, Wojtak A, Paredes A, Benador N, Melnick JZ, Williams LA, Salusky IB. Intravenous calcitriol for treatment of hyperparathyroidism in children on hemodialysis. Pediatr Nephrol. 2005;20:622–30.
157. Greenbaum LA, Benador N, Goldstein SL, Paredes A, Melnick JZ, Mattingly S, Amdahl M, Williams LA, Salusky IB. Intravenous paricalcitol for treatment of secondary hyperparathyroidism in children on hemodialysis. Am J Kidney Dis. 2007;49:814–23.
158. Brown AJ, Finch J, Slatopolsky E. Differential effects of 19-nor-1,25-dihydroxyvitamin D(2) and 1,25-dihydroxyvitamin D(3) on intestinal calcium and phosphate transport. J Lab Clin Med. 2002; 139:279–84.
159. Coburn JW, Maung HM, Elangovan L, Germain MJ, Lindberg JS, Sprague SM, Williams ME, Bishop CW. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis. 2004;43:877–90.
160. Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, Johnson HK, Zager PG. Mortality risk among hemodialysis patients receiving different vitamin D analogs. Kidney Int. 2006;70:1858–65.
161. Al-Aly Z, Qazi RA, Gonzalez EA, Zeringue A, Martin KJ. Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment

with ergocalciferol in patients with CKD. Am J Kidney Dis. 2007;50:59–68.
162. Wada M, Nagano N. Control of parathyroid cell growth by calcimimetics. Nephrol Dial Transplant. 2003;18(Suppl 3):iii13–17.
163. Lopez I, Aguilera-Tejero E, Mendoza FJ, Almaden Y, Perez J, Martin D, Rodriguez M. Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol. J Am Soc Nephrol. 2006;17:795–804.
164. 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;23:1823–9.
165. Silverstein DM, Kher KK, Moudgil A, Khurana M, Wilcox J, Moylan K. Cinacalcet is efficacious in pediatric dialysis patients. Pediatr Nephrol. 2008;23:1817–22.
166. Platt C, Inward C, McGraw M, Dudley J, Tizard J, Burren C, Saleem MA. Middle-term use of Cinacalcet in paediatric dialysis patients. Pediatr Nephrol. 2010;25:143–8.
167. Fukuda N, Tanaka H, Tominaga Y, Fukagawa M, Kurokawa K, Seino Y. Decreased 1,25-dihydroxyvitamin D3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. J Clin Invest. 1993;92:1436–43.
168. Arnold A, Brown MF, Urena P, Gaz RD, Sarfati E, Drueke TB. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. J Clin Invest. 1995;95:2047–53.
169. Mawad HW, Sawaya BP, Sarin R, Malluche HH. Calcific uremic arteriolopathy in association with low turnover uremic bone disease. Clin Nephrol. 1999;52:160–6.

The Cardiovascular Status of Pediatric Dialysis Patients

26

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Keywords
Pediatric dialysis • Cardiovascular status • Children • CVD CKD

Introduction

Since the inception of pediatric dialysis programs nearly 50 years ago, there have been vast improvements in both the technology and expertise in the care of children with chronic kidney disease (CKD). Nevertheless, children on dialysis continue to have an unacceptably high mortality, and cardiovascular disease (CVD) is the most common cause of death in this group. CKD poses the "perfect storm" of risk factors for the development of CVD. Among these, hypertension and dysregulated mineral metabolism leading to ectopic vascular calcification have been consistently implicated in clinical, epidemiological, and cell biology studies as key, but importantly modifiable, risk factors in the development of CVD. Identifying potentially modifiable damage-inducing agents in the uremic milieu and understanding their role in the pathophysiology of CVD may allow us to inhibit progression or even induce regression of existing cardiac and vascular injury in CKD patients.

In this chapter we discuss the epidemiology, risk factors, clinical and cell biology studies investigating the pathophysiology of CVD and ectopic vascular calcification in CKD, and explore the investigation modalities and treatment options available.

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

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(ESRD) [2, 3], but also occurs in children with CKD. The mortality from CVD is 1,000 times more common in children on dialysis than in the general pediatric population [4].

Subsequently, several large national registries have published similar findings for pediatric dialysis recipients. The United States Renal Data Systems (USRDS) analyzed 1,380 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]. The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry has shown similar results: 45% of all deaths were due to CVD, with 57% of deaths on HD and 43% 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 1,454 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 per cent of the deaths during the study period were cardiac deaths. The incidence of valvular heart disease and arrhythmias was highest among the teenagers [6].

Cardiovascular Disease Begins Early in the Course of CKD

Recent studies have shown disturbing evidence of the development of CVD even in the very early stages of CKD. The National Kidney Foundation 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 from CVD [7]. In a recent 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 [8]. 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 [9] and the Bogalusa Heart Study [10]. 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 [9, 11]. The PDAY study also showed that 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 [12]. As in the PDAY study, the Bogalusa autopsy study [10] 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. The study also demonstrated that an increased number of risk factors was associated with the extent of fatty streaks in the aorta and coronary arteries in young people. These risk factors are highly prevalent even in children with early stages of CKD and might potentiate the development and progression of atherosclerosis. They are discussed at length later in the chapter.

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 [13] 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."

Risk Factors for the Development of CVD in CKD

CKD patients have a higher prevalence of both the "traditional" Framingham risk factors as well as nontraditional risk factors that increase their cardiovascular risk (Table 26.1).

"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 [14–18]. In children, hypertension is the single most prevalent and significant "traditional" risk factor for left ventricular hypertrophy (LVH) [19, 20] as well as for vascular damage and remodeling [21].

Table 26.1 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

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 accumulation of the circulating nitric oxide synthetase (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 [22]. 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 [23–26].

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 progression of CVD, but also for progressive CKD [27]. The degree of dyslipidemia parallels the degree of renal impairment. Underlying mechanisms of uremic dyslipidemia include insulin resistance [28], hyperparathyroidism [29], malnutrition, acidosis [30], and impaired catabolism of triglyceride-rich lipoproteins by decreased activity of lipoprotein lipase and hepatic triglyceride lipase [31, 32], whereas lipoprotein synthesis appears to be unaltered. Lipoprotein (a) (Lp(a)), exerting a pro-atherosclerotic and pro-thrombotic effect, is 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 [33]. 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 increased calorie supply by dialysate glucose administration in combination with a polymorphism in the UCP2 gene, regulating adipose tissue accumulation [34].

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 [35], 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 [36].

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 that 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. 25) 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 [37]. 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 [38]. Fibroblast growth factor-23 (FGF-23) is a hormone produced by the osteocyte, and together with its obligate co-receptor, Klotho results in negative phosphate balance, by decreasing renal tubular phosphate reabsorption and suppressing renal 1-α hydroxylase, thereby reducing the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) [38]. 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 [37]. Hyperphosphatemia has also been shown to be an independent risk factor for death in the pre-dialysis population [39, 40]. 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 [41, 42], 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 and dialysate Ca, and reduced or absent Ca removal via the kidneys. Current K/DOQI guidelines recommend a maximum elemental calcium load of 2,000 mg/day, including calcium-containing medication (maximum 1,500 mg/day) and a maximum dialysate calcium concentration of 1.25 mmol/L (to avoid intradialytic Ca loading) [43]. 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 exogenous Ca load from diet or binders [44]. 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 [45] and in the "Treat-to-Goal" study the Ca-treated group had significantly more hypercalcemic episodes than the sevelamer group [46].

Oxidative stress is a major contributor to increased atherosclerosis and cardiovascular morbidity and mortality in CKD. Malnutrition and hypoalbuminemi\a reduce the antioxidant defense and increase vulnerability to oxidant injury. Retained uremic solutes, like 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 procedures, such as vascular catheters, dialysis membranes, and exposure to dialysate or oxidants in HD water, can also induce further pro-atherogenic insults [47].

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 [48–50]. The inflammatory state is often associated with malnutrition, and the combination is directly linked with a high risk of atherosclerosis [51], often known as the malnutrition-inflammation-atherosclerosis (MIA) complex. The presence of MIA in a CKD patient is associated with a significantly higher mortality [52]. The physiological calcification inhibitor, fetuin-A, is a negative acute phase reactant and its production is downregulated in an inflammatory milieu [53]; fetuin-A may be the missing link between inflammation and atherosclerosis [54]. 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 [55, 56].

Hyperhomocysteinemia is a significant risk factor for atherosclerosis [57, 58] and has been associated with increased carotid artery intima-medial thickness (cIMT) and LVH in children [50, 59]. 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 [60]. 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 [61].

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), it remains common. Recent data from the CKD cohort demonstrated that below a measured GFR of 43 mL/min/1.73 m^2, hemoglobin decreased by 0.3 g/dL for every 5 mL/min/1.73 m decrement in GFR[2] [62]. Data from the NAPRTCS registry supports that anemia is common in pediatric CKD patients (increasing from 18.5% in stage 2 CKD to 68% in stage 5 predialysis patients); furthermore, patients with anemia were 55% more likely to be hospitalized than those with normal hemoglobin

[63]. Anemia remains a significant risk for both morbidity and mortality [63, 64]. Until recently, posttransplant anemia has been under-appreciated. However, with introduction of more potent immunosuppression therapy, recently reported anemia prevalence rates have ranged from 61% to 86% [65, 66].

Surrogate Measures of Cardiovascular Risk in CKD Patients

Unlike studies in adult CKD patients where "hard" end points like 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 coronary artery calcification (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 distensability of the common carotid artery measured by ultrasound (Fig. 26.1). 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 [67]. In addition, numerous biomarkers of vascular damage and future cardiovascular events have been described and some validated against "hard end-points." 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

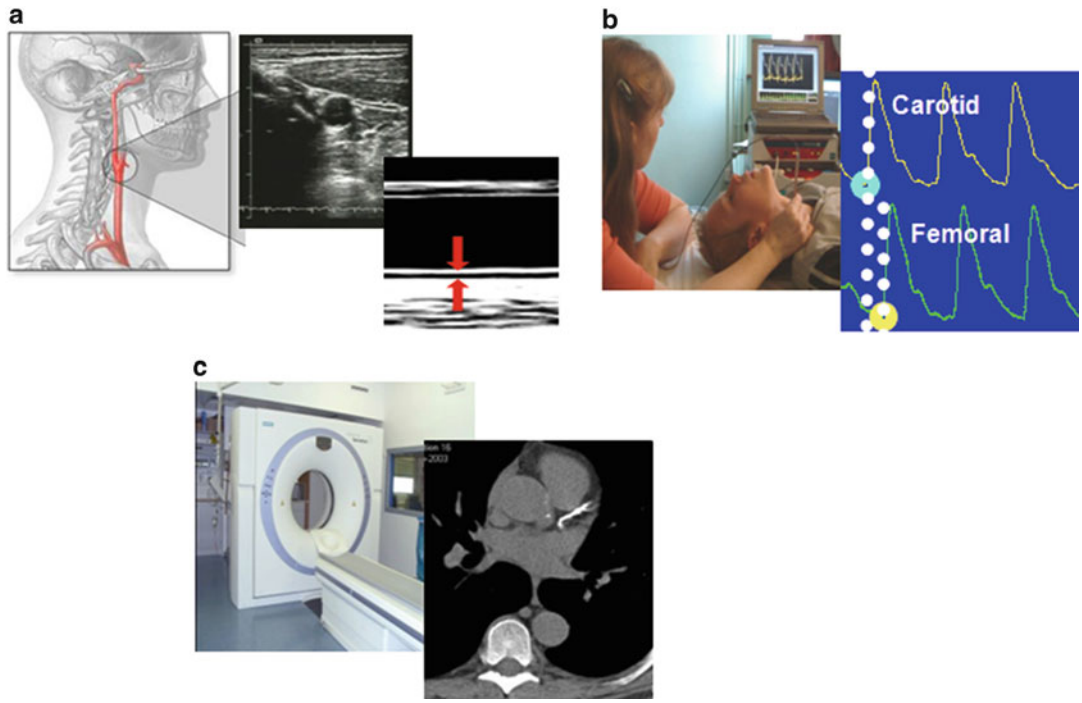

Fig. 26.1 Surrogate measures of cardiovascular risk in CKD patients. (**a**) High-resolution ultrasound of the common carotid artery to measure the carotid artery intima-media thickness (cIMT). (**b**) Tonometry to measure the pulse wave velocity. Inset shows carotid and femoral waveforms. (**c**) Multislice CT scan showing coronary artery calcification (*inset*)

described above. Some of the better defined biomarkers are vitamin D levels (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) [68–70] and FGF-23 [71], the physiological calcification inhibitors (fetuin-A, matrix Gla-protein, and osteoprotegerin) [72], endothelial microparticles, and cardiac troponin levels [73].

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 [20, 74, 75] and up to 80% of pediatric dialysis patients have LVH [3, 19, 76, 77]. Beyond childhood, in 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].

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 [74, 78, 79]. Given that many patients with advanced CKD are chronically hypervolemic, E/A ratio may not be an 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 studies have documented the presence of diastolic dysfunction by TDI [80–82], 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 [83]. 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 of overt systolic function abnormalities as assessed by LV contractility or endocardial shortening fraction (eSF), recent studies have demonstrated that subclinical systolic dysfunction 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 [84]. 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.

Key Pediatric Studies

A number of cross-sectional observational studies in pediatric dialysis patients or young adult survivors of pediatric dialysis programs have described surrogate measures of cardiovascular 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. Key studies in pediatric dialysis patients are presented in Table 26.2 and discussed below.

Table 26.2 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	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	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 0.3–3.7years)	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	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

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, 21, 85–87]. 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, 21, 59, 85–90], and PTH levels [2, 85, 90, 91], as well as 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 are shown to begin even in the first decade of life in children on dialysis [90] and in pre-dialysis CKD stages 2–4 as well [21, 87]. Importantly, although structural vascular changes are found in pre-dialysis patients, the vessel retains its normal compliance and distensibility properties as compared to controls [87]. 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 so that an increase in the carotid artery lumen occurs, possibly to counter the stiffness or loss of compliance of the vessel [21]. 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.

Although pediatric studies have no outcome data to support the poor prognostic effects of increased vascular stiffness, an association with increased cIMT and greater left ventricular mass index have been shown [89, 90]. In some studies, functional changes in the large arteries have shown a greater correlation with the systolic and diastolic blood pressure than with biochemical measures [21, 87].

Direct evidence of calcification in the coronary vessels has been shown in 15–20% of pediatric chronic dialysis patients [85, 90] 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 vs. 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 first shown by Goodman et al. [86, 90]. 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 [86, 90]. 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 [59]. 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. Fascinatingly, in all studies patients who did not have baseline calcification continued to remain free of calcification despite exposure to similar uremic conditions.

By ameliorating the uremic milieu, renal transplantation could intuitively be thought to reverse some of the cardiovascular damage from dialysis, but there is increasing evidence from adult studies to show that CVD remains a significant problem posttransplantation and 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 strict blood pressure control [92]. As cIMT progressively increases with age, this can be interpreted as a regression in cIMT when hypertension is ameliorated after transplantation [93]. Litwin et al. have shown that cIMT thickening and remodeling of the vessel wall begin early in CKD and progress rapidly on dialysis, correlating with the blood pressure and mean serum phosphate levels. Successful transplantation can improve the cIMT toward predialysis values, but cannot normalize it [94].

Physiological Inhibitors of Calcification

Vascular calcification occurs in the majority of patients with CKD, but a subset of patients do not develop calcification despite exposure to a similar uremic environment [53]. 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 [67].

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 by "shielding" mechanisms prevents further crystal growth. Fetuin-A is a negative acute phase reactant, and in the pro-inflammatory dialysis milieu its production may be reduced [53]. Several studies have reported that adults on dialysis have significantly lower fetuin-A levels than controls. Interestingly, a protective upregulation of fetuin-A has been reported in pediatric dialysis patients, but with increasing dialysis vintage, in the pro-calcific and pro-inflammatory uremic milieu fetuin-A levels decreased [72]. At the VSMC level, fetuin-A can inhibit apoptosis, enhance phagocytosis, and protect the smooth muscle cell from calcifying [72, 95]. Another group has reported lower fetuin-A levels in pediatric transplant recipients, but did not find an association with vascular measures [96].

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]. 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 [72, 97]. Osteoprotegerin and pyrophosphate are other potent calcification inhibitors that are shown to be perturbed in children with CKD [72]. While further longitudinal studies are required to fully characterize these circulating biomarkers, 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% [98], and have shown that deficiency begins early in the course of renal decline [99]. 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 [99]. 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 $1,25(OH)_2D$ [100]. The synthesis, metabolism, and interactions of vitamin D in the Ca–P–PTH axis are shown in Fig. 26.2.

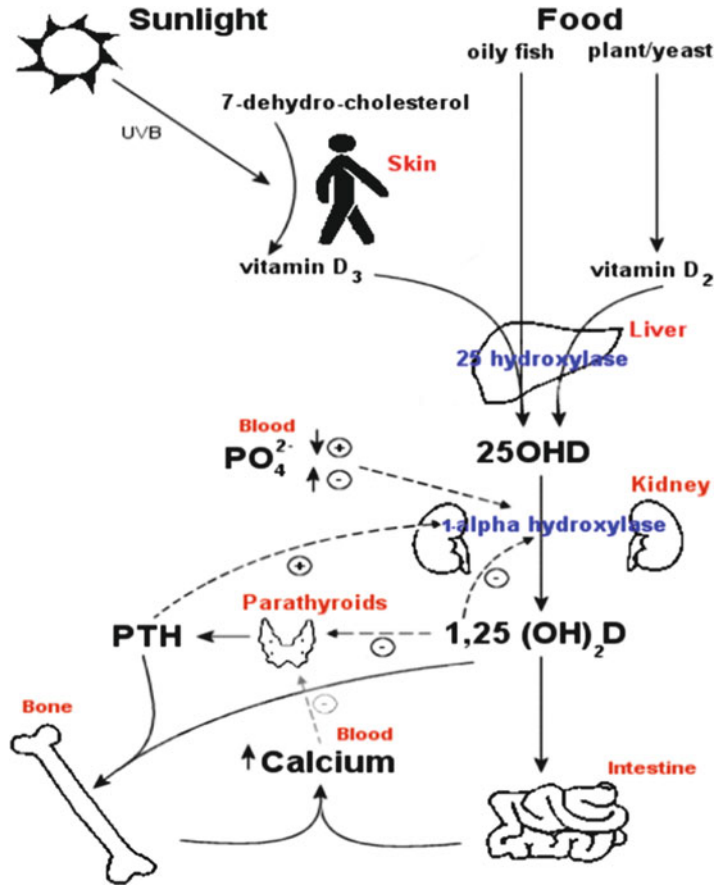

Fig. 26.2 The synthesis, metabolism, and interactions of vitamin D in the Ca–P–PTH axis

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 $1,25(OH)_2D$ [98]. In the cardiovascular system, vitamin D acts as a negative endocrine regulator of the renin–angiotensin system [101], inhibits atrial natriuretic peptide [102], increases myocardial contractility, and reduces cardiomyocyte hypertrophy [103]. 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 [68–70].

Clinical studies in children have examined the effects of vitamin D therapy on vascular measures and calcification (Table 26.2) and shown that both CAC and cIMT correlated with a higher calcitriol dosage [21, 56, 87, 90]. 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 [56]. These effects may be determined by the effects of vitamin D on Ca–P homeostasis as well as its pro-inflammatory effect [56].

The Vascular Biology of Calcification

In recent years, converging evidence from in vitro studies, molecular genetics 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 [42]. In response to raised extracellular Ca and P levels, VSMCs undergo specific phenotypic changes including apoptosis, osteo/chondrocytic differentiation,

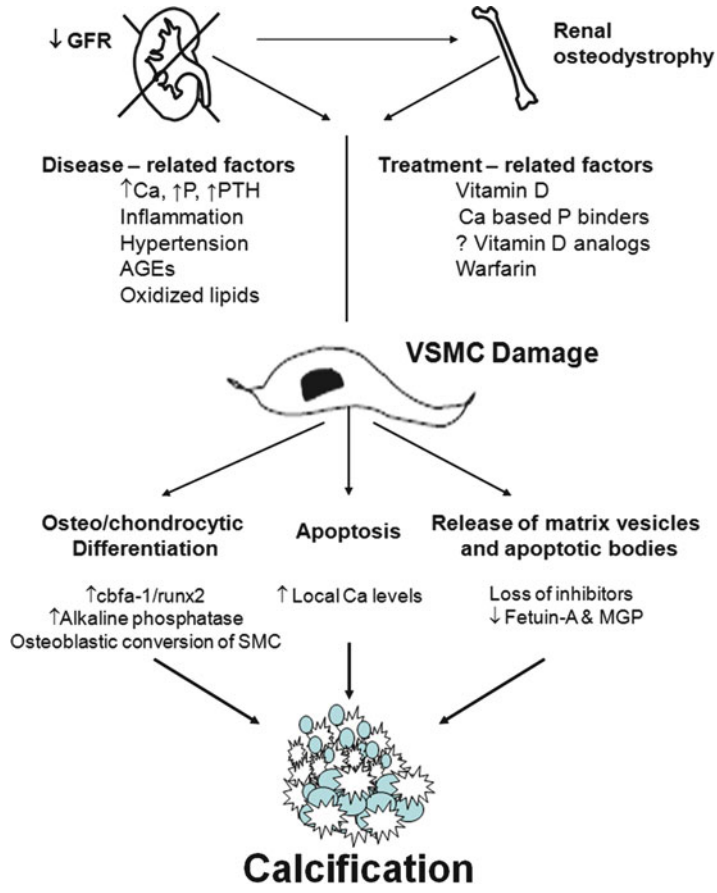

Fig. 26.3 A schematic diagram showing disease-related and treatment-related risk factors that lead to vascular smooth muscle cell (VSMC) damage and the mechanisms that drive accelerated calcification

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 [42]. 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 [41, 42, 104]. A schematic diagram showing key events in the calcification process is shown in Fig. 26.3.

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 [67]. 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 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 [105]. This suggests that dialysis vessels have lost protective mechanisms; exposure to the uraemic 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 [105], 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 analogues.

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 [42]. 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) [106]. They propose 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 osteodystrophy 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 analogues 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 (predialysis, 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 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 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 more aggressive HD to improve patient outcome [24, 107–109]. The adult literature also supports the potential for improved outcomes with more frequent and more aggressive HD [110, 111] 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 [112, 113], but not all patients are willing or able to perform home-based therapy [114].

Management of Key Modifiable Risk Factors That Contribute to the Development and Progression of CVD in CKD

Fluid overload with associated hypertension 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 adults cardiovascular risk is a function of blood pressure, even below the arbitrary level that defines hypertension. This has led to a steady lowering of the recommended blood pressure target ranges in adults over the last few decades [115]. Pediatric studies linking blood pressure to cardiovascular outcomes are lacking so far. Therefore, the pediatric definition of hypertension is based on the blood pressure distribution in the general pediatric population from birth to age 18 years and is dependent on gender, age, and height. While earlier reports regarded children at the 95th blood pressure percentile as "high-normal," the most recent guidelines [116], recognizing the trend in adults, label blood pressure values between the 90th and 95th percentile or any value above 120/80 mmHg (whatever blood pressure threshold is lower, irrespective of age) as "pre-hypertensive." Systolic or diastolic blood pressure values exceeding the 95th percentile are labeled as hypertensive.

Ambulatory blood pressure monitoring (ABPM) is the method of choice for the diagnosis and therapeutic monitoring of arterial hypertension in pediatric as well as in adult patients [117–121]. ABPM correlates best with hypertensive end-organ damage in adults, and by providing a more representative observation of blood pressure throughout day and night in a nonmedical environment, ABPM allows recognition of intra- and interdialytic blood pressure changes over 24 or even 48 h (entire interdialytic interval). Moreover, ABPM allows quantification of circadian and even ultradian blood pressure and heart rate variability [122–124]. Ultradian rhythms are physiologic cycles that are completed in less than 24 h. In a large multicenter study of children with CKD, the ESCAPE Trial Group described marked blunting and delay of rhythmicity of both blood pressure and heart rate [125]. Observed changes in ultradian and circadian rhythms were independent of each other in these children; ultradian blood pressure amplitudes, but not the circadian amplitudes or conventional dipping parameters, were correlated with indices of renal function. This raises the possibility that ultradian rhythms play an independent role in CKD and that maintaining normal circadian blood pressure variation is a positive predictor of cardiovascular outcome. Recent data from the CKD cohort utilizing ABPM confirmed a high prevalence of hypertension in children with CKD stages 2–4 [126]. Based on a combination of ambulatory and casual blood pressure assessment, 38% of children had masked (normal casual but elevated ambulatory blood pressure) and 18% had confirmed (elevated casual and ambulatory blood pressure) hypertension. More importantly, the likelihood of having LVH was four times higher in those children identified as having masked hypertension compared to children with normal clinic and ambulatory BP.

In the child on dialysis, the presence of hypertension, as discussed above, is mostly related to fluid overload. Attainment of dry weight will result in lowering 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 [127] or assessment of the inferior vena cava diameter [128] may be helpful tools for the assessment of dry weight in combination with standard clinical measures. However, normotension does not exclude hypervolemia. 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 [129]. More frequent [24] or nocturnal dialysis [130] might also be helpful to maintain dry weight. Long-term data on the effects of strict blood pressure control on CVD in the pediatric dialysis population is lacking. An appropriate target for clinical use may be an interdialytic blood pressure below the 95th percentile.

Only when hypertension cannot be controlled by adequate volume control should pharmacological antihypertensive treatment be considered.

Drug classes acceptable for use in children include ACE inhibitors, angiotensin-receptor blockers, ß-receptor blockers, calcium channel blockers, and diuretics [116]. Angiotensin-converting enzyme inhibitors (ACEi), Ca-channel blockers, and ß-blocker, 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 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).

Meticulous attention to volume control is the treatment strategy most likely to result in improvement of LVH in the maintenance dialysis patient, although there is a role for antihypertensive therapy (specifically ACE inhibition) as well. There is no consensus on how frequent echocardiographic monitoring for LVH should be performed in pediatric CKD patients. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients [131] 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 structure and function. There is also no consensus on the definition of LVH in children. Some define LVH based on the left ventricular mass (LVM) index, defined as left ventricular mass in grams/(height in meters)$^{2.7}$. An LVM index ≥ 38 g/m$^{2.7}$, the 95th percentile value in healthy children, has been used as a single cut point to define LVH [132]. However, the use of this single cut point overestimates the prevalence of LVH, especially in young children. Recently published pediatric reference values for LVM index might be more appropriate for use in children since they are age and gender-specific [133]. On 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 [134]. Given that children with CKD have significantly reduced height relative to age, normative values according to age should take into account the patient's height, especially in those with height <110 cm.

Ca–P–PTH 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 [43, 135]. 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. The K/DOQI have set higher levels 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 [106].

Although dietary management may be adequate to control plasma phosphate in its early stages, most patients develop hyperphosphataemia 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 [136].

A normal diet contains around 800–1,500 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 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.

Phosphate 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., 2,400 mg per week) and 300 mg per day in adults on PD (i.e., 2,100 mg/week). In a diet containing ~1,000 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 [137]. 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 the most effective for removing phosphate, to the point that some patients need phosphate supplementation [114].

Phosphate binders are usually divided into calcium containing and non-calcium containing [137, 138]. Calcium-containing preparations have been used the longest but have fallen out of favor because of their theoretical link with soft tissue calcification; the fear of ectopic calcification with excess calcium intake has led to a switch to newer non-calcium-containing drugs. Currently there is no calcium-free phosphate binder that is licensed for use in children. 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, whereas maximal binding of calcium to phosphate is at a higher pH. It is not, therefore, 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 [137].

Several new non-calcium-containing phosphate binders: magnesium carbonate, sevelamer hydrochloride, and lanthanum carbonate are now available [137, 138]. Sevelamer, the most widely used in children, is a nonabsorbable polymer of allyamine hydrochloride, that acts like an exchange resin [139]. As well as phosphate, sevelamer also binds bile salts, thereby exerting a beneficial effect on plasma total and low-density cholesterol, but it also binds fat-soluble vitamins. The first report of the use of sevelamer in children appeared in 2003 [139]. In a randomized, crossover trial of 8 weeks of treatment with sevelamer alternating with calcium acetate in 18 children with CKD, phosphate control was similar but with fewer episodes of hypercalcemia in the sevelamer group, although acidosis was more common [140]. In two studies from the same center, children on PD with bone biopsy proven secondary hyperparathyroidism who were also taking vitamin D were randomly assigned to calcium carbonate or sevelamer for 8 months. 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 increase the safety of treatment with activated vitamin D in patients with secondary hyperparathyroidism [141, 142]. On the other hand, 20% of the sevelamer treated group needed calcium supplements [141], and the development of hypocalcaemia is as high as 24% in adult studies [143].

There is evidence that sevelamer can attenuate the progress of coronary and aortic calcification when compared to calcium-based phosphate binders, either by increasing bone turnover, and/or through its effects on lipid metabolism [46]. However, a study of progression of CAC in 48 children over 2 years with CKD stage 5 was not

able to demonstrate such a link [144]. Despite the benefits of sevelamer seen in relatively short-term studies, these benefits have not been shown to be translatable into an improvement in mortality. The Dialysis Clinical Outcomes Revisited trial found no difference in the mortality rate at 2 years in just over 2,000 adult HD patients randomized to either sevelamer or calcium-based binders, being 26% and 27%, respectively, despite the additional lipid-lowering benefits of sevelamer [145].

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 is used [43]. An interesting new approach is the use of chewing gum to remove salivary phosphate between meals: Chitosan is a natural polymer that binds phosphate [146]. 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 [146].

The use of calcimimetics presents a paradigm shift in our management of mineral dysregulation in CKD [147–149]. They allow for higher vitamin D usage and are overall thought to be safe in children [149], but 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 [150].

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 [29, 151, 152]. 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 [153]. 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. Dietary supplementation of fish oil effectively improved lipid profiles in a small cohort of children receiving renal replacement therapy [154].

Statins effectively lower cholesterol and triglyceride levels in CKD patients by up to 30% [43]. This is suggestive of a beneficial effect on CVD, and most studies demonstrated significant CVD risk reduction [155–157]. However, a recent large randomized prospective trial in hemodialyzed adults with diabetic nephropathy [155] showed no effect of statin therapy on overall patient mortality despite significant reduction of lipid levels. A pooled analysis of 30 completed clinical trials [156] analyzing the efficacy and safety of fluvastatin in adult patients with mild to severe chronic renal failure suggested a reduction of cardiac death and nonfatal myocardial infarction. However, treatment did not reduce the rate of coronary intervention procedures. No conclusive data are available on the overall mortality risk reduction associated with statin therapy in CKD patients.

In younger children, statins are used reluctantly as the impact of HMG-CoA reductase inhibitors on nutrition, growth, and pubertal maturation has not been fully elucidated. For children on dialysis, K/DOQI recommends restricting statin treatment to children >10 years with LDL levels >160 mg/dL (> 4.16 mmol/L) and non-HDL cholesterol > 190 mg/dL (>4.94 mmol/L) [43]. Long-term data on efficacy in pediatric patients is not available and safety information on use of statins in children is not conclusive. 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. This includes optimal nutrition (with tube feeding as necessary), prevention or correction of hypoalbuminemia, 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 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:S112–9.
2. 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.
3. Gruppen MP, Groothoff JW, Prins M, van der Wouw P, Offringa M, Bos WJ, Davin JC, Heymans HS. Cardiac disease in young adult patients with end-stage renal disease since childhood: a Dutch cohort study. Kidney Int. 2003;63:1058–65.
4. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. J Pediatr. 2002; 141:191–7.
5. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350:2654–62.
6. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62:648–53.
7. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright Jr JT. 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: 853–906.
8. 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;351:1296–305.
9. McGill Jr HC, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC, Strong JP. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000;20:1998–2004.
10. Berenson GS, Srinivasan SR, Bao W, Newman III WP, 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;338:1650–6.
11. PDAY Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA. 1990;264:3018–24.
12. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman III WP, Herderick EE, Cornhill JF. 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: 727–35.
13. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. 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;114:2710–38.
14. Lingens N, Dobos E, Witte K, Busch C, Lemmer B, Klaus G, Schärer K. Twenty-four-hour ambulatory blood pressure profiles in pediatric patients after renal transplantation. Pediatr Nephrol. 1997;11: 23–6.
15. Schaefer F, Mehls O. Hypertension in chronic kidney disease. In: Portman RJ, Sorof JM, Ingelfinger JR, Totowa NJ, editors. Pediatric Hypertension. Totowa: Humana Press; 2004. p. 371–87.
16. Seeman T, Simkova E, Kreisinger J, Vondrak K, Dusek J, Gilik J, Feber J, Dvorak P, Janda J. Control

of hypertension in children after renal transplantation. Pediatr Transplant. 2006;10:316–22.
17. 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.
18. Tkaczyk M, Nowicki M, Balasz-Chmielewska I, Boguszewska-Baczkowska H, Drozdz D, Kollataj B, Jarmolinski T, Jobs K, Kilis-Pstrusinska K, Leszczynska B, Makulska I, Runowski D, Stankiewicz R, Szczepanska M, Wiercinski R, Grenda R, Kanik A, Pietrzyk JA, Roszkowska-Blaim M, Szprynger K, Zachwieja J, Zajaczkowska MM, Zoch-Zwierz W, Zwolinska D, Zurowska A. Hypertension in dialysed children: the prevalence and therapeutic approach in Poland – a nationwide survey. Nephrol Dial Transplant. 2006;21:736–42.
19. 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;14:898–902.
20. 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;107:864–8.
21. Litwin M, Wuhl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, Jobs K, Grenda R, Wawer ZT, Rajszys P, Troger J, Mehls O, Schaefer F. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol. 2005;16:1494–500.
22. Vandevoorde RG, Barletta GM, Chand DH, Dresner IG, Lane J, Leiser J, Lin JJ, Pan CG, Patel H, Valentini RP, Mitsnefes MM. Blood pressure control in pediatric hemodialysis: the Midwest Pediatric Nephrology Consortium Study. Pediatr Nephrol. 2007;22:547–53.
23. Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J. In-center daily on-line hemodiafiltration: a 4-year experience in children. Clin Nephrol. 2008;69: 279–84.
24. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children in chronic dialysis. Nephrol Dial Transplant. epub ahead of print: 2009.
25. Mitsnefes MM, Barletta GM, Dresner IG, Chand DH, Geary D, Lin JJ, Patel H. Severe cardiac hypertrophy and long-term dialysis: the Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol. 2006;21:1167–70.
26. Ulinski T, Genty J, Viau C, Tillous-Borde I, Deschenes G. Reduction of left ventricular hypertrophy in children undergoing hemodialysis. Pediatr Nephrol. 2006;21:1171–8.
27. Muntner P, Coresh J, Clinton Smith J, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int. 2000;58:293–301.
28. Cheng SC, Chu TS, Huang KY, Chen YM, Chang WK, Tsai TJ, Wu KD. Association of hypertriglyceridemia and insulin resistance in uremic patients undergoing CAPD. Perit Dial Int. 2001;21:282–9.
29. Mak RH. 1,25-Dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia. Kidney Int. 1998;53:1353–7.
30. Mak RH. Effect of metabolic acidosis on hyperlipidemia in uremia. Pediatr Nephrol. 1999;13:891–3.
31. 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: 88–95.
32. Horkko S, Huttunen K, Kesaniemi YA. Decreased clearance of low-density lipoproteins in uremic patients under dialysis treatment. Kidney Int. 1995; 47:1732–40.
33. Saland MJ, Ginsberg H, Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology, and management. Curr Opin Pediatr. 2002;14: 197–204.
34. Wang X, Axelsson J, Nordfors L, Qureshi AR, Avesani C, Barany P, Schalling M, Heimbürger O, Lindholm B, Stenvinkel P. 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: 196–202.
35. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis. 2001;38:1343–50.
36. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol. 2004;43:1439–44.
37. 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;31:607–17.
38. Prie D, Urena TP, Friedlander G. Latest findings in phosphate homeostasis. Kidney Int. 2009;75:882–9.
39. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16:520–8.
40. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22:2909–16.
41. Giachelli CM. Vascular calcification: in vitro evidence for the role of inorganic phosphate. J Am Soc Nephrol. 2003;14:S300–4.
42. Shroff RC, Shanahan CM. The vascular biology of calcification. Semin Dial. 2007;20:103–9.

43. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003;42: S1–201.
44. Sigrist MK, McIntyre CW. Vascular calcification is associated with impaired microcirculatory function in chronic haemodialysis patients. Nephron Clin Pract. 2008;108:c121–6.
45. 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;15:1943–51.
46. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62:245–52.
47. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim R. The elefant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62:1524–38.
48. Wanner C, Zimmermann J, Schwedler S, Metzger T. Inflammation and cardiovascular risk in dialysis patients. Kidney Int Suppl. 2002;80:S99–102.
49. Herzig KA, Purdie DM, Chang W, Brown AM, Hawley CM, Campbell SB, Sturtevant JM, Isbel NM, Nicol DL, Johnson DW. Is c-reactive protein a useful predictor of outcome in peritoneal dialysis patients? J Am Soc Nephrol. 2001;12:814–21.
50. Bakkaloglu S, 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 Peritoneal Dialysis Study Group (TUPEPD) report. Nephrol Dial Transplant. 2009;24:3525–32.
51. Aguilera A, Sanchez-Tomero JA, Bajo MA, Ruiz-Caravaca ML, Alvarez V, Del PG, Herranz A, Cuesta MV, Castro MJ, Selgas R. Malnutrition-inflammation syndrome is associated with endothelial dysfunction in peritoneal dialysis patients. Adv Perit Dial. 2003;19:240–5.
52. Pecoits-Filho R, Sylvestre LC, Stenvinkel P. Chronic kidney disease and inflammation in pediatric patients: from bench to playground. Pediatr Nephrol. 2005;20:714–20.
53. Ketteler M, Wanner C, Metzger T, Bongartz P, Westenfeld R, Gladziwa U, Schurgers LJ, Vermeer C, Jahnen-Dechent W, Floege J. Deficiencies of calcium-regulatory proteins in dialysis patients: a novel concept of cardiovascular calcification in uremia. Kidney Int Suppl. 2003;84:S84–7.
54. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, Lui SF, Li PK, Sanderson JE. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. 2005;20:1676–85.
55. Levin A, Li YC. Vitamin D and its analogues: do they protect against cardiovascular disease in patients with kidney disease? Kidney Int. 2005;68:1973–81.
56. Shroff R, Egerton M, Bridel M, Shah V, Donald AE, Cole TJ, Hiorns MP, Deanfield JE, Rees L. A bimodal association of vitamin D levels and vascular disease in children on dialysis. J Am Soc Nephrol. 2008;19: 1239–46.
57. Sasaki T, Watanabe M, Nagai Y, Hoshi T, Takasaw M, Nukata M, Taguchi A, Kitagawa K, Kinoshita N, Matsumoto M. Association of plasma homocysteine concentration with atherosclerotic carotid plaques and lacunar infarction. Stroke. 2002;33:1493–6.
58. Taruangsri P, Ong-Ajyooth L, Ong-Ajyooth S, Chaiyasoot W, Leowattana W, Sritippayawan S, Vreesangthip K, Chanchairujira T, Vasuvattakul S, Shayakul C, Vanichakarn S. Relationship between hyperhomocysteinemia and atherosclerosis in chronic hemodialyis patients. J Med Assoc Thai. 2005;88:1373–81.
59. Civilibal M, Caliskan S, Oflaz H, Sever L, Candan C, Canpolat N, Kasapcopur O, Bugra Z, Arisoy N. Traditional and 'new' cardiovascular risk markers and factors in pediatric dialysis patients. Pediatr Nephrol. 2007;22:1021–9.
60. Nett-Richards K, Kattenhorn M, Donald A, Oakley G, Varghese Z, Rees L, Deanfield JE. Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure? Circulation. 2002;105:1810–5.
61. Ebbing M, Bonaa KH, Nygard O, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, Njolstad I, Refsum H, Nilsen DW, Tverdal A, Meyer K, Vollset SE. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA. 2009;302: 2119–26.
62. 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: 457–62.
63. Staples AO, Wong CS, Smith JM, Gipson DS, Filler G, Warady BA, Martz K, Greenbaum LA. Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2009;4: 48–56.
64. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol. 2003;18:1055–62.
65. 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;12:80–4.
66. White CT, Schisler T, Er L, Djurdjev O, Matsuda-Abedini M. CKD following kidney transplantation in children and adolescents. Am J Kidney Dis. 2008;51:996–1004.
67. 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.

68. 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;349:446–56.
69. Tentori F, Hunt WC, Stidley CA, Rohrscheib MR, Bedrick EJ, Meyer KB, Johnson HK, Zager PG. Mortality risk among hemodialysis patients receiving different vitamin D analogs. Kidney Int. 2006;70:1858–65.
70. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo Jr CA, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72:1004–13.
71. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359:584–92.
72. Shroff RC, Shah V, Hiorns MP, Schoppet M, Hofbauer LC, Hawa G, Schurgers LJ, Singhal A, Merryweather I, Brogan P, Shanahan C, Deanfield J, Rees L. 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;23:3263–71.
73. Kanderian AS, Francis GS. Cardiac troponins and chronic kidney disease. Kidney Int. 2006;69:1112–4.
74. 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;50:998–1006.
75. Matteucci MC, Wühl E, Picca S, Mastrostefano A, Rinelli G, Romano C, Rizzoni G, Mehls O, de Simone G, Schaefer F. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. J Am Soc Nephrol. 2006;17:218–26.
76. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol. 1999;10:1606–15.
77. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol. 2002;13:1918–27.
78. Goren A, Glaser J, Drukker A. Diastolic function in children and adolescents on dialysis and after kidney transplantation: an echocardiographic assessment. Pediatr Nephrol. 1993;7:725–8.
79. Morris KP, Skinner JR, Wren C, Hunter S, Coulthard MG. Cardiac abnormalities in end stage renal failure and anaemia. Arch Dis Child. 1993;68:637–43.
80. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Impaired left ventricular diastolic function in children with chronic renal failure. Kidney Int. 2004;65:1461–6.
81. Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Abnormal cardiac function in children after renal transplantation. Am J Kidney Dis. 2004;43:721–6.
82. 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;94:1055–9.
83. Weaver Jr DJ, Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, Witt S, Glascock BJ, Kartal J, Khoury P, Mitsnefes MM. Decreased maximal aerobic capacity in pediatric chronic kidney disease. J Am Soc Nephrol. 2008;19:624–30.
84. Chinali M, De SG, Matteucci MC, Picca S, Mastrostefano A, Anarat A, Caliskan S, Jeck N, Neuhaus TJ, Peco-Antic A, Peruzzi L, Testa S, Mehls O, Wuhl E, Schaefer F. Reduced systolic myocardial function in children with chronic renal insufficiency. J Am Soc Nephrol. 2007;18:593–8.
85. Civilibal M, Caliskan S, Adaletli I, Oflaz H, Sever L, Candan C, Canpolat N, Kasapcopur O, Kuruoglu S, Arisoy N. Coronary artery calcifications in children with end-stage renal disease. Pediatr Nephrol. 2006;21:1426–33.
86. 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.
87. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: role of calcium-phosphorus metabolism. J Am Soc Nephrol. 2005;16:2796–803.
88. Briese S, Wiesner S, Will JC, Lembcke A, Opgen-Rhein B, Nissel R, Wernecke KD, Andreae J, Haffner D, Querfeld U. 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;21:1906–14.
89. Covic A, Mardare N, Gusbeth-Tatomir P, Brumaru O, Gavrilovici C, Munteanu M, Prisada O, Goldsmith DJ. Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant. 2006;21:729–35.
90. Shroff R, Donald A, Hiorns M, Watson A, Feather S, Milford D, Ellins E, Storry C, Deanfield J, Rees L. Parathyroid hormone level and the dose of calcitriol therapy relate to arterial structure and calcification in children on dialysis. J Am Soc Nephrol. 2007;Ref Type: In Press.
91. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Abnormal carotid artery structure and function in children and adolescents with successful renal transplantation. Circulation. 2004;110:97–101.
92. 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;12:412–9.
93. Mitsnefes MM. Understanding carotid artery intima-media thickness in childhood: lessons from studies

in children with renal transplants. Pediatr Transplant. 2008;12:377–80.
94. 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(8):2552.
95. Reynolds JL, Skepper JN, McNair R, Kasama T, Gupta K, Weissberg PL, Jahnen-Dechent W, Shanahan CM. Multifunctional roles for serum protein fetuin-a in inhibition of human vascular smooth muscle cell calcification. J Am Soc Nephrol. 2005; 16:2920–30.
96. van Summeren MJ, Hameleers JM, Schurgers LJ, Hoeks AP, Uiterwaal CS, Kruger T, Vermeer C, Kuis W, Lilien MR. Circulating calcification inhibitors and vascular properties in children after renal transplantation. Pediatr Nephrol. 2008;23(6):985–93.
97. Schurgers LJ, Teunissen KJ, Knapen MH, Kwaijtaal M, Van DR, Appels A, Reutelingsperger CP, Cleutjens JP, Vermeer C. 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;25:1629–33.
98. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
99. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL. 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;71:31–8.
100. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int. 1999;56:383–92.
101. 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;110:229–38.
102. Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS, Rigor DL, Stillman I, Tamez H, Kroeger PE, Wu-Wong RR, Karumanchi SA, Thadhani R, Kang PM. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci USA. 2007;104:16810–5.
103. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr. 2005;94:483–92.
104. Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM. Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? Kidney Int. 2008;73:384–90.
105. Shroff RC, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, Rees L, Shanahan CM. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. J Am Soc Nephrol. 2010;21:103–12.
106. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69:1945–53.
107. Bell L, Espinosa P. Intensive in-center hemodialysis for children: a case for longer dialysis duration. Hemodial Int. 2003;7:290–5.
108. Goldstein SL, Silverstein DM, Leung JC, Feig DI, Soletsky B, Knight C, Warady BA. Frequent hemodialysis with N×Stage system in pediatric patients receiving maintenance hemodialysis. Pediatr Nephrol. 2008;23:129–35.
109. Warady BA, Fischbach M, Geary D, Goldstein SL. Frequent hemodialysis in children. Adv Chronic Kidney Dis. 2007;14:297–303.
110. Maduell F, Navarro V, Torregrosa E, Rius A, Dicenta F, Cruz MC, Ferrero JA. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. Kidney Int. 2003;64:305–13.
111. 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;23:2634–46.
112. Coyte PC, Young LG, Tipper BL, Mitchell VM, Stoffman PR, Willumsen J, Geary DF. An economic evaluation of hospital-based hemodialysis and home-based peritoneal dialysis for pediatric patients. Am J Kidney Dis. 1996;27:557–65.
113. 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;69:798–805.
114. 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.
115. Chobanian AV, Barkis GL, Black DL, Cushman WC, Green LA, Izzo JLJ, Jones DW, Materson BJ, Oparil S, Wright JTJ, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. JAMA. 2003;289: 2560–71.
116. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114: 555–76.
117. Mancia G, Parati G. Experience with 24-hour ambulatory blood pressure monitoring in hypertension. Anaheim, CA: Proceedings of the Annual Scientific Sessions of the American Heart Association; 1987. p. 1134–40.
118. Portman RJ, Yetman RJ, West MS. Efficacy of 24-hour ambulatory blood pressure monitoring in children. J Pediatr. 1991;118:842–9.
119. Reichert H, Lindinger A, Frey O, Mortzeck J, Kiefer J, Busch C, Hoffmann W. Ambulatory blood pressure monitoring in healthy schoolchildren. Pediatr Nephrol. 1995;9:282–6.

120. Flynn JT. Impact of ambulatory blood pressure monitoring on the management of hypertension in children. Blood Press Monit. 2000;5:211–6.
121. Koch VH, Colli A, Saito MI, Furusawa EA, Ignes E, Okay Y, Mion Jr D. Comparison between casual blood pressure and ambulatory blood pressure monitoring parameters in healthy and hypertensive adolescents. Blood Press Monit. 2000;5:281–9.
122. Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. Hypertension. 1987;9:209–15.
123. Sorof JM, Portman RJ. White coat hypertension in children with elevated casual blood pressure. J Pediatr. 2000;137:493–7.
124. Hadtstein C, Wühl E, Soergel M, Witte K, Schaefer F. Normative values for circadian and ultradian cardiovascular rhythms in childhood. Hypertension. 2004;43:547–54.
125. Wühl E, Hadtstein C, Mehls O, Schaefer F, ESCAPE trial group. Ultradian but not circadian blood pressure rhythms correlate with renal dysfunction in children with chronic renal failure. J Am Soc Nephrol. 2005;16:746–54.
126. Mitsnefes M, Flynn J, Cohn S, Samuels J, Blydt-Hansen T, Saland J, Kimball T, Furth S, Warady B. Masked hypertension associates with left ventricular hypertrophy in children with CKD. J Am Soc Nephrol. 2010;21:137–44.
127. Wühl E, Fusch C, Schärer K, Mehls O, Schaefer F. Assessment of total body water in paediatric patients on dialysis. Nephrol Dial Transplant. 1996;11:75–80.
128. Krause I, Birk E, Davidovits M, Cleper R, Blieden L, Pinhas L, Gamzo Z, Eisenstein B. Inferior vena cava diameter: a useful method for estimation of fluid status in children on hemodialysis. Nephrol Dial Transplant. 2001;16:1203–6.
129. Katzarski KS, Charra B, Luik AJ, Nisell J, Vino Filho JC, Leypoldt JK, Leunissen KM, Laurent G, Bergstrom J. Fluid state and blood pressure control in patients treated with long and short haemodialysis. Nephrol Dial Transplant. 1999;14:369–75.
130. 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.
131. National Kidney Foundation. K/DOQI clinical practice guidelines for Cardiovascular Disease in Dialysis Patients. www.kidney.org/Professionals/kdoqi/guidelines_cvd/dody_weight.htm. (2010). Ref Type: Electronic Citation.
132. De SG, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, Galderisi M, Devereux RB. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. Hypertension. 2005;45:64–8.
133. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr. 2009;22:709–14. (Epub 2009 May 7).
134. 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;117:2769–75.
135. Klaus G, Watson A, Edefonti A, Fischbach M, Ronnholm K, Schaefer F, Simkova E, Stefanidis CJ, Strazdins V, Vande WJ, Schroder C, Zurowska A, Ekim M. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. Pediatr Nephrol. 2006;21:151–9.
136. Isakova T, Gutierrez OM, Chang Y, Shah A, Tamez H, Smith K, Thadhani R, Wolf M. Phosphorus binders and survival on hemodialysis. J Am Soc Nephrol. 2009;20:388–96.
137. Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2009;25(3):385–94.
138. Salusky IB. A new era in phosphate binder therapy: what are the options? Kidney Int Suppl. 2006;105:S10–5.
139. Mahdavi H, Kuizon BD, Gales B, Wang HJ, Elashoff RM, Salusky IB. Sevelamer hydrochloride: an effective phosphate binder in dialyzed children. Pediatr Nephrol. 2003;18:1260–4.
140. Pieper AK, Haffner D, Hoppe B, Dittrich K, Offner G, Bonzel KE, John U, Frund S, Klaus G, Stubinger A, Duker G, Querfeld U. A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD. Am J Kidney Dis. 2006;47:625–35.
141. Salusky IB, Goodman WG, Sahney S, Gales B, Perilloux A, Wang HJ, Elashoff RM, Juppner H. 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;16:2501–8.
142. Wesseling-Perry K, Harkins GC, Wang HJ, Sahney S, Gales B, Elashoff RM, Juppner H, Salusky IB. Response of different PTH assays to therapy with sevelamer or CaCO3 and active vitamin D sterols. Pediatr Nephrol. 2009;24:1355–61.
143. Hutchison AJ. Oral phosphate binders. Kidney Int. 2009;75:906–14.
144. Civilibal M, Caliskan S, Kurugoglu S, Candan C, Canpolat N, Sever L, Kasapcopur O, Arisoy N. Progression of coronary calcification in pediatric chronic kidney disease stage 5. Pediatr Nephrol. 2009;24:555–63.
145. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT, Burke SK. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. Kidney Int. 2007;72:1130–7.
146. Savica V, Calo LA, Monardo P, Davis PA, Granata A, Santoro D, Savica R, Musolino R, Comelli MC, Bellinghieri G. Salivary phosphate-binding chewing gum reduces hyperphosphatemia in dialysis patients. J Am Soc Nephrol. 2009;20:639–44.

147. Drueke TB. Treatment of secondary hyperparathyroidism of dialysis patients with calcimimetics as a valuable addition to established therapeutic means. Pediatr Nephrol. 2005;20:399–403.
148. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2010; CD008327.
149. McKay CP, Portale A. Emerging topics in pediatric bone and mineral disorders 2008. Semin Nephrol. 2009;29:370–8.
150. Schaefer B, Schlosser K, Wuhl E, Schall P, Klaus G, Schaefer F, Schmitt CP. Long-term control of parathyroid hormone and calcium-phosphate metabolism after parathyroidectomy in children with chronic kidney disease. Nephrol Dial Transplant. 2010; 25(10):3213–21.
151. Mak RH. Metabolic effects of erythropoietin in patients on peritoneal dialysis. Pediatr Nephrol. 1998;12:660–5.
152. Mak RH. Effect of metabolic acidosis on insulin action and secretion in uremia. Kidney Int. 1998;54: 603–7.
153. National Kidney Foundation. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis. 2003;41(Suppl 3):S1–91.
154. Goren A, Stankiewicz H, Goldstein R, Drukker A. Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. Pediatrics. 1991;88:265–8.
155. Wanner C, Krane V. Lessons learnt from the 4D trial. Nephrol Ther. 2006;2:3–7.
156. Holdaas H, Wanner C, Abletshauser C, Gimpelewicz C, Isaacsohn J. The effect of fluvastatin on cardiac outcomes in patients with moderate to severe renal insufficiency: a pooled analysis of double -blind, randomized trials. Int J Cardiol. 2006; epub ahead of print.
157. Holdaas H, Fellstrom B, Jardine AG, Nyberg G, Gronhagen Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambuhl P, Logan JO, Staffler B, Gimpelewicz C, Alert Study Group. Beneficial effect of early initiation of lipid lowering therapy following renal transplantation. Nephrol Dial Transplant. 2005;20:974–80.

Management of Renal Anemia in Children with Chronic Kidney Disease

27

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Keywords
Renal anemia • Chronic kidney disease • Children pediatric diaylsis

Introduction

Renal anemia management is on the cusp of dramatic changes due to development of novel erythropoiesis-stimulating agents (ESAs) and new understandings of iron metabolism. As a result of a greater understanding of hypoxia-inducible factor (HIF) regulation and erythropoietin receptor binding site kinetics, the next generation of ESAs are being developed. The adverse effects of erythropoietin, which has been the treatment standard for renal anemia, have become more apparent and concerning. The increased risk of cardiac death associated with normalizing hemoglobins in adult dialysis patients and the lack of a survival benefit for cancer patients have pharmaceutical corporations "smelling blood in the water." The mechanism of action of hepcidin, a new iron-regulating molecule produced by the liver, provides a better understanding of why dialysis patients do not absorb oral iron well. There is also great interest in exploring how new ESAs, and particularly the prolyl hydroxylase inhibitors, impact hepcidin levels.

Interestingly, the early testing ground for many of the novel ESAs has been the world of road bicycle racing, where higher hemoglobins can yield faster racing times and victories. Some athletes have even been trying some of the new red blood cell replacement therapies. This chapter will review the new basic science findings, while providing a practical approach to the day-to-day management of anemia in children who require renal replacement therapy. So let us strap on our helmets and get ready for an adventure in anemia!

Normal Erythropoiesis

The formation of adequate numbers of mature erythrocytes is dependent on intricate regulation of many factors including HIF, erythropoietin (EPO), iron, vitamins, minerals, the transcription and translation of key proteins including hemoglobin (Hgb), transferrin, tissue ferritin, red blood cell membrane transport proteins, the formation of a phospholipid bilayer, and maintenance of a

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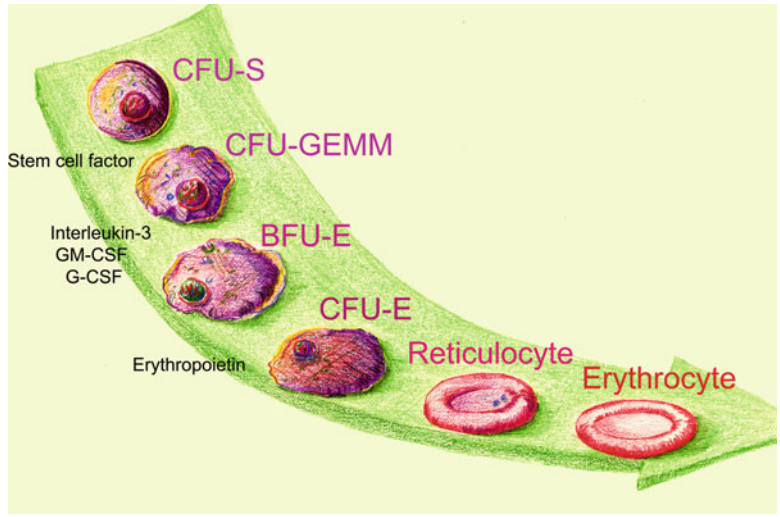

Fig. 27.1 Normal erythropoiesis. In the bone marrow, stem cells (CFU-S) give rise in sequence to colony forming unit- granulocyte, erythrocyte, macrophage, megakaryocyte (CFU-GEMM) cells, burst-forming unit-erythroid (BFU-E) cells, colony forming unit-erythroid (CFU-E) cells, reticulocytes, and mature erythrocytes. The sites of action for various cytokines, growth factors, and EPO are shown

normal bone marrow environment. Other, less critical factors which impact erythropoiesis will be discussed in the section related to rHuEPO (recombinant Human Erythropoietin) resistance.

Normal Erythropoiesis Begins with the Pluripotential Hematopoietic Stem Cell

Erythrocytes arise from pluripotential hematopoietic stem (CFU-S) cells in the bone marrow which, in sequence, give rise to the colony forming unit- granulocyte, erythrocyte, macrophage, megakaryocyte (CFU-GEMM) cells, primitive burst-forming unit-erythroid (BFU-E) cells, and colony forming unit-erythroid (CFU-E) cells (Fig. 27.1) [1]. With further maturation, CFU-E cells are transformed into erythroblasts which can synthesize Hgb. A small number of reticulocytes, young red blood cells which still have remnants of cytoplasmic RNA, are released in normal individuals. The number of reticulocytes released by the bone marrow increases in response to anemia and rHuEPO therapy. Once the remnants of cytoplasmic RNA are extruded, the cell is characterized as a mature erythrocyte. Under normal circumstances, the vast majority of erythrocytes released from the bone marrow are mature erythrocytes.

The normal differentiation and development of erythrocytes is dependent on the sequential cascade of various cytokines, growth factors, and EPO. Differentiation from pluripotent hematopoietic stem cells to more mature erythroid cells is influenced by stem cell factor (SCF) [2, 3], interleukin-3 (IL-3) [4–7], granulocyte colony-stimulating factor (G-CSF) [8–11], granulocyte macrophage colony-stimulating factor (GM-CSF) [12], and thrombopoietin. Androgens [13, 14], thyroid hormone [15, 16], insulin [17], insulin-like growth factor I [18], and catecholamines [19, 20] appear to play stimulatory roles in erythropoiesis, while tumor necrosis factor alpha (TNF α) [21–24], interferon α [25], and transforming growth factor beta (TGF β) [26–28] appear to inhibit erythropoiesis.

Absence of EPO causes Fas-mediated apoptosis of BFU-E [2, 29–31]. Late-stage erythroid progenitor cells have been shown to be dependent on the continuing presence of EPO [32]. Thus, EPO does not induce erythrocyte proliferation, but instead, suppresses erythroid apoptosis [33, 34], which is employed by the bone marrow to regulate the production of specific cell lines. Maturing erythroid cells are primed for apoptosis. Apoptosis begins when erythroid cells are EPO deprived for as little as 2 h [35]. The process of apoptosis can be inhibited by either SCF or EPO and can be totally prevented by the presence of both factors. Stem cell factor has been shown to downregulate the expression of Fas ligand, through the PI3 pathway [36]. Erythropoietin appears to inhibit apoptosis via the extracellular signal-regulated kinase

(ERK) pathway [36]. Erythropoietin induction of c-Jun [37] and maintenance of GATA-2 and the Bcl-2 expression through activation of protein kinase C (PKC) [35, 38] appear to play minor roles in the inhibition of apoptosis.

Mature erythrocytes are biconcave cells with the unique and specific task of oxygen and carbon dioxide transport [39, 40]. Erythrocytes are unique due to the absence of any nucleus, ribosomes, mitochondria, DNA, or RNA. After the reticulocyte degrades and expels all remaining RNA, the cell is incapable of synthesizing proteins. Erythrocyte energy is derived from aerobic glycolysis; the Krebs cycle is inactive. The deformable erythrocyte membrane is composed of a phospholipid bilayer that acts like a viscous solution with mobile proteins "floating" within it. In response to hemodialysis, the phospholipid bilayer changes, making the erythrocyte more osmotically fragile [41]. Interestingly, erythropoietin therapy appears to improve erythrocyte deformability [42].

The erythrocyte life span is reduced in children with chronic renal failure (CRF) [43] and in healthy neonates [44]. In a study of 19 hemodialysis-dependent children performed by Muller-Wiefel et al. [45], erythrocyte life span decreased to approximately 60 days (healthy adult = 120 days) when the mean blood urea nitrogen was 80 mg/dL. After the erythrocytes have circulated, they are degraded by mononuclear phagocytes in the spleen.

Iron is Needed to Form the Erythrocyte Hemoglobin Molecule

More than 95% of the erythrocyte's protein is hemoglobin (Hgb). Iron is an integral component of the Hb molecule and is essential for a multitude of cellular processes. Although quantitatively Hgb and myoglobin contain by far the most iron, a vast number of other proteins and enzymes utilize iron for energy metabolism and DNA synthesis [46, 47].

The majority of iron available for use or storage results from the catabolism of Hgb from senescent red blood cells by the reticuloendothelial system. However in order to maintain steady state, the 1–2 mg of iron lost in the stool is replaced by iron absorbed from food in the duodenum and upper jejunum [48]. Iron can be found in the diet as either heme iron, in which the iron is within myoglobin or hemoglobin, or non-heme iron found in vegetables and cereals. Heme iron has a relatively higher bioavailability compared to non-heme iron and in the future iron supplementation may take advantage of this greater bioavailability (see below) [49]. Non-heme iron, in the form of Fe3+ is first reduced by an iron reductatase (likely duodenal cytochrome B, although other reductases may be involved) located on the brush border of enterocytes [50]. Fe2+ is then transported into enterocytes via the divalent metal ion transporter 1 (DMT1) [51]. Once inside the enterocyte, Fe2+'s fate depends on the body's iron demand. If iron is not required, it is stored within the polymeric protein ferritin and eventually returns to the intestinal lumen when the enterocyte is shed [52]. However if the iron is required it is transported across the basolateral membrane by ferroportin, the only plasma membrane iron export protein to be identified. Iron is then oxidized to Fe3+ and bound to transferrin, a plasma glycoprotein with a molecular weight of 80 kD that is responsible for transporting the iron to storage and utilization sites [53].

Transferrin delivers its iron payload to cells principally via high affinity binding to the plasma membrane protein transferrin receptor 1 (TfR1) [54]. Transferrin along with TfR1 enters the cell's interior via receptor-mediated endocytosis. The resultant endosomes are acidified, and iron is released from transferrin. Iron then moves out of the endosomes through DMT1 and if needed it is used for incorporation into literally hundreds of proteins, including the most abundant iron-containing proteins, hemoglobin and myoglobin. Iron that is not immediately needed is stored within ferritin, the main storage molecule for intracellular iron. Ferritin is a hollow sphere with an external diameter of 12–13 nm made up of 2 subunits (H and L) [55] which can store up to 4,000 iron atoms. Iron can also be stored in hemosiderin which results from the aggregation and breakdown of ferritin by lysosomal enzymes

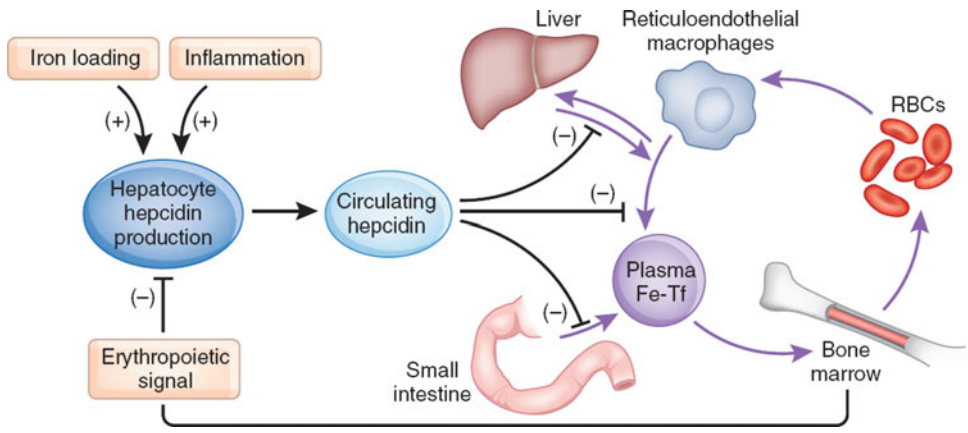

Fig. 27.2 Hepcidin regulation

Due to chronic blood loss, often thought to be from the gastrointestinal tract, and frequent laboratory testing, adults on peritoneal dialysis require roughly 0.7–1 g of parenteral iron annually. Hemodialysis patients, presumably due to additional blood loss in the dialyzer and tubing have a higher requirement of approximately 2–2.5 g of iron per year [56, 57]. Due to the paucity of data, the annual iron requirements for pediatric dialysis patients are based on adult data with an estimated annual iron need of 0.9 gm/1.73 m [2] and 1.6 g/1.73 m [2] for pediatric peritoneal and hemodialysis patients respectively.

Hepcidin Regulates the Ferroportin-Based Movement of Iron

Recently there have been tremendous advances in our understanding of iron homeostasis. Specifically a small peptide produced by the liver, hepcidin, has been identified as the key regulator of iron homeostasis (Fig. 27.2) [58–60]. Hepcidin's biological actions are mediated by its binding to ferroportin. Once hepcidin is bound, it causes the rapid internalization and degradation of ferroportin [61]. In the case of duodenal enterocytes, high hepcidin prevents the movement of dietary iron through ferroportin into the circulation. In macrophages and hepatocytes, high hepcidin levels similarly prevent the movement of stored iron into the circulation. The rapid sequestration of iron in macrophages and the long-term decrease of enteral iron absorption eventually lead to anemia by decreasing iron availability for erythropoiesis. Conversely, the absence of hepcidin leads to unregulated duodenal iron absorption and subsequent iron overload. In fact it is now apparent that most forms of hereditary hemochromatosis result from a deficiency of hepcidin, either through mutation of the hepcidin gene or mutations of genes that are suspected to regulate hepcidin expression [62].

Hepcidin levels are regulated by at least three independent mechanisms. While both inflammation and iron loading induce hepcidin production, erythropoietic activity suppresses its production. Studies in humans with chronic infections and severe inflammatory disease have shown markedly increased levels of hepcidin, strongly suggesting that elevated hepcidin levels play a key role in the anemia of inflammation and reticuloendothelial blockade [63]. The regulation of hepcidin via iron loading appears to be mediated by the bone morphogenetic protein receptor (BMP) complex at the surface of hepatocytes [64–66]. This complex includes two proteins known to be mutated in various forms of hereditary hemochromatosis, HFE and hemojuvelin. Although the exact molecular mechanism is not yet completely understood, this BMP receptor complex interacts with transferrin receptors 1 and 2, likely linking the sensing of serum iron with hepcidin production [67, 68]. Finally, the regulation of hepcidin production by erythropoiesis remains poorly understood. One or more

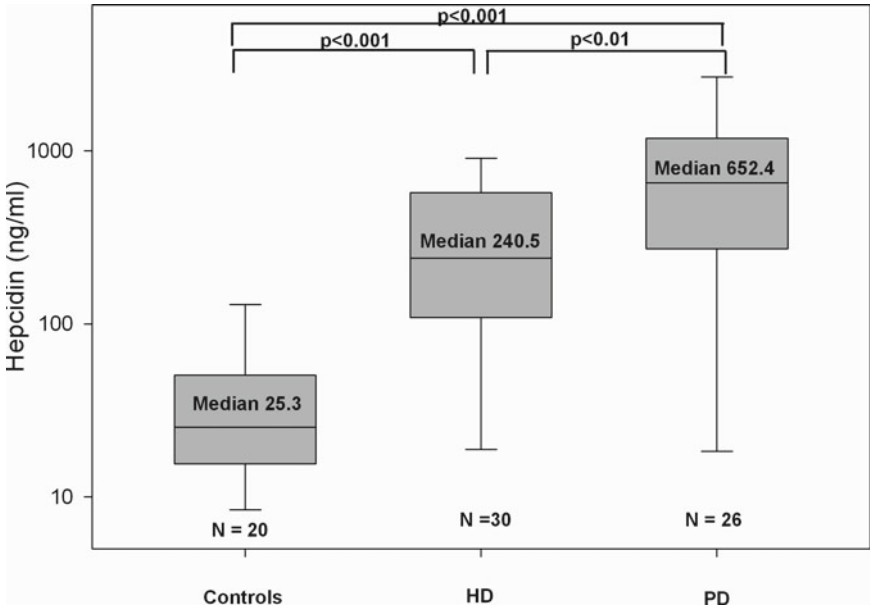

Fig. 27.3 Hepcidin levels

unidentified bone marrow derived signals generated during increased erythropoiesis causes decreased hepcidin production [69, 70]. Thus, the increased demand for iron incorporation into hemoglobin is met by increased enteral iron absorption and release of stored iron from the reticuloendothelial system.

Preliminary studies have demonstrated that hepcidin levels are elevated across the spectrum of CKD [71, 72]. In particular, both pediatric peritoneal and hemodialysis patients have been shown to have hepcidin levels several times that of healthy controls (Fig. 27.3). Although the etiology of this increase has yet to be determined, elevated levels of hepcidin may help to explain the relative resistance to enteral iron seen in dialysis patients and the frequent need for intravenous iron therapy.

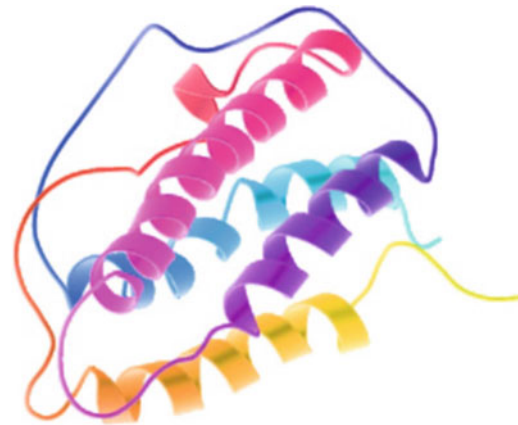

Fig. 27.4 Molecular structure of erythropoietin (Published with permission from Cheetham et al. [119])

Transcriptional Control of the Erythropoietin Gene is Controlled by Hypoxia-Inducible Factor (HIF)

Erythropoiesis is primarily regulated by erythropoietin [32, 73] (Fig. 27.4). EPO is primarily produced by kidney fibroblast-like interstitial cells [74–77], adjacent to the proximal tubule (Fig. 27.5) [74, 78], and is released into peritubular capillaries. Interestingly, hypoxia increases kidney interstitial fibroblast cell numbers [79]. A small amount of EPO is produced by hepatocytes (~10%) [80, 81] and macrophages [82], and is detectable in human breast milk [83]. In the fetus, EPO mRNA is found in the liver, renal interstitial and proximal tubule cells, neural retina of the eye, and in the adrenal cortex [77]. The human EPO gene [81], characterized by four introns and five exons, is located on chromosome

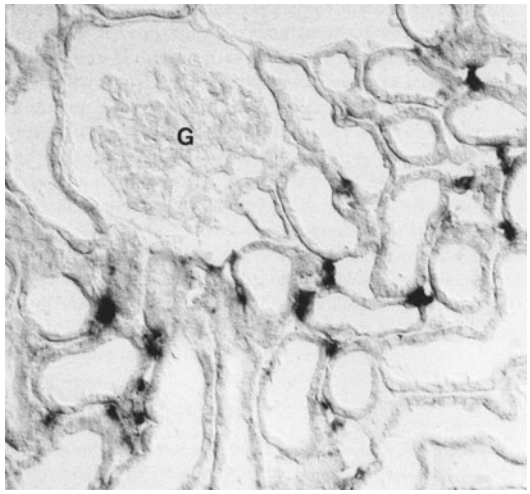

Fig. 27.5 Erythropoietin RNA expression in kidney interstitial cells. Erythropoietin-synthesizing cells in the rat renal cortex. The dark areas indicate the location of EPO mRNA. G= glomerulus (Published with permission from Bachmann [74])

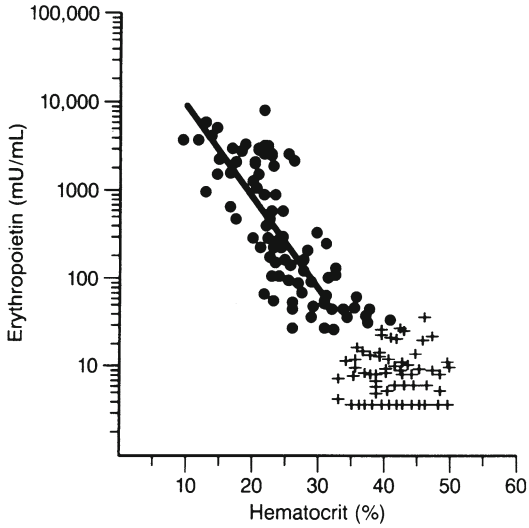

Fig. 27.6 Correlation between serum EPO levels and Hct values for patients with various renal diseases, rheumatoid arthritis, and sickle-cell disease. Patients represented by a "+" are normal blood donors bled one to three units (Published with permission from Erslev [178])

7 [84–86]. Transcriptional upregulation is primarily regulated by hypoxia-inducible factor (HIF-1) which binds in a downstream OCT-4 regulatory region of the EPO gene [87, 88]. Serum EPO levels increase logarithmically in response to decreasing Hct (Fig. 27.6) [89].

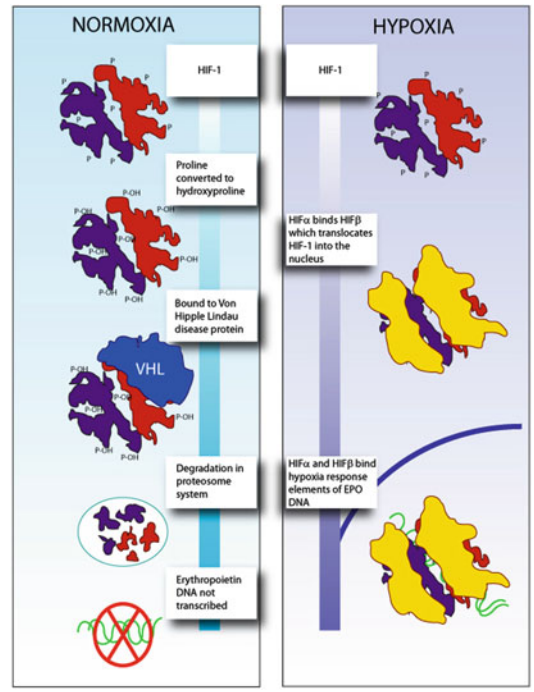

Fig. 27.7 Hypoxia-inducible factor. Normoxia causes prolyl hydroxylase to hydroxylate the proline molecules in the HIF. Van Hippel–Lindau protein binds to HIF causing transport via the ubiquitin system to the proteosome, where it is degraded. In conditions of hypoxia, prolyl hydroxylase function is inhibited. HIF binds to HIFb, translocated to the nucleus where is regulates the transcription of erythropoietin

Hypoxia-inducible factor is 120 kDa oxygen-sensitive basic-helix-loop-helix protein in the Per-ARNT-Sim (PAS) family [90]. There are three HIFs, a HIF-1α, HIF-2α, and HIF-3α. While HIF-1α is expressed in all tissues, HIF-2 α appears to be the dominant isoform regulating erythropoietin production in kidney interstitial cells [91–94]. Hypoxia-inducible factor-2α heterodimerizes with HIF −1 and -3β, which is also known as the aryl hydrocarbon receptor nuclear translocator (ARNT) [95] (Fig. 27.7). Together they translocate into the nucleus where they induce the transcription the erythropoietin gene [96–98]. Intracellular HIF levels increase exponentially in response to worsening hypoxia [99].

Prolyl hydroxylases play a major role regulating HIF function. There are three prolyl hydroxylases, PHD1, PHD2, and PHD3, which are inhibited by hypoxia, iron, and cobalt. Ascorbate,

which maintains iron in its reduced form, is required for the normal function of prolyl hydroxylases. PHD2 primarily interacts with HIF-2α. With normoxia, HIF is degraded by binding to the ubiquitin ligase Von Hippel–Lindau Disease (VHLD) protein complex and is targeted for proteosomal degradation [100]. Prolyl hydroxylase gene defects have been identified as causes of some polycythemias [94, 101–104]. Di-oxogluatarate carries oxygen to prolyl hydroxylase [105, 106] which uses it in the hydroxylation reaction involving the HIF proline molecules. Recent studies with prolyl hydroxylase inhibitors confirm that EPO production in the liver can be upregulated in adult dialysis patients to levels sufficient to maintain normal levels of hemoglobin [107].

The Erythropoietin Receptor

Erythropoietin binds to a specific erythropoietin receptor EPO-R [108], a 55 kD transmembrane protein. EPO-R is expressed on CFU-E and BFU-E [109, 110], endothelial cells [111, 112], myocardiocytes [113], renal podocytes [114], and neuronal cells [115, 116]. Erythropoietin and the EPO-R are widely distributed in the developing fetus [117, 118]. The EPO-R amino acid regions which are critical for EPO binding have been described [119–124]. Studies investigating the binding sites have determined that weak binding to the EPOR in the region are most effective in activating the receptor [125, 126]. When stimulated, the EPO receptor triggers signal transducers and activators of transcription (Stat) proteins [127], phosphorylation of RAS [128–130], Rho family GTPases [131], MAP kinase [3, 132] and PI3 [132–134] pathways.

The Clinical Management of Anemia

Definitions of Anemia in Children

Anemia can be defined by assessing a patient's Hb or Hct relative to normative values for an appropriate population or by using physiologic criteria. Population-based studies, like the National Health and Nutrition Examination Survey III [135, 136], have yielded important pediatric data relevant to the issue of anemia (Table 27.1). Normal Hb and Hct values were chosen based on ±2 standard deviations. The prevalence of anemia in otherwise healthy children between the ages of 1 and 18 years ranged from 1.5% to 5.9% [137] and was highest in infants (5.7%) and teenage girls (5.9%). There were differences in normative Hb levels relative to ethnicity. At all ages, African American children have lower Hb values than Caucasians [136] (Table 27.1). The lower Hb value in African Americans may have been attributable to mild thalassemias, which are frequently associated with lower Hct values. Evaluation of the Native American population demonstrates that Hb levels were similar to those seen in Caucasians [138].

As valuable as population-based definitions of anemia are, a specific Hct or Hb below normal may not correlate with clinical symptoms or demonstrable physiologic changes. No comprehensive study has been performed which correlates

Table 27.1 Comparison of normative hemoglobin values between White and African American Children

	White non-Hispanic			African American			
Age (years)	Mean	−2 STD	Sample size	Mean	−2 STD	Sample size	*P* Value
2–5	12.21	10.80	730	11.95	10.37	846	$P = 0.0006$
6–10	12.87	11.31	718	12.40	10.74	898	$P < 0.0001$
11–15 male	13.76	11.76	266	13.06	10.88	356	$P < 0.0001$
11–15 female	13.32	11.50	263	12.61	10.85	388	$P < 0.0001$
16–18 male	15.00	13.24	124	14.18	12.42	184	$P < 0.0001$
16–18 female	13.39	11.61	163	12.37	10.37	206	$P < 0.0001$

Sample size is 5,142 (White, 2,264; African American, 2,878)

Source: With permission from Robins and Blum [136]

specific Hct or Hb values with physiologic changes in cardiac function, cognitive function, and exercise tolerance.

Dialysis Outcome Quality Initiative (DOQI) Hemoglobin Targets for Children with End-Stage Renal Disease

The management of the anemia of renal disease has been a major focus of the Dialysis Outcomes Quality Initiative (DOQI) and the Kidney Disease Outcomes Quality Initiative (KDOQI). An evaluation for anemia should be triggered when the estimated glomerular filtration rate is less than 60 mL/min/1.73 m^2 [139]. A hemoglobin target of 11–12 g/dL has been established for adults. Although there were no specific recommendations regarding the treatment of children, pediatric nephrologists have adopted the DOQI treatment guidelines for the treatment of their patients.

Hb, rather than Hct, was selected as the more accurate indicator of anemia [140] because Hb is not affected by storage of the blood sample at room temperature [141], is more accurate in patients with hyperglycemia [142], is not affected by changes in plasma water and is more reproducible when different automated counters are used [143]. The NKF-K/DOQI definition of anemia is similar to the World Health Organization (WHO) definition of <120 g/L (<12 g/dL).

Incidence and Prevalence of Anemia in Children on Dialysis

Since EPO is produced by renal interstitial cells, one would anticipate worsening anemia as interstitial scarring and fibrosis worsens concurrent with decreasing renal excretory function. Indeed, Hct values decline in relationship to the glomerular filtration rate (GFR) [140]. Significant anemia is detected in nearly all CKD patients when their GFR is below 20 mL/min/1.73 m^2 [144].

Without intravenous or subcutaneous rHuEPO therapy, dialysis patients require red blood cell transfusions to avoid the adverse effects associated with profound anemia. In an era when rHuEPO was not available, a study of 93 pediatric peritoneal dialysis patients reported transfusions were required once per 1.5 treatment months in anephric patients and once per 3.3 treatment months in patients with kidneys [145]. In the absence of rHuEPO therapy, nearly all dialysis patients will require transfusions. There are significant risks associated with repeated blood transfusions including iron overload [146–150] and hemochromatosis, and the transmission of infectious agents such as hepatitis B, hepatitis C, cytomegalovirus, Epstein–Barr virus, and human immunodeficiency virus. In addition, the formation of anti-HLA-antibodies due to recipient exposure to donor leukocyte HLA antigens contained in blood transfusions prolongs the waiting time for deceased donor transplantation and can preclude living donor transplantation. Multiple (>5) pre-transplant blood transfusions have been shown to be a significant risk factor for graft failure in pediatric recipients [151].

The Clinical Presentation of Anemia

The clinical presentation of anemia depends on the rate of blood loss, the volume of blood lost, and the adaptability of the body (particularly the heart and lungs) to decreases in Hb concentration. If development of anemia occurs slowly, symptoms may include slight fatigue, pallor, increased somnolence, tachypnea, tachycardia, impaired cognition [152–159], depression [160], decreased skeletal muscle function [161], insomnia, and loss of appetite [162, 163]. Anemic adult dialysis patients are more likely to experience increased numbers of hospitalizations and increased mortality [164].

If the anemia is more rapid in onset or more severe, the symptoms may include dyspnea, tachycardia, dizziness, muscle weakness, fatigue, drowsiness, headache, and impaired mental concentration. If the anemia is severe and prolonged, salt and water retention occurs and edema develops. The clinical signs of anemia-induced volume overload may include a bounding pulse, a cardiac murmur, and gallop rhythms.

Patients with iron deficiency may have fatigue and lethargy out of proportion to the degree of the anemia. The tongue may become smooth and the patient may have pica, a condition in which the patient eats dirt, clay, or other non-digestible substances in response to cravings. Spooning of the fingernails or an esophageal web are rare presentations of severe iron deficiency.

The Benefits of Treating Anemia

Anemia has been shown to decrease exercise capacity in healthy children [165, 166]. Kapoor et al. [166] reported that anemic children had a lower gain in heart rate at peak exercise and lower total exercise duration at peak exercise when compared to normal controls. The partial correction of anemia in children with CKD improved exercise capacity [167] and decreased heart rate and resting oxygen consumption [168]. In a study performed by Martin et al. [167], half of the children studied were characterized as having decreased exercise capacity prior to rHuEPO therapy. One month after achieving partial correction of the Hct the group mean exercise capacity improved. Similar effects on exercise capacity were also reported by Morris et al. [168] who conducted a single-blind, placebo-controlled crossover study in 11 children with end-stage renal disease (ESRD). Warady et al. [162] compared the exercise capacity of nine PD-dependent children with five healthy controls. After partial correction of the Hct from 21.9 ± 3.5% to 33.2 ± 3.0%, graded exercise testing demonstrated an increase in peak oxygen consumption and an increase in oxygen consumption at anaerobic threshold. Treadmill time increased from 5.3 ± 1.2 to 7.5 ± 1.3 min for the PD patients treated with rHuEPO.

Cardiac function is improved by the correction of anemia. In the study by Martin and his coworkers, partial correction of the Hct was associated with a decrease in heart rate and resting oxygen consumption [167]. There was no change, however, in ventricular thickness, even after 6 months of rHuEPO therapy.

Other studies have documented improvement in the child's sense of well-being [168, 169], appetite [162, 163, 169, 170], activity levels [163, 169], school attendance [168], and overall quality of life. An increase in growth velocity has been seen in some children receiving rHuEPO [170, 171]; however, this effect has not been confirmed by other investigators.

There have been three studies of PD patients which reported increased ultrafiltration (UF) in response to increasing the Hct [172–174]. In a study of anemic adults, Lubrich-Birkner et al. [174] reported a 47% improvement in UF with normalization of the Hct. The observed increase in UF was thought to be due to improved mesenteric perfusion.

The Diagnostic Evaluation of Anemia

A potentially large number of laboratory studies can be performed to determine the etiology of anemia. Traditionally, the evaluation of anemia starts with an analysis of mean corpuscular volume (MCV), which quantifies red blood cell volume, and facilitates the classification of the anemia as microcytic, normocytic, or macrocytic. The combination of red blood cell distribution width (RDW), which is the coefficient of variation in red blood cell size, and MCV can further delineate the type of anemia (Table 27.2). Patients with renal failure typically have microcytic or normocytic anemia due to inappropriately low EPO levels. The other forms of anemia, along with appropriate diagnostic testing for each category, are shown in Table 27.2.

By using both RDW and MCV, there is greater distinction of iron deficiency anemia from heterozygous thalassemia or the anemia of chronic disease [175]. An elevated RDW is more sensitive than MCV and mean corpuscular hemoglobin (MCH) for identifying patients with folate, iron, or vitamin B12 deficiency [176]. The RDW also is useful in the identification of anemias caused by red cell fragmentation or agglutination.

The corrected reticulocyte count, which is an indicator of erythropoietic activity, can provide

Table 27.2 Differentiation of types of anemia based on MCV and RDW

	Low MCV (Microcytic)	Normal MCV (Normocytic)	High MCV (Macrocytic)
High RDW	Iron deficiency Hb S-β thalassemia Hemoglobin H Red cell fragmentation • Serum iron • Ferritin • Transferrin • Transferrin saturation • Hemoglobin electrophoresis • Blood smear • Lactic dehydrogenase • Carboxyhemoglobin • Haptoglobin	Early iron deficiency Hemoglobinopathy (SS, SC) Myelofibrosis Sideroblastic • Serum iron • Ferritin • Transferrin • Transferrin saturation • Hemoglobin electrophoresis • Sideroblastic anemia gene defect: 5-aminolevulinate • Clinical trial of vitamin B6	Folate deficiency Vitamin B12 deficiency Hemolytic anemia Immune hemolytic anemia Cold agglutinin • Blood smear • RBC folate • Serum Vitamin B12 • Direct and Indirect Coombs • Cytoskeletal protein analysis • Thermal fragmentation • Osmotic fragility • Sucrose lysis • Pyruvate kinase assay • G-6-PD • Copper, ceruloplasmin • Bone marrow aspiration
Normal RDW	Heterozygous thalassemia Chronic disease • Hemoglobin electrophoresis	Normal Chronic disease Chronic renal failure Chronic liver disease Hemoglobinopathy (AS, AC) Transfusion Chemotherapy Chronic myelocytic leukemia Hemorrhage Hereditary spherocytosis • Erythropoietin level • C-reactive protein • Blood smear • Hemoglobin electrophoresis • Bone marrow aspiration • Reticulocyte count • Osmotic fragility test	Aplastic anemia Pre-leukemia • Ham's test • Bone marrow aspiration

Laboratory testing which may be useful in evaluating the cause of anemia is shown in the gray areas
Source: Modified with permission from Bessman et al. [175]

insight into erythrocyte kinetics. A corrected reticulocyte count >1.5% of all red blood cells suggests increased red blood cell production due to hemolysis or blood loss. Failure to increase reticulocyte percentages in the context of severe anemia indicates diminished erythropoiesis due to marrow hypoplasia, cancer, medications, or inadequate erythrocyte substrates, including EPO and iron.

Erythropoietin Levels

Endogenous EPO production decreases as kidney excretory function decreases. However, there are significant inter-patient differences in the amount of kidney interstitial cell loss relative to GFR. A serum EPO level plotted relative to the Hct can be helpful to identify patients who have low levels of EPO despite having good renal function [177]. The EPO level must be plotted relative to Hct since low EPO levels are perfectly normal in the context of a patient with a normal Hct [89]. In patients with ESRD, the normal inverse relationship between Hct and EPO levels is lost (Fig. 27.8) [178].

The EPO level may be decreased due to diminished renal production or loss. Patients who have nephrotic-range proteinuria may have inappropriately low EPO levels and are suspected to lose significant amounts of EPO in their urine [179].

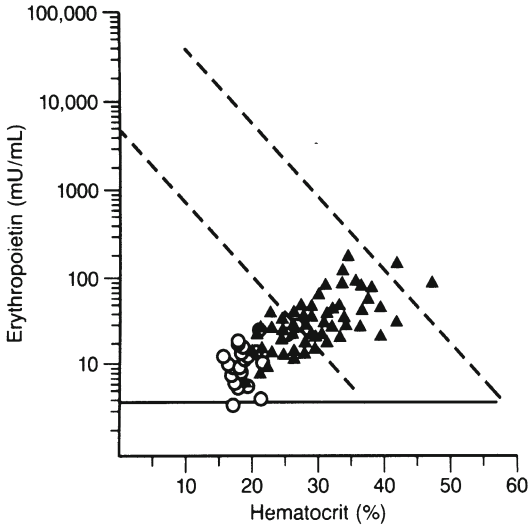

Fig. 27.8 Serum EPO levels in kidney failure and anephric patients. *Open circles* represent anephric patients, *closed triangles* are patients with chronic renal disease (Published with permission Erslev [178])

The Laboratory Analysis of Iron Deficiency

Although there are multiple laboratory tests aimed at determining iron status of a patient, the K/DOQI anemia workgroups have recommended that ferritin and the transferrin saturation (TSAT) be the primary indices used (see recommendations below) [180]. Ferritin enters the circulation likely from leakage of tissue ferritin [181, 182]. Therefore, its level is thought to reflect a balance between tissue production and clearance by the reticuloendothelial system. Hence, increases in serum ferritin can reflect increased tissue ferritin. Under normal circumstances, the primary driving force for increased tissue ferritin is iron loading. Plasma levels generally reflect overall iron storage, with each ng/mL of ferritin corresponding to 10 mg of total iron stores. However, with inflammation, cytokines including TNF-alpha increase tissue ferritin production independent of iron status [52, 183, 184]. Similarly, liver dysfunction can lead to increased serum ferritin via reduced serum clearance. This at times limits the sensitivity of ferritin as a marker of iron deficiency. When compared to a functional gold standard of iron deficiency or an anatomical one (e.g., bone marrow stained for iron) most adult studies using a cutoff of 100 ng/mL have shown a sensitivity between 35% and 48% [185–187]. In contrast, serum ferritin's specificity using the same cutoff is quite high (75–100%) indicating that most CKD patients with ferritin levels below 100 ng/mL are truly iron deficient.

Unfortunately, diurnal and inter-laboratory serum iron measurement variations severely limit its value in determining iron deficiency [188]. Instead, the circulating iron available for erythropoiesis is measured by the TSAT. It is calculated by dividing the total serum iron (the vast majority of which is bound to transferrin) by the total iron-binding capacity (TIBC), which reflects the total amount of transferrin in serum. Thus, the TSAT provides some insight into the amount of circulating iron available for erythropoiesis. Unfortunately TSAT, like ferritin, has some acute-phase reactivity, meaning that if the level of circulating iron is constant, increased production of transferrin due to inflammation can cause the TSAT to drop. Additionally, TSAT levels can be high independent of circulating iron in the setting of malnutrition due to decreased transferrin production. Using a cutoff of 20%, TSAT's sensitivity ranges from 59% to 88%, while its specificity is slightly lower at 63–78% [185–187].

Currently, the K/DOQI 2006 practice guidelines for pediatric CKD recommend iron administration during ESA therapy to maintain a serum ferritin greater than 100 ng/mL and a TSAT greater than 20% [180]. Given the lack of pediatric data, these recommendations are largely based on adult guidelines. One exception is the continued use of the lower 100 ng/mL ferritin cutoff for pediatric hemodialysis patients, while for adult hemodialysis patients that cutoff has risen to 200 ng/mL. Given the poor sensitivity of serum ferritin (especially at levels >200 ng/mL) and the safety concerns of superphysiological ferritin levels, the current guidelines state that "there is insufficient evidence to recommend routine administration of IV iron if serum ferritin is greater than 500 ng/mL" and thus the upper limit of ferritin remains undefined (see below).

It is important to recognize that the limited sensitivity and specificity of ferritin and TSAT

have significant consequences when deciding whether a pediatric patient should receive iron therapy. A common example of this problem is whether an anemic CKD patient with a TSAT <20% and a ferritin >500 ng/mL needs iron supplementation. These patients are frequently assumed to have a functional iron deficiency where the supra-physiologic rate of RBC production driven by ESA therapy has outstripped the ability of transferrin to deliver sufficient iron for hemoglobin synthesis. In this case, iron supplementation may be beneficial. However, an extreme case of functional iron deficiency can occur when increased inflammation results in reticuloendothelial blockade, a state in which iron release from stores is inhibited. Under such circumstances, iron supplementation would be ineffective and could lead to iron overload. Because current iron parameters are unable to distinguish reticuloendothelial blockade from functional iron deficiency, the treatment of functional iron deficiency often involves empiric iron supplementation. In the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study, hemodialysis patients with a TSAT <20% and a ferritin >500 ng/mL were randomly assigned to either parenteral iron therapy or no iron therapy [189]. Those who received iron therapy had a 25% reduction in their ESA requirement, though a wide variability of patient response was noted. In a follow-up analysis, neither TSAT nor ferritin levels were predictors of a response to parenteral iron in this setting [190].

In an attempt to address the limitations of serum ferritin and TSAT, several other markers of iron status have been proposed and examined. To date, reticulocyte hemoglobin content (Chr Hb) appears to be the most promising of these additional markers, showing improved sensitivity and specificity over ferritin and TSAT in adult studies [191, 192]. CHr Hb is a measure of the amount of Hb in reticulocytes. Given the very short life span of reticulocytes (1–2 days), it should reflect how much iron is available for incorporation into new red blood cells. Additionally CHr Hb is available on many of the current multichannel hematology analyzers that do complete blood counts. The current K/DOQI guidelines include CHr Hb measures (cutoff 29 pg/cell) but have not been extended to pediatric CKD because the cutoff values remain unclear [180, 193].

Two other measures of iron status which bear mentioning include percentage of hypochromic red cells and soluble transferrin receptor. Percentage of hypochromic red cells is a measure of the Hb concentration in RBCs by taking into account the absolute amount of Hb as well as the size of the RBC. Although its utility is likely comparable to CHr Hb [187, 194] its use in the United States has been hampered by the need for rapid analysis, as red cells tend to expand while they are stored. Soluble transferrin receptor (sTFR) levels reflect the expression of membrane transferrin receptors on premature erythroblasts and thus reflect the need for iron. In a situation where erythropoiesis has been stimulated by an ESA and the patient does not have sufficient iron, the sTFR levels rise [195]. However, sTFR also provides an estimate of the erythroblast mass in the bone marrow. Thus, an ESA-treated patient may have a high sTFR due to iron deficiency or increased erythroblastic activity or a combination of both [196]. Studies of sTFR in adult CKD have been mixed, and no clear cutoff has been established [187, 197].

With further validation, hepcidin may become an important biomarker of iron status in CKD [198]. For example, hepcidin may hypothetically distinguish patients with simple functional iron deficiency from those with reticuloendothelial blockade. In the former, hepcidin would be expected to be low due to the decreased availability of iron for erythropoiesis. Conversely, in reticuloendothelial blockade, hepcidin, as the pathogenic mediator of inflammation, would be expected to be high. Furthermore, as hepcidin levels increase with iron loading, following its rise may help delineate when sufficient iron stores have been achieved and alert physicians to those at risk for possible harmful effects of iron overload. Finally, low hepcidin levels may identify those patients most likely to respond to oral iron. Whether hepcidin measurements can guide iron supplementation requires future study.

Patients on peritoneal dialysis exhibited no hematological indices with good sensitivity or specificity for detecting iron depletion [199]. Even the absence of stainable iron in bone

marrow aspirates was not a sensitive marker for iron-deficient anemia.

Recombinant Human Erythropoietin Therapy

Recombinant Human Erythropoietin is Available in Many Forms

Cloning of the human EPO gene into Chinese hamster ovary (CHO) cells facilitated commercial production of rHuEPO [200]. The protein encoded by the EPO gene is a heavily glycosylated 165 amino acid protein [201, 202] (molecular weight = 30.4 kDa) characterized by a classic four helix bundle cytokine motif which is typical of hematopoietic growth factors [119] (Fig. 27.4). Erythropoietin's heavy glycosylation, 40% of the 30 kD protein, prevented analysis of the molecular structure until a recent study of a mutated EPO protein, by Cheetham and coworkers [119], provided some insight. There are at least five recombinant forms of erythropoietin α, β, δ, Ω, ζ that have been developed and commercially marketed. rHuEPO α and β are both made in CHO cells, and have only slight differences in isoforms and glycosylation. rHuEPO β has a higher molecular weight and a lower number of sialylated glycan residues [203]. rHuEPO δ, produced in human cell lines, was thought to have potential advantages in half-life due to the human glycosylation pattern. Pharmacokinetic studies, however, have not demonstrated any difference in half-life when compared to rHuEPO α and β. rHuEPO Ω, which is produced in baby hamster kidney (BHK) cells and has smaller amounts of O-bound sugars and is less acidic, has been shown to be effective and safe in adult dialysis patients [204]. Smaller doses of rHuEPO Ω, relative to rHuEPO α may be needed to maintain the Hgb [205].

Recombinant Human Erythropoietin Dosing for Children

Prior to initiating rHuEPO therapy, it is important to select a target Hb range. The range selected may reflect DOQI/KDOQI recommendations, a Hb range of 11–12 g/dL, or may be individualized to meet a child's specific medical needs. The rHuEPO-mediated erythropoietic response is dose dependent and correlates with the units administered relative to body weight.

Table 27.3 Suggested initial rHuEPO dosing based on age

Age group	Hemodialysis dependent	Peritoneal dialysis dependent
Children <5 years of age	250–300 units/kg/week	100–150 units/kg/week
Children >5 years of age	150–200 units/kg/week	50–100 units/kg/week

Suggested rHuEPO dosing extrapolated for reports of rHuEPO dosing from various sources [162, 208, 209, 218, 235]

The initial dose of rHuEPO can be difficult to determine due to inter-patient differences in erythrocyte survival time and the remaining amount of endogenous EPO production. The choice of a higher rHuEPO weekly dose means that there is a possibility of overshooting the Hb target, while a dose that is too low will lead to a slow or partial correction of the anemia and more costs attributable to additional laboratory testing. Some of the earliest rHuEPO studies contrasted the use of high-dose (150 units/kg/week) versus low-dose (50 units/kg/week) rHuEPO initial treatment [169, 206].

Initial investigations suggested that the dose of rHuEPO required to achieve a target Hb value is affected by the age [207–209] of the child and the mode of dialysis. Some investigators have concluded that a dose of 100–150 units/kg/week is a reasonable starting dose for hemodialysis-dependent children >5 years of age (Table 27.3). For children <5 years of age receiving hemodialysis the rHuEPO dose should be 250–300 units/kg/week and 100–150 units/kg/week for those receiving peritoneal dialysis. Peritoneal dialysis patients require rHuEPO doses one-third lower than of those in children on hemodialysis. Children, less than 5 years of age require higher doses of rHuEPO [209] than older children due, in part, to more rapid rHuEPO clearance [207, 210]. The manufacturers of rHuEPO generally suggest starting with a dose of 150 units/kg/week divided three times weekly.

Table 27.4 Different forms of erythropoietin

	Erythropoietin alpha	Erythropoietin beta	Erythropoietin delta	Erythropoietin omega	Darbepoetin
Brand names	Epogen, Procrit	NeoRecormon	DynEPO	EpoMax	Aranesp
Half-life	IV: 4–13 h SQ: 13–37 h	IV: 4–12 h SQ: 8–22 h	IV: 4.7–13.2 h	SQ: 23.4 ± 9.6 h	IV: 12–39 h SQ: 21–144 h
Source	Chinese hamster ovary cells	Chinese hamster ovary cells	Human cell line	Hamster kidney cells	Chinese hamster ovary cells
FDA approval	Approved	Not approved, approved in Europe	Not approved in USA, approved in Europe	Approved	Approved

In neonates, where rHuEPO is used to decrease the requirement for red blood transfusions, the dose of rHuEPO studied has been quite high, up to 300 units/kg/day [211] or 1,500 units/kg/week [212]. The higher rHuEPO dose is thought to be due to a larger volume of distribution and more rapid clearance [213].

More recently, studies by Bamgbola et al. [214] and Port and Mehls have shown a lack of correlation between age and weight and the rHuEPO dose needed to achieve a normal hemoglobin level. Other factors may correlate better with the erythropoietin response including (Kt/V), intact parathyroid hormone (iPTH), blood loss, normalized protein catabolic rates (nPCRs), and indices of malnutrition and inflammation. Port and Mehls developed a new formula, independent of age and weight [215].

$$\sim 2{,}400\ \text{IU}\sqrt{\left(\frac{9.6}{\text{hgb}_{ss}-\text{hgb}_{0}}\right)-1}$$

Erythropoietin can be given by subcutaneous, intravenous, and intraperitoneal (IP) routes. The initial reports described the use of subcutaneous rHuEPO three times per week in pediatric patients with ESRD [206, 216]. Three times per week dosing was chosen based on pharmacokinetic information that smaller doses given more frequently were more effective than larger doses given less frequently. A recent Cochrane Review concluded, however, that there was no statistical advantage to more frequent, as compared to once weekly, dosing [217].

Intravenous rHuEPO is cleared much more rapidly than subcutaneously injected rHuEPO. The differences in the available forms of rHuEPO and their different half-lives are shown in Table 27.4.

Hemoglobin levels should be monitored at least weekly (the manufacturers recommend twice weekly monitoring) for 2–6 weeks after starting rHuEPO and weekly following any dose adjustment. Monthly Hb monitoring is recommended once the Hb has stabilized.

Adjustments in the rHuEPO dose are indicated in the following situations: (1) the Hb is rapidly approaching or above the target Hb, (2) if at any time Hb increases by more than 1.3 g/dL in a 2-week period, or (3) if a Hb increase of 1.6–2 g/dL (Hct > 5–6%) is not achieved over an 8-week period. Based on the erythropoietic response to rHuEPO, it is important to make small (10–25%) incremental changes in the rHuEPO dose, as frequent adjustments in rHuEPO can hinder the maintenance of a steady-state Hb level. If the Hb is rising rapidly, >1.3 g/dL (Hct > 4%) in 2 weeks, then the rHuEPO dose should be decreased by 25%. An effort should be made to avoid discontinuation of rHuEPO, as a dramatic decline in Hb occurs in 1–2 months due to the lack of newly released erythrocytes (Fig. 27.9). A temporary discontinuation of rHuEPO therapy should only occur when the Hb is high, e.g., >13 g/dL.

Cost-effectiveness favors the subcutaneous route. Doses of subcutaneous rHuEPO are about one-third smaller than intravenous doses to maintain the same Hct [207, 218]. The cost of rHuEPO is significant (approximately $5,000–10,000 per

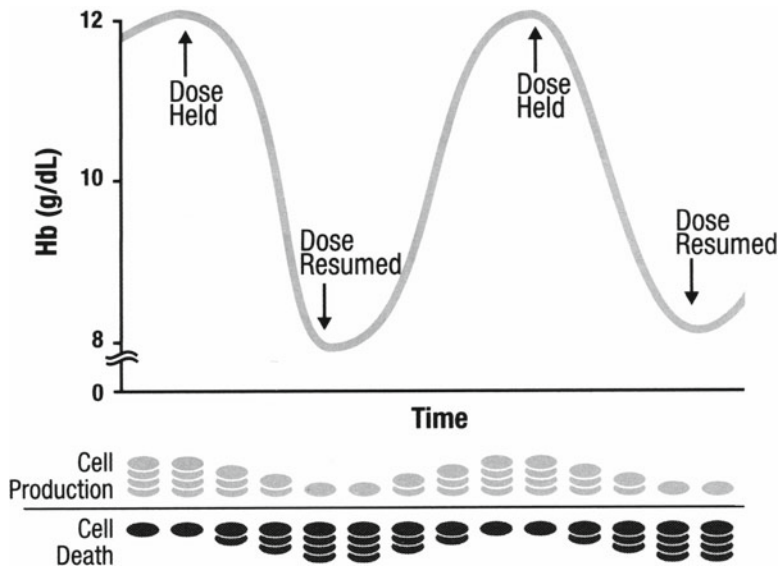

Fig. 27.9 Effect of discontinuing rHuEPO on hemoglobin

patient year). Because pharmacokinetic data and cost-effectiveness favor the subcutaneous route, the DOQI committee has expressed the opinion that even hemodialysis patients should be treated with subcutaneous rHuEPO [140]. However, in many hemodialysis centers intravenous rHuEPO remains the preferred route due to the ease of the infusion, the lack of pain associated with the injection, and the ability to insure compliance with therapy.

Although there have been reports of successful responses to intraperitoneal (IP) rHuEPO [218–220], especially when the peritoneum is dry or when a small dialysate volume is used, the bioavailability of IP rHuEPO is poor. About 80% of the rHuEPO can be recovered after a 4 h dwell. The use of IP rHuEPO requires that the patient forego any indwelling dialysate (last bag fill) or any exchanges during the treatment time. A more recent study by Rijk et al. showed success with intraperitoneal darbepoetin at a mean dose of 0.79 mcg/kg/week [221].

Darbepoetin Alpha

One of the major limitations of rHuEPO is the requirement for frequent dosing due to the relatively short half-life. Previous studies demonstrated a relationship between the sialic acid-containing carbohydrate content of the molecule and its serum half-life [222]. However, as carbohydrate content is increased, the receptor binding affinity of rHuEPO decreases. Darbepoetin alpha, with a molecular weight of 37.1 kDa, has 5N-linked oligosaccharide chains while rHuEPO only has three chains. When compared with rHuEPO, intravenous darbepoetin alfa has an approximate threefold longer serum half-life (25.3 h) [223]. Thus, use of darbepoetin alpha allows less frequent administration, perhaps as infrequently as once weekly or every other week by either intravenous or subcutaneous injection [222]. There is conflicting data regarding the potential cost of darbepoetin alfa relative to rHuEPO [224–226]. Greater pain at the injection site, particularly in younger children, treated with subcutaneous darbepoetin [227] has been a concern. Recommended dosing and dose adjustment guidelines have been published [228]. Dosing pharmacokinetics have also been performed in children with chronic kidney disease [229].

The High Cost of rHuEPO Affects Utilization

After atorvastatin, erythropoietin is the best-selling drug in the United States. Recombinant human erythropoietin therapy is relatively expensive, costing approximately $5,000–$10,000 per year

for a typical adult hemodialysis patient. The expense of rHuEPO can be reduced by screening patients for iron depletion, undertreated bone disease, aluminum toxicity, and vitamin depletion prior to initiating rHuEPO therapy [230]. Prescribing rHuEPO via subcutaneous instead of an intravenous route also decreases costs [231].

Erythropoietin Therapy Causes an Increase in Blood Pressure

Hypertension is the most common adverse effect attributed to rHuEPO treatment in adults [217, 232, 233] and children [168, 234–236]. Twenty to seventy percent of patients treated with rHuEPO experience worsening of hypertension or develop new-onset hypertension [232, 233]. There is evidence that the increase in Hgb alone does not cause the hypertension. Patients who had an increase in Hgb in response to iron therapy alone did not become hypertensive [237]. Recombinant human erythropoietin-induced hypertension occurs even in iron-depleted patients who do not experience an increase in Hgb [237]. Similarly, multiple small blood transfusions that simulate the effect of rHuEPO do not cause hypertension [237].

While correction of Hgb alone does not appear to cause an increase in blood pressure, controversy exists as to whether a rapid rate of Hgb rise influences the development of hypertension [232, 238]. In some of the early rHuEPO trials in adults, where there was a rapid rise in Hct, there was a disturbing incidence of hypertensive encephalopathy and seizures.

Recombinant human erythropoietin-mediated hypertension is not caused by renin–angiotensin system [239], endothelin [239, 240] or atrial natriuretic peptide-mediated mechanisms [239]; instead, there is evidence that rHuEPO causes hypertension due to an increase in blood volume, increased blood viscosity especially after hemodialysis [241], modified nitric oxide synthesis and resistance [242, 243], increased cytosolic calcium [242, 244], a direct rHuEPO vasopressor effect possibly due to vascular alpha-adrenergic responsiveness [245, 246], increased catecholamine production [247, 248], enhanced response to norepinephrine [249], and arterial remodeling [238, 250]. A review of the pediatric rHuEPO literature by Jabs and Harmon reported that exacerbation or the development of hypertension was the most significant adverse effect seen with rHuEPO treatment of anemia [251]. When defined by an increase in the dose of antihypertensive medications, an increase in blood pressure occurred in 30% of rHuEPO-treated children. There was no difference in the incidence of rHuEPO-associated hypertension between children on hemodialysis and peritoneal dialysis.

If hypertension is a problem during the correction phase of renal anemia, close monitoring of blood pressure, administration of antihypertensive drugs, and, if needed, downward adjustment of the rHuEPO dosage are required. There is a suggestion that calcium channel blockers may be particularly effective at blocking rHuEPO-mediated hypertension [242]. The route of rHuEPO may influence blood pressures, as blood pressures are less likely to increase after subcutaneous administration [252].

rHuEPO Increases the Risk of Thrombosis

An increased risk of thrombosis is one of the major concerns related to the use of rHuEPO. In a placebo-controlled trial with a small number of hemodialysis-dependent adults with AV fistulas, rHuEPO did not induce any prothrombotic change in hemostatic parameters, nor did thrombosis occur more frequently [253]. In the largest study of the relationship between graft patency and rHuEPO, Martino et al. studied PTFE graft function in 173 ESRD patients who were receiving rHuEPO. Martino compared the results of the PTFE patients with 308 patients who were not receiving rHuEPO. For patients receiving rhEPO, primary patency was 8.9 months, compared to 7.8 months in the group not receiving rHuEPO.

Conversely, other investigators have concluded that rHuEPO plays a significant role in the thrombosis of vascular access [254, 255]. Platelet counts increase [254, 255] and bleeding times

decrease [254, 256] in rHuEPO-treated patients. Studies have concluded that increased platelet aggregation [234, 254], increased blood viscosity [257], decreased Protein C and S [254], and free protein S [254, 258], are the major reasons for rHuEPO-induced thrombosis. The risk of thrombosis is also influenced by platelet numbers and function. A small increase in platelet number is observed during the correction period due to an increase in new platelet number [254, 255] and function [234, 259, 260] in response to rHuEPO. Bleeding times decrease with EPO therapy [260]. During the maintenance phase of rHuEPO the platelet count usually returns to normal.

While some investigators reported that heparin infusions during hemodialysis should be higher in children receiving rHuEPO to avoid thrombosis and loss of the hemofilter [169, 210], Campos et al. reported that no increase in heparin was required [163]. Low-dose aspirin therapy does not appear to be of any benefit in decreasing the risk of thrombosis [256].

Patients Receiving rHuEPO Therapy May Develop Problems with Hyperkalemia

Serum potassium levels rise slightly in response to rHuEPO therapy [255, 261–263]; however, the rise in potassium rarely requires significant dialysis prescription changes. Hyperkalemia is thought to be due to an improvement in appetite and a slight decrease in potassium clearance during dialysis in patients with higher Hb levels. Recombinant human erythropoietin-induced hyperkalemia can be corrected by more stringent restriction of dietary potassium or increased dialysis time and decreased dialysate potassium concentration.

Subcutaneous Injections of rHuEPO Can Be Painful

Many patients complain of pain at the injection site due to rHuEPO therapy [264–266]. The pain has been attributed to the use of a citrate buffer in some formulations of rHuEPO [265]. The pain associated with injection of rHuEPO may be reduced by the use of rHuEPO in the multiuse vial, which uses a different buffer, less volume with higher rHuEPO concentrations [266], dilution of the rHuEPO with bacteriostatic saline [266], and by warming the syringe filled with rHuEPO prior to injection.

rHuEPO Therapy Can Cause Influenza-Like Symptoms

A small number of patients (4%) report "flu-like" symptoms after receiving rHuEPO. The flu-like symptoms have been attributed to increased peripheral blood mononuclear cells (PBMCs) production of IL-1 and TNFα [267].

rHuEPO Does not Cause a Reduction in Renal Function

Shortly after the introduction of rHuEPO, there was concern that rHuEPO caused a reduction in renal function [255, 261]. However, several studies have shown that renal excretory function deteriorates no more rapidly in individuals treated with rHuEPO than in controls [169, 268–270].

Novel Erythropoiesis-Stimulating Agents

An entirely new group of medications capable of increasing erythropoiesis, erythropoiesis-stimulating agents (ESAs), are currently being developed. The new medications can be divided into four groups: (1) medications which positively impact bone-marrow production of hematopoietic stem cells and progenitors, (2) medications, which like rHuEPO, which are capable of binding to the erythropoietin receptor, (3) new erythropoietin receptor agonists that have no sequence homology with rHuEPO, and (4) medications which inhibit molecules which downregulate erythropoietin gene transcription. Incidentally, the competitive cycling world has obtained access to quite a few of these new medications, making it much harder for officials to determine whether doping is occurring [271].

New Medications Which Increase Hematopoietic Stem and Progenitor Cells

Leridistim

Patients who have received chemotherapy or radiation often have problems with prolonged and severe leukopenia. In an effort to achieve faster neutrophil recovery, leridistim, a dual G-CSF and IL-3 receptor agonist, was created for use prior to chemotherapy/radiation. Plasmon resonance analysis demonstrated that leridistim binds to both IL-3R and G-CSFR simultaneously and activates both receptors at the same time [272].While G-CSF appears to be better in preventing neutropenia [273], leridistim also has potential as a hematopoietic stem cell stimulator [274–276].

Small-Molecule c-MPL Agonists

The thrombopoietin receptor, c-MPL, has been presumed to primarily stimulate the production of megakaryocytes, with minimal stimulation of the hematopoietic cell line. Experiments using a small-molecule c-MPL agonist, NR101, unexpectedly increased hematopoietic stem numbers in cord blood greater than twofold when compared to thrombopoietin [277].

New Recombinant Human Erythropoietin-Based Proteins

Pegylating Recombinant Human Erythropoietin Prolongs Its Half-Life

The most obvious way to enhance erythropoiesis would be to modify rHuEPO so that the molecule is more effective or longer lasting. Methoxy polyethylene glycol-epoetin beta (Mircera™) is an erythropoietin beta to which polyethylene glycol (PEG) has been attached. When given by intravenous or subcutaneous route every 2–4 weeks [278], methoxy polyethylene glycol-epoetin beta achieves hemoglobin levels similar to darbepoetin and erythropoietin in adult dialysis patients [279–288]. Methoxy polyethylene glycol-epoetin beta has a safety profile comparable to rHuEPO [289] and has been Food and Drug Administration (FDA) approved. Methoxy polyethylene glycol-epoetin beta has not been studied in children. There are some concerns related to the pegylation of rHuEPO. Rare patients experience anaphylactic reactions due to polyethylene glycol (PEG) and have complement activation [290]. With high doses, nephrotoxicity can occur [291].

Fusion of Proteins with Recombinant Human Erythropoietin

Investigators have created rHuEPO fusion proteins, using proteins including the truncated amino acid sequences from thrombopoietin and human chorionic gonadotropin (hCG) [292]. By adding a truncated 28 amino acids portion of the carboxy terminal of the hCG beta subunit to form a fusion protein (Epo-CGC), the half-life was slightly longer than darbepoetin [292]. It is also possible to create a fusion protein which maintains the function of both fused proteins. A fusion protein combining the N-terminal 153 peptides of thrombopoietin and rHuEPO has been shown to increase erythrocytes and megakaryocytes in vitro and in animal models [293].

Other investigators have created fusion proteins with rHuEPO and the FC portion of IgG [293–298]. Monomeric and dimeric rHuEPO+FC molecules have been tested as an inhalational treatment. Phase 1 studies have reported therapeutic blood rhEPO levels with inhaled rHuEPO+FC molecules [299, 300].

Synthetic Erythropoiesis-Stimulating Proteins

CNTO 528 and 530: A New Fc Domain Fusion Protein with a Peptide Segment Capable of Erythropoietin Receptor Binding

Studies of the erythropoietin receptor binding sites yielded information that has been used by pharmaceutical companies to develop novel molecules with EPO-R binding activity without any sequence homology to EPO [292, 301]. CNTO 528 and CNTO 530 have no sequence homology with rHuEPO [302]. There is a signal peptidase consensus site, an EMP1 sequence, a flexible linker, a human J chain, and a human IgG4 Fc

domain. Phase 1 trials have shown reticulocyte responses and normalization of the hemoglobin values when CNTO has been intravenously injected [303]. The initial effects of CNTO 528 were seen 9–10 days after injection and maximal effects were seen 19–26 days later.

Hematide Is a Pegylated Synthetic Peptide Capable of Erythropoietin Receptor Binding

The use of a small EPO-R binding peptide attached to polyethylene glycol is an attractive option due to the lack of sequence homology with rHuEPO and the prolonged half-life conferred by the polyethylene glycol. Hematide™, consisting of a dimeric peptide and polyethylene glycol, has been tested in phase I–III trials and has a safety profile similar to placebo [304]. A recent study performed by MacDougall et al., demonstrated the efficacy of Hematide™ in 14 adult dialysis patients who had red cell aplasia due to anti-erythropoietin antibodies [305]. All patients had a treatment response with improved hemoglobin values; however one subject developed anti-Hematide™ antibodies. Animal model studies have failed to show anti-Hematide™ antibody or significant adverse effects outside of the effects of polycythemia [306, 307].

Therapies Which Downregulate Erythropoietin Gene Transcription

Prolyl Hydroxylase Inhibitors Increase Hypoxia Heterodimer Upregulation of the Erythropoietin Receptor

Analysis of a subgroup of patients with polycythemia identified a gene defect in prolyl hydroxylase 2 as a cause [94, 103, 104, 308, 309]. When dimethyloxalylglycine was identified as a prolyl hydroxylase inhibitor, investigators began thinking of prolyl hydroxylase regulation as a means of treating renal anemia. To date, two prolyl hydroxylase inhibitors, F2216 and F4592, have been extensively studied. Early studies of nephrectomized rats treated with F2216 revealed an increase in erythropoietin levels from hepatocyte production [310]. Treatment of study subjects showed a hemoglobin dose–response curve [311]. Interestingly, the hemoglobin response of prolyl hydroxylase inhibitors was not inhibited by inflammation, and oral iron absorption increased due to an effect on hepcidin [311, 312]. Hemoglobin responses were similar with F4592 [312]. It is concerning that during a phase II study one adult subject died of acute liver failure. The FDA has recently approved phase III trials using both prolyl hydroxylase inhibitors.

Asparaginase Hydroxylase Inhibition

Asparaginase hydroxylase is the factor inhibiting hypoxia-inducible factor (HIF), which provides fine regulation of erythropoietin transcription by hydroxylating asparaginine in HIF [313, 314]. While prolyl hydroxylases have a profound effect on erythropoietin transcription, asparaginase hydroxylase appear to have a minor regulatory effect. Inhibition of asparaginase hydroxylase would be expected to have a positive effect on erythropoietin production.

GATA Inhibitors

GATA-2 and GATA-3 negatively control the transcriptional activity for the erythropoietin gene [315] in kidney interstitial cells. Interleukin-1β and tumor necrosis factor α, increases GATA binding to the erythropoietin promoter, thus blocking erythropoietin transcription. A GATA inhibitor, K-7174, when injected intraperitoneally in an animal model reversed the decreases in erythropoietin due to IL-1β and TNF α [316].

Erythropoietic Failure Despite Recombinant Human Erythropoietin Therapy

Erythropoietin resistance, the inability to maintain a Hb within an appropriate target range despite generous doses of rHuEPO (>500 units/kg/week), can be caused by iron depletion, immunologic activation, secondary hyperparathyroidism, chronic blood loss, vitamin depletion, medications, inadequate dialysis, aluminum toxicity, fluid shifts, malnutrition, and rarely, hemoglobinopathies.

Infection and Inflammation Can Inhibit Erythropoiesis

Observations that hospitalized patients [317], and those with infections and rheumatologic diseases [318, 319] experience rHuEPO resistance, led to the theory that immune activation is a major cause of rHuEPO resistance [320]. Early studies hypothesized that T-cell circulating factors were suppressing CFU-E [321]. More recent studies have demonstrated that inhibition of EPO production [322, 323] and cytokine-mediated inhibition of erythropoiesis cause immune-mediated rHuEPO resistance. Interleukin 1 (IL-1) [323–325], interferon α and β [323], TNFα [323, 325], and TGFβ [325] have been shown to decrease EPO formation in perfused rat kidneys. Others have reported similar findings when using hepatoma cell cultures [324, 326–328] and in serum-free cultures of human erythroid progenitors [329].

Inflammatory disease is a major cause of anemia in otherwise healthy children and in those requiring dialysis [330, 331]. Clinically, C-reactive protein (CRP) levels correlate with rHuEPO hyporesponsiveness [331–333]. In a study of 30 hemodialysis patients, Barany and his coworkers reported that patients with CRP levels >20 mg/L had rHuEPO doses 80% higher than patients with CRP values <20 mg/L. Hemodialysis patients with high CRP levels also absorb less iron [334].

Inflammatory and infectious agents can cause significant bone marrow suppression. Anemia attributed to viral disease processes has been reported. Parvovirus B19 causes a pancytopenia in immunosuppressed renal transplant patients [335–337].

An evaluation of possible sources of infection, blood cultures drawn from hemodialysis catheter lines, viral studies and rheumatologic studies may be of value in determining the cause of the anemia associated with inflammation.

Bone Disease due to Secondary Hyperparathyroidism Contributes to Anemia

Poorly controlled bone disease can contribute to rHuEPO hyporesponsiveness [210, 338]. Several studies have shown an improvement in Hct or Hb with parathyroidectomy [339–345] and treatment of secondary hyperparathyroidism using vitamin D analogs [346–349].

The mechanism of parathyroid hormone (PTH)-induced anemia appears to be direct inhibition of erythroid cells [345], inhibition of platelet function which can increase blood loss through bleeding [350], and the replacement of the cellular components of the bone marrow by fibrous tissue [351]. Parathyroid hormone does not appear to influence red blood cell osmotic fragility [352].

The diagnosis and treatment of secondary hyperparathyroidism is reviewed in Chap. 25.

Chronic Blood Loss

Gastrointestinal blood loss and blood loss associated with dialysis including blood draws, removal of clots in hemodialysis catheters, and blood not returned to the patient during a rinse back are significant contributory factors to the development of anemia. In a study by Muller-Wiefel et al. [45], children with CRF experienced a daily intestinal blood loss of 6 mL/m^2. Hemodialysis patients lost even more, 11 mL/m^2/day. Patients lost a mean of 8 mL/m^2 per dialysis, almost half being lost in the blood circuit tubing. Blood loss also occurs with removal of heparin from the catheter and during assessment of hemodialysis catheter patency.

Fastidious rinse back of blood in the dialysis lines, stool guaiac testing, and avoidance of medications that inhibit platelet function or coagulation should decrease hemodialysis blood loss.

Vitamin and Mineral Deficiency

Vitamins and minerals play critical roles in erythropoiesis. The B vitamins are water soluble and thus are removed during dialysis. Deficiency of vitamin B12 causes megaloblastic anemia because vitamin B12 is required for DNA synthesis. Individuals who are deficient have large erythrocytes due to the abnormal maturation process. Vitamin B12 is found only in products derived from animal sources; thus, vegetarians

are at greater risk of becoming vitamin B12 deficient. Patients with gastrectomy, surgical removal of ileum, or chronic malabsorption disorder are more likely to have vitamin B12 deficiency. Vitamin B12 deficiency occurs rarely in patients receiving hemodialysis [353].

Folic acid deficiency also causes a macrocytic anemia indistinguishable from vitamin B12 deficiency. Pyridoxine (vitamin B6) deficiency causes a microcytic anemia that can be easily confused with iron deficiency.

Vitamins developed for dialysis-dependent patients are excellent sources of the water-soluble B vitamins. The addition of 0.25 mg/month of vitamin B12 may be necessary in selected patients [354]. A weekly dose of 2–3 mg of folic acid and 100–150 mg of vitamin B6 is recommended for adult hemodialysis patients receiving rHuEPO therapy.

Vitamin C (1–1.5 g/week) was shown to overcome functional iron deficiency in patients with high ferritin levels [354]. The potential increase of oxidative stress induced by intravenous iron therapy may be blunted by concomitant administration of vitamin E (1,200 IU) [355].

Copper is an essential component of several enzymes that are required for blood formation. Factors that are associated with copper deficiency include prolonged diarrhea, premature birth, excessive zinc intake, and Menkes Kinky Hair Syndrome which is due to a genetic defect in copper absorption. Copper deficiency causes an anemia that is very similar to iron deficiency. Cobalt, a critical component in the vitamin B12 molecule, is required in trace amounts for erythropoiesis. Cobalt deficiency is very rare.

Medications

Medications can cause anemia by bone marrow toxicity, aplastic anemia, immune-mediated hemolytic anemia, or hemolysis in patients with G-6-PD deficiency. A partial list of medications reported to cause anemia is shown in Table 27.5.

While a complete discussion of the mechanism of drug-induced anemia is beyond the scope of this chapter, the cause of angiotensin-converting enzyme inhibitor (ACEi)-induced anemia appears to be unique. Angiotensin-converting enzyme inhibitors cause anemia [356, 357] by increasing the serum levels of an inhibitor of erythropoiesis, N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP). N-acetyl-seryl-aspartyl-lysyl-proline levels decrease in response to dialysis and can increase fourfold when an ACEi is used [358]

Table 27.5 Common medications known to cause anemia

Aplastic anemia
Chloramphenicol
Bone marrow toxicity/aplasia/hypoplasia
Acetazolamide
Aspirin
Azathioprine
Chlorpromazine
Cisplatin
Ethanol
Gold salts
Methotrexate
Penicillamine
Sulfonamides
Thiazide diuretics
Trimethoprim
Hemolytic anemia
Cephalosporins
Hepatitis A and B vaccine
Methyldopa
Penicillins
Procainamide
Quinidine
Quinine
Tetracycline
Oxidant-induced hemolysis (G-6-PD-deficient patients)
Chloramphenicol
Dapsone
Methylene blue
Nitrofurantoin
Quinidine
Sulfonamides
Increased serum levels of AcSDKP
Angiotensin-converting enzyme inhibitors
Sideroblastic anemia
Isoniazid

Source: Modified from Shinton [404]

The Dialysis Membrane and Duration of Dialysis Affect rHuEPO Dosing

The selection of the dialysis membrane may have a significant effect on the rHuEPO dose. Eiselt et al. [359] conducted a study where 20 patients were randomized for treatment with either

acetate-free biofiltration or low-flux hemodialysis membranes. Although Kt/V did not differ between groups, the rHuEPO doses in the acetate-free biofiltration group were significantly lower.

There is also a correlation between Hb and hours of dialysis per week, and number of years on renal replacement therapy [360]. There is also a relationship between lower KT/Vurea and erythropoietin resistance [332].

Aluminum Toxicity

Although aluminum-based compounds are used far less frequently in the management of hyperphosphatemia than in the past, a few patients still have problems with aluminum toxicity. Chronic use of aluminum-based antacids and phosphate binders remains the most common cause of aluminum toxicity in patients with end-stage renal disease. In animal studies [361, 362] aluminum has been shown to induce partial resistance to erythropoietin and to increase heme oxygenase activity [362], which subsequently increases the destruction of the heme protein. Aluminum also causes an osteomalacia which can negatively impact erythropoiesis.

Changes in Fluid Status Affect the Hematocrit

Hemodialysis patients experience significant shifts in Hct related to their fluid status. As a patient becomes more fluid overloaded, the Hct falls due to hemodilution. Conversely, during dialysis the Hct rises in relationship to the amount of fluid removed [263, 363]. A 5% weight loss over 3 h will increase the Hct by 15% [263]. Monitoring the rise in Hct during hemodialysis has been recognized as a means by which intradialytic hypotension can be predicted and avoided [364, 365].

It is important to note that all research studies related to anemia in hemodialysis patients report pre-dialysis Hct. One of the criticisms of the seminal study by Besarab and coworkers [366], which dealt with the effects of a higher target Hct in 618 patients with clinical evidence of congestive heart failure or ischemic heart disease, was that post-hemodialysis Hct values may have been much higher than the target, thus causing the increase in deaths.

Interestingly, there can be a significant decline (4–10%) in Hct in response to assuming a recumbent position. The orthostatic change in Hct is thought to be due to the mobilization of fluid from the extravascular space into the circulation.

Malnutrition Influences Erythropoiesis

Malnutrition can be a factor that contributes to the development of anemia. In adult hemodialysis patients, laboratory surrogates of malnutrition, serum creatinine, and albumin were found to significantly correlate with Hb [367]. Aggressive management of malnutrition should be employed using higher caloric value foods or dietary supplements.

Anti-rHuEPO Antibodies

Although likely to be extremely uncommon, anti-rHuEPO antibodies have been described in 13 patients with chronic renal failure [368]. Discontinuation of the rHuEPO led to a slow decrease in anti-rHuEPO antibody titers.

Iron Therapy

Oral Iron Supplementation

Iron supplements are necessary to meet the demand for increased erythropoiesis during rHuEPO therapy in children with CKD. The current K/DOQI guidelines again closely follow adult recommendations and state that oral therapy is likely adequate for non-dialysis and peritoneal dialysis patients while hemodialysis patients likely require intravenous iron therapy (see below). However, some investigators have advocated for oral iron therapy in pediatric

hemodialysis patients. One small randomized trial of 35 pediatric hemodialysis patients demonstrated that while IV iron did result in increased ferritin levels, it did not show a significant advantage over oral iron in terms of maintaining adequate iron stores for erythropoiesis [369]. It is important to note that at the beginning of this trial, all patients were iron replete by current K/DOQI standards. Additionally most adult studies of hemodialysis patients have shown that IV iron is superior to oral iron [370, 371].

Oral iron is usually dosed at 3–6 mg/kg/day of elemental iron divided BID with a maximum dose of 300 mg/day. Generally, the dose should be taken at least 2 h before or 1 h after phosphate binders and food to maximize absorption. Coadministration of iron with other medications such as phosphate binders and antacids limits its absorption due to changes in gastric pH [57]. As an aside, oral iron preparations can be used as phosphorus binders but have not been widely marketed as such. High-dose vitamin C has been found to enhance the iron absorption in the gut but has the potential side effect of oxalate deposition in the presence of decreased kidney function [372]. Compliance with oral iron therapy in children can be limited by gastrointestinal intolerance which is dose related and occurs in up to 20% of patients. Additionally, the use of the oral suspension can cause teeth discoloration and staining.

There are a multitude of oral iron preparations available with varying amounts of elemental iron, including ferrous sulfate, ferrous fumarate, ferrous gluconate, ferrous succinate, iron polymaltose, and polysaccharide-iron complex. Ferrous sulfate is the most commonly prescribed iron compound containing 65 mg of elemental iron per 325 mg tablet [373]. There is very limited data comparing the efficacy of one preparation versus another in CKD patients. One small study of 46 adult hemodialysis patients randomized patients to receive 200 mg of elemental iron daily in one of four preparations (1) Chromagen (ferrous fumarate), (2) Feosol (ferrous sulfate), (3) Niferex (polysaccharide-iron complex), or (4) Tabron (ferrous fumarate) [374]. Although the Tabron group tended to have the highest percentage of patients with a TSAT >20% followed by Feosol, Chromagen, and Niferex groups, these differences were not statistically significant. Importantly, despite intensive compliance monitoring during the study the mean hemocrit remained below 30% and the mean TSAT remained below 20% in three of the four groups, reinforcing the poor efficacy of oral iron supplementation in hemodialysis patients.

Recently, there has been growing interest in oral supplementation using iron in its heme form. Heme iron polypeptide is absorbed via a different mechanism than non-heme iron and appears to have greater bioavailability (see above). One open label trial in adult hemodialysis patients demonstrated that heme iron was able to replace intravenous iron therapy in a majority of patients; [375] there is a multicenter trial now enrolling peritoneal dialysis patients in order to compare heme iron against traditional non-heme iron supplements [376].

Intravenous Iron Supplementation

The current K/DOQI guidelines recommend intravenous iron as the preferred route of administration in hemodialysis patients. These recommendations are based on both adult and pediatric data. Evidence in adult patients is from several randomized controlled trials comparing IV to oral iron that demonstrated that IV iron administration is superior to oral iron in hemodialysis patients [377–379]. In pediatric patients, there are several prospective randomized trials showing that IV iron is effective at repleting and maintaining iron stores in children on HD [369, 380, 381]. In the case of pediatric peritoneal dialysis patients, intravenous iron is often only administered after the patient has not shown a response to a course of oral iron. This is likely a function of the overall decreased need for iron in peritoneal dialysis patients due to their much smaller obligate blood loss and the lack of easy IV access and inconvenience of the small but frequent dosing strategies used in hemodialysis patients.

In general, treatment with IV iron is delivered in two phases: a loading phase, where consecutive doses are given in order to replete the

patient's iron stores, and then a maintenance phase, where a smaller dose is given weekly. Currently four iron preparations are available for parenteral use within the United States with a fifth, ferric carboxymaltose, undergoing testing in Europe. These different preparations avoid the toxicity of an iron salt by complexing it with a carbohydrate (i.e., dextran, sucrose, or gluconate). Before the iron within these parental compounds can be used directly for erythropoiesis, it must first be processed by the reticuloendothelial system.

Iron dextran, a complex of ferric oxyhydroxide complexed with polymerized dextran, was the first parental formulation to become available for the treatment of iron deficiency. Until recently, it was the only parental compound that had the advantage of a single infusion up to one gram which is both convenient and cost-effective. However, its popularity has decreased due to the FDA black box warning of potential fatal anaphylaxis which has been estimated at 0.6–0.7% [382, 383]. Hence, a test dose of between 10 and 25 mg is required before the full infusion to check for the possibility of an allergic response. Other adverse reactions which have also been reported with the preparation are not thought to be immune mediated and include delayed reactions of hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting [384]. Of the two forms currently marketed within the United States, INFeD and DexFerrum, InFed appears to have a lower incidence of adverse effects [385].

Sodium ferric gluconate, a complex of sodium ferric gluconate in sucrose, was FDA approved in 1999 and has a lower rate of adverse reactions with no fatal hypersensitivity reactions reported to date [386]. Ferric gluconate has had an allergy-event reporting rate of 3.3 episodes per million doses compared to 8.7 with iron dextran, and although when it was first marketed a test dose was recommended, that recommendation has since been dropped [387]. An international prospective multicenter trial of 66 pediatric patients investigated the safety and efficacy of ferric gluconate at both a 1.5 mg/kg dose and a 3 mg/kg dose over eight consecutive doses in pediatric hemodialysis patients on ESA therapy [381]. Both dosing regimens resulted in significant increases in mean hemoglobin, hematocrit, transferrin saturation, serum ferritin, and reticulocyte hemoglobin content with no unexpected adverse reactions reported. Another multicenter study of 23 pediatric hemodialysis patients showed that a weekly ferric gluconate dose of 1 mg/kg was effective as a maintenance regimen [388].

Iron sucrose, a complex of iron hydroxide and sucrose was FDA approved in 2000. Several studies have demonstrated its effectiveness and like ferric gluconate is it well tolerated with minimal adverse effects [389, 390]. Dosing in children is 1–4 mg/kg weekly for 12 weeks [391, 392]. In a study by Morgan et al., iron sucrose was successfully used in pediatric hemodialysis patients at a dose of 2 mg/kg/week [392]. No adverse events were reported even when patients with suspected iron deficiency received a single loading dose of 7 mg/kg (maximum of 200 mg), followed by 2 mg/kg/week. Another study of 14 pediatric hemodialysis patients concluded that a dosage of 1 mg/kg/dialysis and 0.3 mg/kg/dialysis were sufficient for loading and maintenance therapy respectively [391].

Finally ferumoxytol, was recently approved by the United States Food and Drug Administration. It is a novel iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating that can be administered as a single rapid dose of up to 510 mg. It has been shown to be safe and effective in adult CKD patients [393–396]; however, data describing its dosing and use in pediatric patients is lacking.

Iron Safety

While the use of ESAs, often at high doses has been embraced by nephrologists, iron therapy has been approached rather conservatively. Ironically, there are now important safety concerns with the use of ESAs while the data linking iron administration to poorer outcomes remains lacking. Much of the discomfort with iron administration can be attributed to problems of iron overload as a result of multiple transfusions during the pre-ESA era. In addition, several observational studies have described an association between high serum ferritin levels and infection or mortality [397–399].

However, the acute-phase reactant behavior of ferritin remains a large confounding factor as increased ferritin levels do not necessarily reflect iron status and instead may simply be due to increased levels of inflammation present in CKD patients. Thus the link between high ferritin levels and infection and mortality may be an epiphenomenon. Indeed, while no randomized controlled study of whether intravenous iron therapy leads to an increased risk of infection or death has been performed, a retrospective epidemiological study of 50,000+ hemodialysis patients found that iron administration was associated with improved survival [398]. Finally many of the concerns regarding the adverse effects of iron, including oxidative stress are based on in vitro studies. Regardless, when one considers the benefits of improved response to ESA agents, the overall risk benefit ratio favors the use of IV iron in hemodialysis patients [400].

As far as the upper limit of ferritin, most investigators agree that extremely high levels (>2,000 ng/mL) are reflective of simple iron overload or hemosiderosis [188, 401]. Levels of greater than 1,200 ng/mL are still associated with increased mortality risk even after adjustment for markers of malnutrition and inflammation [398]. Thus, most clinicians would feel uncomfortable with the use of IV iron at these high ferritin levels. In contrast, it remains unclear if therapy with IV iron is warranted at ferritin levels between 500 and 1,200 ng/mL even when the TSAT is less than 20%. The results of the DRIVE study did demonstrate that IV iron therapy in patients with a serum ferritin between 500 and 1,200 ng/mL resulted in a 25% reduction in ESA dose [189]. Additionally the large retrospective study of 50,000+ dialysis patients mentioned above showed that the greatest ESA responsiveness occurred in patients with a TSAT of 30–50% and a ferritin of 800–1,200 ng/mL [398]. However, the lack of randomized controlled trials comparing the safety and efficacy of targeting ferritin levels greater than 500 ng/mL versus less than 500 ng/mL has led to the current K/DOQI guidelines that "when ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status" [180].

Future Directions

Despite the dramatic improvements in the diagnosis and management of anemia in patients with renal failure over the last decade, physicians still underrecognize and undertreat anemia. Carmel et al. reported that despite familiarity with normative Hb levels, physicians have a tendency to initiate an investigation of anemia only when patients have very low Hb levels [402]. Physicians appear to do no better when prescribing iron therapy [403]. A review of the North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) chronic renal insufficiency database reported that for patients who received rHuEPO by 30 days after dialysis initiation, the mean Hct value after 6 months of rHuEPO therapy was 31.9% for patients who received rHuEPO by 30 days after dialysis initiation. Fifty-four percent of patients who received rHuEPO had Hct values less than the 1997 DOQI target of 33–36% [208]. Closer monitoring and assurance that Hb targets are met and maintained with rHuEPO therapy is needed.

There is a need for clinical studies in dialysis-dependent children to (1) determine the optimal age- and gender-appropriate Hb targets; (2) demonstrate the safety, pharmacokinetics, and efficacy of new ESAs; and (3) compare the efficacy and safety of the newer intravenous iron preparations. The findings reported in these studies will undoubtedly lead to even better outcomes in anemic children who require renal replacement therapy.

References

1. Rothstein G. Origin and development of the blood and blood-forming tissues. In: Cann C, editor. Wintrobe's clinical hematology, vol. 1. Malvern: Lea & Febiger; 1993. p. 41–78.
2. Nishio M, et al. Stem cell factor prevents Fas-mediated apoptosis of human erythroid precursor cells with Src-family kinase dependency. Exp Hematol. 2001;29:19–29.
3. Sui X, Krantz SB, You M, Zhao Z. Synergistic activation of MAP kinase (ERK1/2) by erythropoietin and stem cell factor is essential for expanded erythropoiesis. Blood. 1998;92:1142–9.
4. Ottmann OG, Abboud M, Welte K, Souza LM, Pelus LM. Stimulation of human hematopoietic progenitor

cell proliferation and differentiation by recombinant human interleukin 3. Comparison and interactions with recombinant human granulocyte-macrophage and granulocyte colony-stimulating factors. Exp Hematol. 1989;17:191–7.
5. Sawada K, et al. Transitional change of colony stimulating factor requirements for erythroid progenitors. J Cell Physiol. 1991;149:1–8.
6. Abboud M, Xu F, LaVia M, Laver J. Study of early hematopoietic precursors in human cord blood. Exp Hematol. 1992;20:1043–7.
7. Bastion Y, et al. IL-3 increases marrow and peripheral erythroid precursors in chronic pure red cell aplasia presenting in childhood. Br J Haematol. 1995;89:413–6.
8. Miles SA, et al. Recombinant human granulocyte colony-stimulating factor increases circulating burst forming unit-erythron and red blood cell production in patients with severe human immunodeficiency virus infection. Blood. 1990;75:2137–42.
9. Park K, et al. Positive effect of granulocyte-colony stimulating factor on erythropoiesis in humans. Osaka City Med J. 1991;37:123–32.
10. Negrin RS, et al. Treatment of the anemia of myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor in combination with erythropoietin. Blood. 1993;82:737–43.
11. Bessho M, et al. Treatment of the anemia of aplastic anemia patients with recombinant human erythropoietin in combination with granulocyte colony-stimulating factor: a multicenter randomized controlled study. Multicenter Study Group. Eur J Haematol. 1997;58:265–72.
12. Migliaccio G, Migliaccio AR, Adamson JW. In vitro differentiation of human granulocyte/macrophage and erythroid progenitors: comparative analysis of the influence of recombinant human erythropoietin, G-CSF, GM-CSF, and IL-3 in serum-supplemented and serum-deprived cultures. Blood. 1988;72:248–56.
13. Claustres M, Sultan C. Stimulatory effects of androgens on normal children's bone marrow in culture: effects on BFU-E, CFU-E, and uroporphyrinogen I synthase activity. Horm Res. 1986;23:91–8.
14. Moriyama Y, Fisher JW. Effects of testosterone and erythropoietin on erythroid colony formation in human bone marrow cultures. Blood. 1975;45:665–70.
15. Fandrey J, Pagel H, Frede S, Wolff M, Jelkmann W. Thyroid hormones enhance hypoxia-induced erythropoietin production in vitro. Exp Hematol. 1994;22:272–7.
16. Dainiak N, Hoffman R, Maffei LA, Forget BG. Potentiation of human erythropoiesis in vitro by thyroid hormone. Nature. 1978;272:260–2.
17. Aoki I, Taniyama M, Toyama K, Homori M, Ishikawa K. Stimulatory effect of human insulin on erythroid progenitors (CFU-E and BFU-E) in human CD34+ separated bone marrow cells and the relationship between insulin and erythropoietin. Stem Cells. 1994;12:329–38.
18. Okajima Y, et al. Insulin-like growth factor-I augments erythropoietin-induced proliferation through enhanced tyrosine phosphorylation of STAT5. J Biol Chem. 1998;273:22877–83.
19. Freudenthaler SM, Schenck T, Lucht I, Gleiter CH. Fenoterol stimulates human erythropoietin production via activation of the renin angiotensin system. Br J Clin Pharmacol. 1999;48:631–4.
20. Gleiter CH, Becker T, Schreeb KH, Freudenthaler S, Gundert-Remy U. Fenoterol but not dobutamine increases erythropoietin production in humans. Clin Pharmacol Ther. 1997;61:669–76.
21. Means Jr RT, Krantz SB. Inhibition of human erythroid colony-forming units by tumor necrosis factor requires beta interferon. J Clin Invest. 1993;91:416–9.
22. Zamai L, et al. TNF-related apoptosis-inducing ligand (TRAIL) as a negative regulator of normal human erythropoiesis. Blood. 2000;95:3716–24.
23. Rusten LS, Jacobsen SE. Tumor necrosis factor (TNF)-alpha directly inhibits human erythropoiesis in vitro: role of p55 and p75 TNF receptors. Blood. 1995;85:989–96.
24. Means Jr RT, Dessypris EN, Krantz SB. Inhibition of human colony-forming-unit erythroid by tumor necrosis factor requires accessory cells. J Clin Invest. 1990;86:538–41.
25. Tarumi T, et al. Interferon-alpha-induced apoptosis in human erythroid progenitors. Exp Hematol. 1995;23:1310–8.
26. Zermati Y, et al. Transforming growth factor inhibits erythropoiesis by blocking proliferation and accelerating differentiation of erythroid progenitors. Exp Hematol. 2000;28:885–94.
27. Dybedal I, Jacobsen SE. Transforming growth factor beta (TGF-beta), a potent inhibitor of erythropoiesis: neutralizing TGF-beta antibodies show erythropoietin as a potent stimulator of murine burst-forming unit erythroid colony formation in the absence of a burst-promoting activity. Blood. 1995;86:949–57.
28. Chuncharunee S, et al. Chronic administration of transforming growth factor-beta suppresses erythropoietin-dependent erythropoiesis and induces tumour necrosis factor in vivo. Br J Haematol. 1993;84:374–80.
29. Takenaka K, et al. In vitro expansion of hematopoietic progenitor cells induces functional expression of Fas antigen (CD95). Blood. 1996;88:2871–7.
30. Quang CT, Wessely O, Pironin M, Beug H, Ghysdael J. Cooperation of Spi-1/PU.1 with an activated erythropoietin receptor inhibits apoptosis and Epo-dependent differentiation in primary erythroblasts and induces their Kit ligand-dependent proliferation. EMBO J. 1997;16:5639–53.
31. Silva M, et al. Erythropoietin can promote erythroid progenitor survival by repressing apoptosis through Bcl-XL and Bcl-2. Blood. 1996;88:1576–82.
32. Wu H, Klingmuller U, Besmer P, Lodish HF. Interaction of the erythropoietin and stem-cell-factor receptors. Nature. 1995;377:242–6.

33. Muta K, Krantz SB. Apoptosis of human erythroid colony-forming cells is decreased by stem cell factor and insulin-like growth factor I as well as erythropoietin. J Cell Physiol. 1993;156:264–71.
34. Muta K, Krantz SB, Bondurant MC, Wickrema A. Distinct roles of erythropoietin, insulin-like growth factor I, and stem cell factor in the development of erythroid progenitor cells. J Clin Invest. 1994;94: 34–43.
35. Gregoli PA, Bondurant MC. The roles of Bcl-X(L) and apopain in the control of erythropoiesis by erythropoietin. Blood. 1997;90:630–40.
36. Sui X, Krantz SB, Zhao ZJ. Stem cell factor and erythropoietin inhibit apoptosis of human erythroid progenitor cells through different signalling pathways. Br J Haematol. 2000;110:63–70.
37. Shimizu R, et al. Role of c-jun in the inhibition of erythropoietin receptor-mediated apoptosis. Biochem Biophys Res Commun. 1996;222:1–6.
38. Tsushima H, et al. Human erythropoietin receptor increases GATA-2 and Bcl-xL by a protein kinase C-dependent pathway in human erythropoietin-dependent cell line AS-E2. Cell Growth Differ. 1997;8:1317–28.
39. Steinberg M, Benz E. Pathobiology of the human erythrocyte and its hemoglobins. In: Hoffman N, editor. Hematology: Basic Principles and Practice. Edinburgh: Churchill Livingstone; 2000.
40. Telen M. In: Cann C, editors. Wintrobe's clinical hematology, vol. 1. Malvern: Lea & Febiger; 1993. p. 101–133.
41. Wu SG, et al. Red blood cell osmotic fragility in chronically hemodialyzed patients. Nephron. 1998;78:28–32.
42. Icardi A, et al. Red cell membrane during erythropoietin therapy in hemodialysis and in hemodiafiltration. Int J Artif Organs. 1991;14:147–9.
43. Rodriguez-Commes JL, Tabernero JM, Martin-Vasallo P, De Castro S, Battaner E. Metabolism of red blood cells in chronic renal failure. I. Glycolytic enzyme levels. Nephron. 1979;24:21–4.
44. Bohler T, Leo A, Stadler A, Linderkamp O. Mechanical fragility of erythrocyte membrane in neonates and adults. Pediatr Res. 1992;32:92–6.
45. Muller-Wiefel DE, Sinn H, Gilli G, Scharer K. Hemolysis and blood loss in children with chronic renal failure. Clin Nephrol. 1977;8:481–6.
46. Ponka P. Tissue-specific regulation of iron metabolism and heme synthesis: distinct control mechanisms in erythroid cells. Blood. 1997;89:1–25.
47. Ponka P, Beaumont C, Richardson DR. Function and regulation of transferrin and ferritin. Semin Hematol. 1998;35:35–54.
48. Conrad ME, Parmley RT, Osterloh K. Small intestinal regulation of iron absorption in the rat. J Lab Clin Med. 1987;110:418–26.
49. Roughead ZK, Hunt JR. Adaptation in iron absorption: iron supplementation reduces nonheme-iron but not heme-iron absorption from food. Am J Clin Nutr. 2000;72:982–9.
50. McKie AT, et al. An iron-regulated ferric reductase associated with the absorption of dietary iron. Science (New York). 2001;291:1755–9.
51. Fleming MD, et al. Nramp2 is mutated in the anemic Belgrade (b) rat: evidence of a role for Nramp2 in endosomal iron transport. Proc Natl Acad Sci USA. 1998;95:1148–53.
52. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. Biochim Biophys Acta. 1996;1275:161–203.
53. Ponka P, Lok CN. The transferrin receptor: role in health and disease. Int J Biochem Cell Biol. 1999;31:1111–37.
54. Aisen P. Transferrin receptor 1. Int J Biochem Cell Biol. 2004;36:2137–43.
55. Koorts AM, Viljoen M. Ferritin and ferritin isoforms I: Structure-function relationships, synthesis, degradation and secretion. Arch Physiol Biochem. 2007;113:30–54.
56. Besarab A, Kaiser JW, Frinak S. A study of parenteral iron regimens in hemodialysis patients. Am J Kidney Dis. 1999;34:21–8.
57. Hudson JQ, Comstock TJ. Considerations for optimal iron use for anemia due to chronic kidney disease. Clin Ther. 2001;23:1637–71.
58. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem. 2001;276:7806–10.
59. Pigeon C, et al. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. J Biol Chem. 2001;276:7811–9.
60. Hunter HN, Fulton DB, Ganz T, Vogel HJ. The solution structure of human hepcidin, a peptide hormone with antimicrobial activity that is involved in iron uptake and hereditary hemochromatosis. J Biol Chem. 2002;277:37597–603.
61. Nemeth E, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science (New York). 2004;306: 2090–3.
62. Papanikolaou G, et al. Hepcidin in iron overload disorders. Blood. 2005;105:4103–5.
63. Nemeth E, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004;113:1271–6.
64. Babitt JL, et al. Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression. Nat Genet. 2006;38:531–9.
65. Lin L, et al. Iron transferrin regulates hepcidin synthesis in primary hepatocyte culture through hemojuvelin and BMP2/4. Blood. 2007;110:2182–9.
66. Babitt JL, et al. Modulation of bone morphogenetic protein signaling in vivo regulates systemic iron balance. J Clin Invest. 2007;117:1933–9.
67. Schmidt PJ, Toran PT, Giannetti AM, Bjorkman PJ, Andrews NC. The transferrin receptor modulates Hfe-dependent regulation of hepcidin expression. Cell Metab. 2008;7:205–14.

68. Goswami T, Andrews NC. Hereditary hemochromatosis protein, HFE, interaction with transferrin receptor 2 suggests a molecular mechanism for mammalian iron sensing. J Biol Chem. 2006;281:28494–8.
69. Vokurka M, Krijt J, Sulc K, Necas E. Hepcidin mRNA levels in mouse liver respond to inhibition of erythropoiesis. Physiol Res/Acad Sci Bohemoslov. 2006;55:667–74.
70. Pak M, Lopez MA, Gabayan V, Ganz T, Rivera S. Suppression of hepcidin during anemia requires erythropoietic activity. Blood. 2006;108:3730–5.
71. Ashby DR, et al. Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. Kidney Int. 2009;75:976–81.
72. Zaritsky J, et al. Hepcidin – a potential novel biomarker for iron status in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:1051–6.
73. Sato T, Maekawa T, Watanabe S, Tsuji K, Nakahata T. Erythroid progenitors differentiate and mature in response to endogenous erythropoietin. J Clin Invest. 2000;106:263–70.
74. Bachmann S, Le Hir M, Eckardt KU. Co-localization of erythropoietin mRNA and ecto-5′-nucleotidase immunoreactivity in peritubular cells of rat renal cortex indicates that fibroblasts produce erythropoietin. J Histochem Cytochem. 1993;41:335–41.
75. Maxwell PH, et al. Identification of the renal erythropoietin-producing cells using transgenic mice. Kidney Int. 1993;44:1149–62.
76. Liapis H, et al. In situ hybridization of human erythropoietin in pre- and postnatal kidneys. Pediatr Pathol Lab Med. 1995;15:875–83.
77. Juul SE, Yachnis AT, Christensen RD. Tissue distribution of erythropoietin and erythropoietin receptor in the developing human fetus. Early Hum Dev. 1998;52:235–49.
78. Schuster SJ, Wilson JH, Erslev AJ, Caro J. Physiologic regulation and tissue localization of renal erythropoietin messenger RNA. Blood. 1987;70:316–8.
79. Norman JT, Orphanides C, Garcia P, Fine LG. Hypoxia-induced changes in extracellular matrix metabolism in renal cells. Exp Nephrol. 1999;7:463–9.
80. Koury ST, Bondurant MC, Koury MJ, Semenza GL. Localization of cells producing erythropoietin in murine liver by in situ hybridization. Blood. 1991;77:2497–503.
81. Jacobs K, et al. Isolation and characterization of genomic and cDNA clones of human erythropoietin. Nature. 1985;313:806–10.
82. Chandra M, Clemons G, Sahdev I, McVicar M, Bluestone P. Intraperitoneal production of erythropoietin with continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1993;7:281–3.
83. Juul SE, Joyce AE, Zhao Y, Ledbetter DJ. Why is erythropoietin present in human milk? Studies of erythropoietin receptors on enterocytes of human and rat neonates. Pediatr Res. 1999;46:263–8.
84. Watkins PC, et al. Regional assignment of the erythropoietin gene to human chromosome region 7pter–q22. Cytogenet Cell Genet. 1986;42:214–8.
85. Law, ML, et al. Chromosomal assignment of the human erythropoietin gene and its DNA polymorphism. Proc Natl Acad Sci USA. 1986;83:6920–4.
86. Powell JS, Berkner KL, Lebo RV, Adamson JW. Human erythropoietin gene: high level expression in stably transfected mammalian cells and chromosome localization. Proc Natl Acad Sci USA. 1986;83:6465–9.
87. Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. Proc Natl Acad Sci USA. 1993;90:4304–8.
88. Gleadle JM, Ratcliffe PJ. Induction of hypoxia-inducible factor-1, erythropoietin, vascular endothelial growth factor, and glucose transporter-1 by hypoxia: evidence against a regulatory role for Src kinase. Blood. 1997;89:503–9.
89. Erslev AJ. Erythropoietin. N Engl J Med. 1991;324:1339–44.
90. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA. 1995;92:5510–4.
91. Paliege A, et al. Hypoxia-inducible factor-2alpha-expressing interstitial fibroblasts are the only renal cells that express erythropoietin under hypoxia-inducible factor stabilization. Kidney Int. 2010;77:312–8.
92. Wiesener MS, et al. Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. FASEB J. 2003;17:271–3.
93. Percy MJ, et al. Novel exon 12 mutations in the HIF2A gene associated with erythrocytosis. Blood. 2008;111:5400–2.
94. Furlow PW, et al. Erythrocytosis-associated HIF-2alpha mutations demonstrate a critical role for residues C-terminal to the hydroxylacceptor proline. J Biol Chem. 2009;284:9050–8.
95. Konietzny R, et al. Molecular imaging: into in vivo interaction of HIF-1alpha and HIF-2alpha with ARNT. Ann N Y Acad Sci. 2009;1177:74–81.
96. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 1992;12:5447–54.
97. Huang LE, Bunn HF. Regulation of erythropoietin gene expression. Curr Opin Hematol. 1995;2:125–31.
98. Wang GL, Semenza GL. Molecular basis of hypoxia-induced erythropoietin expression. Curr Opin Hematol. 1996;3:156–62.
99. Jiang BH, Semenza GL, Bauer C, Marti HH. Hypoxia-inducible factor 1 levels vary exponentially over a physiologically relevant range of O2 tension. Am J Physiol. 1996;271:C1172–80.

100. Jaakkola P, et al. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001; 292:468–72.
101. Pappalardi MB, et al. Biochemical characterization of human prolyl hydroxylase domain protein 2 variants associated with erythrocytosis. Biochemistry (Mosc). 2008;47:11165–7.
102. Al-Sheikh M, Moradkhani K, Lopez M, Wajcman H, Prehu C. Disturbance in the HIF-1alpha pathway associated with erythrocytosis: further evidences brought by frameshift and nonsense mutations in the prolyl hydroxylase domain protein 2 (PHD2) gene. Blood Cells Mol Dis. 2008;40:160–5.
103. Percy MJ, et al. A novel erythrocytosis-associated PHD2 mutation suggests the location of a HIF binding groove. Blood. 2007;110:2193–6.
104. Percy MJ, et al. A family with erythrocytosis establishes a role for prolyl hydroxylase domain protein 2 in oxygen homeostasis. Proc Natl Acad Sci USA. 2006;103:654–9.
105. Mole DR, et al. 2-oxoglutarate analogue inhibitors of HIF prolyl hydroxylase. Bioorg Med Chem Lett. 2003;13:2677–80.
106. McNeill LA, et al. The use of dioxygen by HIF prolyl hydroxylase (PHD1). Bioorg Med Chem Lett. 2002;12:1547–50.
107. Bernhardt WM, Wiesener MS, Schmieder RE, Gunzler V, Eckardt K-U. The Prolyl Hydroxylase Inhibitor FG-2216 Stimulates EPO Production in Nephric and Anephric Dialysis Patients–Evidence for an Underutilized Production Capacity in Liver and Kidneys. J Am Soc Nephrol. 2007;18:515A.
108. Fraser JK, Lin FK, Berridge MV. Expression of high affinity receptors for erythropoietin on human bone marrow cells and on the human erythroleukemic cell line. HEL. Exp Hematol. 1988;16:836–42.
109. Wu H, Liu X, Jaenisch R, Lodish HF. Generation of committed erythroid BFU-E and CFU-E progenitors does not require erythropoietin or the erythropoietin receptor. Cell. 1995;83:59–67.
110. Vannucchi AM, Grossi A, Rafanelli D, Vannucchi L, Rossi Ferrini P. Binding of recombinant human 125I-erythropoietin to CFU-E from the spleen of anemic mice. Haematologica. 1990;75:21–6.
111. Sinclair AM, et al. Functional erythropoietin receptor is undetectable in endothelial, cardiac, neuronal, and renal cells. Blood. 2010;115(21):4264–72.
112. Anagnostou A, et al. Erythropoietin receptor mRNA expression in human endothelial cells. Proc Natl Acad Sci USA. 1994;91:3974–8.
113. Wright GL, et al. Erythropoietin receptor expression in adult rat cardiomyocytes is associated with an acute cardioprotective effect for recombinant erythropoietin during ischemia-reperfusion injury. FASEB J. 2004;18:1031–3.
114. Echigoya MH, Obikane K, Nakashima T, Sasaki S. Glomerular localization of erythropoietin receptor mRNA and protein in neonatal and mature mouse kidney. Nephron Exp Nephrol. 2005;100:e21–9.
115. Wallach I, et al. Erythropoietin-receptor gene regulation in neuronal cells. Pediatr Res. 2009;65:619–24.
116. Masuda S, et al. Functional erythropoietin receptor of the cells with neural characteristics. Comparison with receptor properties of erythroid cells. J Biol Chem. 1993;268:11208–16.
117. Yu X, et al. Erythropoietin receptor signalling is required for normal brain development. Development. 2002;129:505–16.
118. Wu H, Lee SH, Gao J, Liu X, Iruela-Arispe ML. Inactivation of erythropoietin leads to defects in cardiac morphogenesis. Development. 1999;126:3597–605.
119. Cheetham JC, et al. NMR structure of human erythropoietin and a comparison with its receptor bound conformation. Nat Struct Biol. 1998;5:861–6.
120. Broudy VC, Lin N, Brice M, Nakamoto B, Papayannopoulou T. Erythropoietin receptor characteristics on primary human erythroid cells. Blood. 1991;77:2583–90.
121. Caravella JA, Lyne PD, Richards WG. A partial model of the erythropoietin receptor complex. Proteins. 1996;24:394–401.
122. Maouche L, Cartron JP, Chretien S. Different domains regulate the human erythropoietin receptor gene transcription. Nucleic Acids Res. 1994;22:338–46.
123. McCaffery PJ, Fraser JK, Lin FK, Berridge MV. Subunit structure of the erythropoietin receptor. J Biol Chem. 1989;264:10507–12.
124. Wilson IA, Jolliffe LK. The structure, organization, activation and plasticity of the erythropoietin receptor. Curr Opin Struct Biol. 1999;9:696–704.
125. Vadas O, Hartley O, Rose K. Characterization of new multimeric erythropoietin receptor agonists. Biopolymers. 2008;90:496–502.
126. Vadas O, Rose K. Multimeric peptides as agonists of the erythropoietin receptor. Adv Exp Med Biol. 2009;611:505–6.
127. Kirito K, et al. Identification of the human erythropoietin receptor region required for Stat1 and Stat3 activation. Blood. 2002;99:102–10.
128. Torti M, Marti KB, Altschuler D, Yamamoto K, Lapetina EG. Erythropoietin induces p21ras activation and p120GAP tyrosine phosphorylation in human erythroleukemia cells. J Biol Chem. 1992;267:8293–8.
129. Komatsu N, et al. Erythropoietin rapidly induces tyrosine phosphorylation in the human erythropoietin-dependent cell line, UT-7. Blood. 1992;80:53–9.
130. Nosaka Y, Arai A, Miyasaka N, Miura O. CrkL mediates Ras-dependent activation of the Raf/ERK pathway through the guanine nucleotide exchange factor C3G in hematopoietic cells stimulated with erythropoietin or interleukin-3. J Biol Chem. 1999;274: 30154–62.
131. Arai A, Kanda E, Miura O. Rac is activated by erythropoietin or interleukin-3 and is involved in activation of the Erk signaling pathway. Oncogene. 2002;21:2641–51.
132. Chen C, Sytkowski AJ. Erythropoietin activates two distinct signaling pathways required for the initia-

tion and the elongation of c-myc. J Biol Chem. 2001;276:38518–26.
133. Kubota Y, et al. Src transduces erythropoietin-induced differentiation signals through phosphatidylinositol 3-kinase. EMBO J. 2001;20:5666–77.
134. Neri LM, et al. Erythropoietin-induced erythroid differentiation of K562 cells is accompanied by the nuclear translocation of phosphatidylinositol 3-kinase and intranuclear generation of phosphatidylinositol (3,4,5) trisphosphate. Cell Signal. 2002; 14:21–9.
135. Cheng CK, Chan J, Cembrowski GS, van Assendelft OW. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. Lab Hematol. 2004;10:42–53.
136. Robins EB, Blum S. Hematologic reference values for African American children and adolescents. Am J Hematol. 2007;82:611–4.
137. Dallman PR, Yip R, Johnson C. Prevalence and causes of anemia in the United States, 1976 to 1980. Am J Clin Nutr. 1984;39:437–45.
138. Yip R, Schwartz S, Deinard AS. Hematocrit values in white, black, and American Indian children with comparable iron status. Evidence to support uniform diagnostic criteria for anemia among all races. Am J Dis Child. 1984;138:824–7.
139. Anonymous. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative [see comments]. Am J Kidney Dis. 1997;30:S192–240.
140. Anonymous. IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. Am J Kidney Dis [Online]. 2001;37: S182–238.
141. Henry J. Clinical diagnosis and management by laboratory methods. In: Methods hematology: basic methodology. Philadelphia: Saunders; 1996. p. 578–625.
142. Holt JT, DeWandler MJ, Arvan DA. Spurious elevation of the electronically determined mean corpuscular volume and hematocrit caused by hyperglycemia. Am J Clin Pathol. 1982;77:561–7.
143. Paterakis G, et al. The effect of red cell shape on the measurement of red cell volume. A proposed method for hte comparison assessment of this effect among various haematology analysers. Clin Lab Haematol. 1994;16:235–45.
144. Chandra M, Clemons GK, McVicar MI. Relation of serum erythropoietin levels to renal excretory function: evidence for lowered set point for erythropoietin production in chronic renal failure. J Pediatr. 1988;113:1015–21.
145. von Lilien T, Salusky IB, Boechat I, Ettenger RB, Fine RN. Five years' experience with continuous ambulatory or continuous cycling peritoneal dialysis in children. J Pediatr. 1987;111:513–8.
146. Nissenson AR. National cooperative rHu erythropoietin study in patients with chronic renal failure: a phase IV multicenter study. Report of National Cooperative rHu Erythropoietin Study Group. Am J Kidney Dis.1991;18:24–33.
147. Aljama P, et al. Serum ferritin concentration: a reliable guide to iron overload in uremic and hemodialyzed patients. Clin Nephrol. 1978;10:101–4.
148. Moreb J, Popovtzer MM, Friedlaender MM, Konijn AM, Hershko C. Evaluation of iron status in patients on chronic hemodialysis: relative usefulness of bone marrow hemosiderin, serum ferritin, transferrin saturation, mean corpuscular volume and red cell protoporphyrin. Nephron. 1983;35:196–200.
149. Gomez E, et al. Serum ferritin in haemodialysis patients: role of blood transfusions and 'haemochromatosis alleles' HLA A3, B7 and B14. Nephron. 1984;36:106–10.
150. Taccone-Gallucci M, et al. Risk of iron overload and 'hemochromatosis allele(s)' in patients on maintenance hemodialysis. Am J Nephrol. 1987;7:28–32.
151. Chavers BM, Sullivan EK, Tejani A, Harmon WE. Pre-transplant blood transfusion and renal allograft outcome: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Transplant. 1997;1:22–28.
152. Temple RM, Deary IJ, Winney RJ. Recombinant erythropoietin improves cognitive function in patients maintained on chronic ambulatory peritoneal dialysis. Nephrol Dial Transplant. 1995;10: 1733–8.
153. Kambova L. Recombinant erythropoietin improves cognitive function in chronic haemodialysis patients [letter]. Nephrol Dial Transplant. 1998;13:229–30.
154. Marsh JT, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int. 1991;39:155–63.
155. Nelson M. Anaemia in adolescent girls: effects on cognitive function and activity. Proc Nutr Soc. 1996;55:359–67.
156. Nissenson AR. Recombinant human erythropoietin: impact on brain and cognitive function, exercise tolerance, sexual potency, and quality of life. Semin Nephrol. 1989;9:25–31.
157. Temple RM, Langan SJ, Deary IJ, Winney RJ. Recombinant erythropoietin improves cognitive function in chronic haemodialysis patients. Nephrol Dial Transplant. 1992;7:240–5.
158. Weiskopf RB, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. Anesthesiology. 2000;92:1646–52.
159. Wolcott DL, Marsh JT, La Rue A, Carr C, Nissenson AR. Recombinant human erythropoietin treatment may improve quality of life and cognitive function in chronic hemodialysis patients. Am J Kidney Dis. 1989;14:478–85.
160. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000;105:E51.
161. Guthrie M, et al. Effects of erythropoietin on strength and functional status of patients on hemodialysis. Clin Nephrol. 1993;39:97–102.

162. 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: 718–23.
163. Campos A, Garin EH. Therapy of renal anemia in children and adolescents with recombinant human erythropoietin (rHuEPO). Clin Pediatr (Phila). 1992;31:94–9.
164. Portoles J, Lopez-Gomez JM, Aljama P. A prospective multicentre study of the role of anaemia as a risk factor in haemodialysis patients: the MAR Study. Nephrol Dial Transplant. 2007;22:500–7.
165. Nelson M, Bakaliou F, Trivedi A. Iron-deficiency anaemia and physical performance in adolescent girls from different ethnic backgrounds. Br J Nutr. 1994;72:427–33.
166. Kapoor RK, et al. Cardiovascular responses to treadmill exercise testing in anemia. Indian Pediatr. 1997;34:607–12.
167. Martin GR, Ongkingo JR, Turner ME, Skurow ES, Ruley EJ. Recombinant erythropoietin (Epogen) improves cardiac exercise performance in children with end-stage renal disease. Pediatr Nephrol. 1993;7:276–80.
168. 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;69:580–6.
169. Navarro M, Alonso A, Avilla JM, Espinosa L. Anemia of chronic renal failure: treatment with erythropoietin. Child Nephrol Urol. 1991;11:146–51.
170. Jabs K. The effects of recombinant human erythropoietin on growth and nutritional status. Pediatr Nephrol. 1996;10:324–7.
171. Boehm M, et al. Early erythropoietin therapy is associated with improved growth in children with chronic kidney disease. Pediatr Nephrol. 2007;22:1189–93.
172. Steinhauer HB, Lubrich-Birkner I, Dreyling KW, Horl WH, Schollmeyer P. Increased ultrafiltration after erythropoietin-induced correction of renal anemia in patients on continuous ambulatory peritoneal dialysis. Nephron. 1989;53:91–2.
173. Schollmeyer P, Lubrich-Birkner I, Steinhauer HB. Effect of recombinant human erythropoietin on anemia and dialysis: efficiency in patients undergoing CAPD. Contrib Nephrol. 1990;87:95–104.
174. Lubrich-Birkner I, Schollmeyer P, Steinhauer HB. One year experience with subcutaneous human erythropoietin in CAPD: correction of renal anemia and increased ultrafiltration. Adv Perit Dial. 1990;6:302–7.
175. Bessman J, Gilmer Jr P, Gardner F. Improved classification of anemias by MCV and RDW. Am J Clin Pathol. 1983;80:322–6.
176. Fialon P, Leaute AG, Sassier P, Vallot C, Wone C. Use of red blood cell indices (MCV, MCH, RDW) in monitoring chronic hemodialysis patients treated with recombinant erythropoietin. Pathol Biol. 1993; 41:931–5.
177. Besarab A, Caro J, Jarrell BE, Francos G, Erslev AJ. Dynamics of erythropoiesis following renal transplantation. Kidney Int. 1987;32:526–36.
178. Erslev AJ. Erythropoietin titers in health and disease. Semin Hematol. 1991;28:2–7. discussion 7–8.
179. Feinstein S, et al. Erythropoietin deficiency causes anemia in nephrotic children with normal kidney function. Am J Kidney Dis [Online]. 2001;37: 736–42.
180. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006;47:S11–145.
181. Linder MC, et al. Serum ferritin: does it differ from tissue ferritin? J Gastroenterol Hepatol. 1996;11: 1033–6.
182. Worwood M. Ferritin. Blood Rev. 1990;4:259–69.
183. Kwak EL, Larochelle DA, Beaumont C, Torti SV, Torti FM. Role for NF-kappa B in the regulation of ferritin H by tumor necrosis factor-alpha. J Biol Chem. 1995;270:15285–93.
184. Rogers JT, et al. Translational control during the acute phase response. Ferritin synthesis in response to interleukin-1. J Biol Chem. 1990;265:14572–8.
185. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK. The evaluation of iron status in hemodialysis patients. J Am Soc Nephrol. 1996;7:2654–7.
186. Kalantar-Zadeh K, et al. Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. Am J Kidney Dis. 1995;26: 292–9.
187. Tessitore N, et al. The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. Nephrol Dial Transplant. 2001;16:1416–23.
188. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. Nephrol Dial Transplant. 2004;19:141–9.
189. Coyne DW, et al. 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;18:975–84.
190. Singh AK, Coyne DW, Shapiro W, Rizkala AR. Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation. Kidney Int. 2007;71:1163–71.
191. Chuang CL, Liu RS, Wei YH, Huang TP, Tarng DC. Early prediction of response to intravenous iron supplementation by reticulocyte haemoglobin content and high-fluorescence reticulocyte count in haemodialysis patients. Nephrol Dial Transplant. 2003;18:370–7.
192. Mittman N, et al. Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis

patients receiving rHuEPO. Am J Kidney Dis. 1997;30:912–22.
193. Fishbane S, Shapiro W, Dutka P, Valenzuela OF, Faubert J. A randomized trial of iron deficiency testing strategies in hemodialysis patients. Kidney Int. 2001;60:2406–11.
194. Cullen P, et al. Hypochromic red cells and reticulocyte haemglobin content as markers of iron-deficient erythropoiesis in patients undergoing chronic haemodialysis. Nephrol Dial Transplant. 1999;14: 659–65.
195. Chiang WC, Tsai TJ, Chen YM, Lin SL, Hsieh BS. Serum soluble transferrin receptor reflects erythropoiesis but not iron availability in erythropoietin-treated chronic hemodialysis patients. Clin Nephrol. 2002;58:363–9.
196. Tarng DC, Huang TP. Determinants of circulating soluble transferrin receptor level in chronic haemodialysis patients. Nephrol Dial Transplant. 2002;17: 1063–9.
197. Fernandez-Rodriguez AM, et al. Diagnosis of iron deficiency in chronic renal failure. Am J Kidney Dis. 1999;34:508–13.
198. Ganz T. Molecular control of iron transport. J Am Soc Nephrol. 2007;18:394–400.
199. Domrongkitchaiporn S, Jirakranont B, Atamasrikul K, Ungkanont A, Bunyaratvej A. Indices of iron status in continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis. 1999;34:29–35.
200. Lin FK, et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci USA. 1985;82:7580–4
201. Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. J Biol Chem. 1977;252: 5558–64.
202. Lai PH, Everett R, Wang FF, Arakawa T, Goldwasser E. Structural characterization of human erythropoietin. J Biol Chem. 1986;261:3116–21.
203. Deicher R, Horl WH. Differentiating factors between erythropoiesis-stimulating agents: a guide to selection for anaemia of chronic kidney disease. Drugs. 2004;64:499–509.
204. Sikole A, Spasovski G, Zafirov D, Polenakovic M. Epoetin omega for treatment of anemia in maintenance hemodialysis patients. Clin Nephrol. 2002;57:237–45.
205. Bren A, et al. A comparison between epoetin omega and epoetin alfa in the correction of anemia in hemodialysis patients: a prospective, controlled crossover study. Artif Organs. 2002;26:91–7.
206. Sinai-Trieman L, Salusky IB, Fine RN. Use of subcutaneous recombinant human erythropoietin in children undergoing continuous cycling peritoneal dialysis. J Pediatr. 1989;114:550–4.
207. Brem AS, Lambert C, Hill C, Kitsen J, Shemin DG. Outcome data on pediatric dialysis patients from the end-stage renal disease clinical indicators project. Am J Kidney Dis [Online]. 2000;36:310–7.
208. Alexander S, Benfield M, Fine RN, McDonald R, Warady B. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2002 Annual Report. (2002).
209. Jabs K, Alexander S, McCabe D, Lerner G, Harmon WE. Primary results from the U.S. multicenter pediatric recombinant erythropoietin study. J Am Soc Nephrol. 1994;5:456 (abstract 484P).
210. Seeherunvong W, et al. Identification of poor responders to erythropoietin among children undergoing hemodialysis. J Pediatr. 2001;138:710–4.
211. Pollak A, et al. Effect of intravenous iron supplementation on erythropoiesis in erythropoietin-treated premature infants. Pediatrics. 2001;107:78–85.
212. Maier RF, et al. High-versus low-dose erythropoietin in extremely low birth weight infants. The European Multicenter rhEPO Study Group. J Pediatr. 1998; 132:866–70.
213. Brown MS, Jones MA, Ohls RK, Christensen RD. Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. J Pediatr. 1993;122:655–7.
214. 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;24:571–9.
215. Port RE, Mehls O. Erythropoietin dosing in children with chronic kidney disease: based on body size or on hemoglobin deficit? Pediatr Nephrol. 2009;24: 435–7.
216. Scigalla P, et al. Therapy of renal anemia with recombinant human erythropoietin in children with end-stage renal disease. Contrib Nephrol. 1989;76:227–40. discussion 240-221.
217. Cody J, et al. Frequency of administration of recombinant human erythropoietin for anaemia of end-stage renal disease in dialysis patients. Cochrane Database of Systematic Reviews: 2005(3).
218. Brandt JR, Avner ED, Hickman RO, Watkins SL. Safety and efficacy of erythropoietin in children with chronic renal failure [see comments]. Pediatr Nephrol. 1999;13:143–7.
219. Rusthoven E, van de Kar NC, Monnens LA, Schroder CH. Long-term effectiveness of intraperitoneal erythropoietin in children on NIPD by administration in small bags. Perit Dial Int. 2001;21:196–7.
220. Frenken LA, et al. Intraperitoneal administration of recombinant human erythropoietin. Perit Dial Int. 1992;12:378–83.
221. Rijk Y, Raaijmakers R, van de Kar N, Schroder C. Intraperitoneal treatment with darbepoetin for children on peritoneal dialysis. Pediatr Nephrol. 2007;22: 436–40.
222. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Br J Cancer. 2001;84:3–10.
223. Macdougall IC, Chandler G, Elston O, Harchowal J. Beneficial effects of adopting an aggressive intravenous iron policy in a hemodialysis unit. Am J Kidney Dis. 1999;34:S40–6.

224. Vekeman F, et al. Dose and cost comparison of erythropoietic agents in the inpatient hospital setting. Am J Health Syst Pharm. 2007;64:1943–9.
225. Song X, Long SR, Marder WD, Sullivan SD, Kallich J. The impact of methodological approach on cost findings in comparison of epoetin alfa with darbepoetin alfa. Ann Pharmacother. 2009;43:1203–10.
226. Courtney AE, McNamee PT, Maxwell AP. Cost should be the principal determinant of choice of erythropoiesis-stimulating agent in chronic haemodialysis patients. Nephron Clin Pract. 2007;107: c14–9.
227. Schmitt CP, Nau B, Brummer C, Rosenkranz J, Schaefer F. Increased injection pain with darbepoetin-alpha compared to epoetin-beta in paediatric dialysis patients. Nephrol Dial Transplant. 2006;21: 3520–4.
228. Aljama P, et al. Practical guidelines for the use of NESP in treating renal anaemia. Nephrol Dial Transplant. 2001;16:22–8.
229. Lerner G, et al. Pharmacokinetics of darbepoetin alfa in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2002;17:933–7.
230. Hutchinson FN, Jones WJ. A cost-effectiveness analysis of anemia screening before erythropoietin in patients with end-stage renal disease. Am J Kidney Dis. 1997;29:651–7.
231. Kaufman JS. Subcutaneous erythropoietin therapy: efficacy and economic implications. Am J Kidney Dis. 1998;32:S147–51.
232. Buckner FS, Eschbach JW, Haley NR, Davidson RC, Adamson JW. Hypertension following erythropoietin therapy in anemic hemodialysis patients. Am J Hypertens. 1990;3:947–55.
233. Abraham PA, Macres MG. Blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. J Am Soc Nephrol. 1991;2: 927–36.
234. Van Geet C, et al. Recombinant human erythropoietin increases blood pressure, platelet aggregability and platelet free calcium mobilisation in uraemic children: a possible link? Thromb Haemost. 1990;64: 7–10.
235. Yalcinkaya F, Tumer N, Cakar N, Ozkaya N. Low-dose erythropoietin is effective and safe in children on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1997;11:350–2.
236. Scharer K, Klare B, Braun A, Dressel P, Gretz N. Treatment of renal anemia by subcutaneous erythropoietin in children with preterminal chronic renal failure. Acta Paediatr. 1993;82:953–8.
237. Vaziri ND. Cardiovascular effects of erythropoietin and anemia correction. Curr Opin Nephrol Hypertens. 2001;10:633–7.
238. Raine AE, Roger SD. Effects of erythropoietin on blood pressure. Am J Kidney Dis. 1991;18:76–83.
239. Zhou XJ, Pandian D, Wang XQ, Vaziri ND. Erythropoietin-induced hypertension in rat is not mediated by alterations of plasma endothelin, vasopressin, or atrial natriuretic peptide levels. J Am Soc Nephrol. 1997;8:901–5.
240. Cogar AA, Hartenberger CH, Ohls RK. Endothelin concentrations in preterm infants treated with human recombinant erythropoietin. Biol Neonate. 2000;77: 105–8.
241. Raine AE. Hypertension, blood viscosity, and cardiovascular morbidity in renal failure: implications of erythropoietin therapy. Lancet. 1988;1:97–100.
242. Ni Z, Wang XQ, Vaziri ND. Nitric oxide metabolism in erythropoietin-induced hypertension: effect of calcium channel blockade. Hypertension. 1998;32:724–9.
243. Vaziri ND, et al. Role of nitric oxide resistance in erythropoietin-induced hypertension in rats with chronic renal failure. Am J Physiol. 1996;271: E113–22.
244. Schiffl H, Lang SM. Hypertension induced by recombinant human erythropoietin (rHU-EPO) can be prevented by indomethacin. Pathogenetic role of cytosolic calcium. Eur J Med Res. 1997;2:97–100.
245. Allegra A, et al. Administration of recombinant erythropoietin determines increase of peripheral resistances in patients with hypovolemic shock. Nephron. 1996;74:431–2.
246. Abiose AK, et al. Increased vascular alpha1-adrenergic sensitivity in patients with renal failure: receiving recombinant erythropoeitin. Am J Ther. 2007;14:427–34.
247. Fritschka E, et al. Effect of erythropoietin on parameters of sympathetic nervous activity in patients undergoing chronic haemodialysis. Br J Clin Pharmacol. 1990;30:135S–8.
248. Ksiazek A, Zaluska WT, Ksiazek P. Effect of recombinant human erythropoietin on adrenergic activity in normotensive hemodialysis patients. Clin Nephrol. 2001;56:104–10.
249. Hand MF, Haynes WG, Johnstone HA, Anderton JL, Webb DJ. Erythropoietin enhances vascular responsiveness to norepinephrine in renal failure. Kidney Int. 1995;48:806–13.
250. Vaziri ND. Mechanism of erythropoietin-induced hypertension. Am J Kidney Dis. 1999;33:821–8.
251. Jabs K, Harmon WE. Recombinant human erythropoietin therapy in children on dialysis. Adv Ren Replace Ther. 1996;3:24–36.
252. Luft FC. Erythropoietin and arterial hypertension. Clin Nephrol. 2000;53:S61–4.
253. De Marchi S, et al. Long-term effects of erythropoietin therapy on fistula stenosis and plasma concentrations of PDGF and MCP-1 in hemodialysis patients. J Am Soc Nephrol. 1997;8:1147–56.
254. Wirtz JJ, van Esser JW, Hamulyak K, Leunissen KM, van Hooff JP. The effects of recombinant human erythropoietin on hemostasis and fibrinolysis in hemodialysis patients. Clin Nephrol. 1992;38:277–82.
255. Eschbach JW, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med. 1989;111:992–1000.

256. Kooistra MP, van Es A, Marx JJ, Hertsig ML, Struyvenberg A. Low-dose aspirin does not prevent thrombovascular accidents in low-risk haemodialysis patients during treatment with recombinant human erythropoietin. Nephrol Dial Transplant. 1994;9:1115–20.
257. Metry G, et al. Effect of normalization of hematocrit on brain circulation and metabolism in hemodialysis patients. J Am Soc Nephrol. 1999;10:854–63.
258. Jaar B, et al. Effects of long-term treatment with recombinant human erythropoietin on physiologic inhibitors of coagulation. Am J Nephrol. 1997;17: 399–405.
259. Tassies D, et al. Effect of recombinant human erythropoietin treatment on circulating reticulated platelets in uremic patients: association with early improvement in platelet function. Am J Hematol. 1998;59:105–9.
260. el-Shahawy MA, Francis R, Akmal M, Massry SG. Recombinant human erythropoietin shortens the bleeding time and corrects the abnormal platelet aggregation in hemodialysis patients. Clin Nephrol. 1994;41:308–13.
261. 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 [see comments]. N Engl J Med. 1987;316:73–8.
262. Lewis NP, et al. Effects of the correction of renal anaemia by erythropoietin on physiological changes during exercise. Eur J Clin Invest. 1993;23:423–7.
263. Shinaberger JH, Miller JH, Gardner PW. Erythropoietin alert: risks of high hematocrit hemodialysis. ASAIO Trans. 1988;34:179–84.
264. Granolleras C, Leskopf W, Shaldon S, Fourcade J. Experience of pain after subcutaneous administration of different preparations of recombinant human erythropoietin: a randomized, double-blind crossover study. Clin Nephrol. 1991;36:294–8.
265. Frenken LA, et al. Identification of the component part in an epoetin alfa preparation that causes pain after subcutaneous injection. Am J Kidney Dis. 1993;22:553–6.
266. Frenken LA, van Lier HJ, Koene RA. Analysis of the efficacy of measures to reduce pain after subcutaneous administration of epoetin alfa. Nephrol Dial Transplant. 1994;9:1295–8.
267. Takemasa A, Yorioka N, Yamakido M. Investigation of the influenza-like symptoms associated with recombinant human erythropoietin therapy. J Int Med Res. 1997;25:127–34.
268. Kuriyama S, et al. Evidence for amelioration of endothelial cell dysfunction by erythropoietin therapy in predialysis patients. Am J Hypertens. 1996;9: 426–31.
269. Krmar RT, Gretz N, Klare B, Wuhl E, Scharer K. Renal function in predialysis children with chronic renal failure treated with erythropoietin. Pediatr Nephrol. 1997;11:69–73.
270. Albertazzi A, Di Liberato L, Daniele F, Battistel V, Colombi L. Efficacy and tolerability of recombinant human erythropoietin treatment in pre-dialysis patients: results of a multicenter study. Int J Artif Organs. 1998;21:12–8.
271. Jelkmann W. Erythropoiesis stimulating agents and techniques: a challenge for doping analysts. Curr Med Chem. 2009;16:1236–47.
272. Monahan JB, et al. Bivalent binding and signaling characteristics of Leridistim, a novel chimeric dual agonist of interleukin-3 and granulocyte colony-stimulating factor receptors. Exp Hematol. 2001; 29:416–24.
273. Nabholtz JM, et al. Phase III trial comparing granulocyte colony-stimulating factor to leridistim in the prevention of neutropenic complications in breast cancer patients treated with docetaxel/doxorubicin/cyclophosphamide: results of the BCIRG 004 trial. Clin Breast Cancer. 2002;3:268–75.
274. Abegg AL, et al. The enhanced in vitro hematopoietic activity of leridistim, a chimeric dual G-CSF and IL-3 receptor agonist. Leukemia. 2002;16: 316–26.
275. Farese AM, et al. Leridistim, a chimeric dual G-CSF and IL-3 receptor agonist, enhances multilineage hematopoietic recovery in a nonhuman primate model of radiation-induced myelosuppression: effect of schedule, dose, and route of administration. Stem Cells. 2001;19:522–33.
276. Farese AM, et al. A single dose of pegylated leridistim significantly improves neutrophil recovery in sublethally irradiated rhesus macaques. Stem Cells. 2001;19:514–21.
277. Nishino T, et al. Ex vivo expansion of human hematopoietic stem cells by a small-molecule agonist of c-MPL. Exp Hematol. 2009;37:1364–77. e1364.
278. Kessler M, et al. C.E.R.A. once every 4 weeks in patients with chronic kidney disease not on dialysis: the ARCTOS extension study. Hemodial Int. 2009;14:233–9.
279. Canaud B, et al. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. Nephrol Dial Transplant. 2008;23:3654–61.
280. Macdougall IC, et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. Clin J Am Soc Nephrol. 2008;3:337–47.
281. Klinger M, et al. Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. Am J Kidney Dis. 2007;50:989–1000.
282. Spinowitz B, et al. C.E.R.A. maintains stable control of hemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks. Am J Nephrol. 2008;28:280–9.
283. Locatelli F, Reigner B. C.E.R.A.: pharmacodynamics, pharmacokinetics and efficacy in patients with

chronic kidney disease. Expert Opin Investig Drugs. 2007;16:1649–61.
284. Sulowicz W, et al. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. Clin J Am Soc Nephrol. 2007;2:637–46.
285. Macdougall IC, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2006;1:1211–5.
286. Besarab A, et al. Efficacy and tolerability of intravenous continuous erythropoietin receptor activator: a 19-week, phase II, multicenter, randomized, open-label, dose-finding study with a 12-month extension phase in patients with chronic renal disease. Clin Ther. 2007;29:626–39.
287. Provenzano R, et al. The continuous erythropoietin receptor activator (C.E.R.A.) corrects anemia at extended administration intervals in patients with chronic kidney disease not on dialysis: results of a phase II study. Clin Nephrol. 2007;67:306–17.
288. de Francisco AL, et al. Continuous Erythropoietin Receptor Activator (C.E.R.A.) administered at extended administration intervals corrects anaemia in patients with chronic kidney disease on dialysis: a randomised, multicentre, multiple-dose, phase II study. Int J Clin Pract. 2006;60:1687–96.
289. Locatelli F, et al. C.E.R.A. safety profile: a pooled analysis in patients with chronic kidney disease. Clin Nephrol. 2010;73:94–103.
290. Hamad I, Hunter AC, Szebeni J, Moghimi SM. Poly(ethylene glycol)s generate complement activation products in human serum through increased alternative pathway turnover and a MASP-2-dependent process. Mol Immunol. 2008;46:225–32.
291. Laine GA, Hossain SM, Solis RT, Adams SC. Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. Ann Pharmacother. 1995;29:1110–4.
292. Lee DE, Son W, Ha BJ, Oh MS, Yoo OJ. The prolonged half-lives of new erythropoietin derivatives via peptide addition. Biochem Biophys Res Commun. 2006;339:380–5.
293. Lu B, Liu X, Huang P. Construction of a fusion protein between N-terminal 153 peptide of thrombopoietin and erythropoietin. Sci China C Life Sci. 1998;41:426–34.
294. Penno CA, Kawabe Y, Ito A, Kamihira M. Production of recombinant human erythropoietin/Fc fusion protein by genetically manipulated chickens. Transgenic Res. 2010;19:187–95.
295. Joung CH, et al. Production and characterization of long-acting recombinant human albumin-EPO fusion protein expressed in CHO cell. Protein Expr Purif. 2009;68:137–45.
296. Lacy SE, et al. The potency of erythropoietin-mimic antibodies correlates inversely with affinity. J Immunol. 2008;181:1282–7.
297. Schriebl K, et al. Biochemical characterization of rhEpo-Fc fusion protein expressed in CHO cells. Protein Expr Purif. 2006;49:265–75.
298. Sytkowski AJ, Lunn ED, Risinger MA, Davis KL. An erythropoietin fusion protein comprised of identical repeating domains exhibits enhanced biological properties. J Biol Chem. 1999;274:24773–8.
299. Dumont JA, et al. Delivery of an erythropoietin-Fc fusion protein by inhalation in humans through an immunoglobulin transport pathway. J Aerosol Med. 2005;18:294–303.
300. Bitonti AJ, et al. Pulmonary delivery of an erythropoietin Fc fusion protein in non-human primates through an immunoglobulin transport pathway. Proc Natl Acad Sci USA. 2004;101:9763–8.
301. Lee JY. Purification of biologically active human erythropoietin-binding protein and detection of its binding sites. Ann Clin Lab Sci. 2007;37:63–70.
302. Bugelski PJ, et al. CNTO 530: molecular pharmacology in human UT-7EPO cells and pharmacokinetics and pharmacodynamics in mice. J Biotechnol. 2008;134:171–80.
303. Bouman-Thio E, et al. A phase I, single and fractionated, ascending-dose study evaluating the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of an erythropoietin mimetic antibody fusion protein (CNTO 528) in healthy male subjects. J Clin Pharmacol. 2008;48:1197–207.
304. Stead RB, et al. Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. Blood. 2006;108:1830–4.
305. Macdougall IC, et al. A peptide-based erythropoietin-receptor agonist for pure red-cell aplasia. N Engl J Med. 2009;361:1848–55.
306. Woodburn KW, Schatz PJ, Fong KL, Beaumier P. Erythropoiesis equivalence, pharmacokinetics and immune response following repeat hematide™ administration in cynomolgus monkeys. Int J Immunopathol Pharmacol. 2010;23:121–9.
307. Woodburn KW, et al. A subchronic murine intravenous pharmacokinetic and toxicity study of Hematide, a PEGylated peptidic erythropoiesis-stimulating agent. Drug Chem Toxicol. 2010;33:28–37.
308. Minamishima YA, et al. Somatic inactivation of the PHD2 prolyl hydroxylase causes polycythemia and congestive heart failure. Blood. 2008;111:3236–44.
309. Ladroue C, et al. PHD2 mutation and congenital erythrocytosis with paraganglioma. N Engl J Med. 2008;359:2685–92.
310. Hsieh MM, et al. HIF prolyl hydroxylase inhibition results in endogenous erythropoietin induction, erythrocytosis, and modest fetal hemoglobin expression in rhesus macaques. Blood. 2007;110:2140–7.
311. Provenzano RW, et al. A Novel Oral HIF-PHI, Stimulates Erythropoiesis and Increases Hemoglobin Concentration in Patients with Non-Dialysis CKD. Am J Kidney Dis. 2008;51:B80.FG2216.
312. Klaus S, et al. Beneficial Pharmacodynamic Effects Resulting from 'Complete Erythropoiesis' Induced

by Novel HIF Prolyl Hydroxylase Inhibitors FG-2216 and FG-4592. Presented at the 41st Annual Meeting of the American Society of Nephrology (Abstract F-PO1835) 2008.
313. Hewitson KS, et al. Structural and mechanistic studies on the inhibition of the hypoxia-inducible transcription factor hydroxylases by tricarboxylic acid cycle intermediates. J Biol Chem. 2007;282:3293–301.
314. Hewitson KS, et al. Hypoxia-inducible factor (HIF) asparagine hydroxylase is identical to factor inhibiting HIF (FIH) and is related to the cupin structural family. J Biol Chem. 2002;277:26351–5.
315. Obara N, et al. Repression via the GATA box is essential for tissue-specific erythropoietin gene expression. Blood. 2008;111:5223–32.
316. Nakano Y, et al. Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease. Blood. 2004;104:4300–7.
317. Yaqub MS, Leiser J, Molitoris BA. Erythropoietin requirements increase following hospitalization in end-stage renal disease patients. Am J Nephrol. 2001;21:390–6.
318. Vreugdenhil G, Wognum AW, van Eijk HG, Swaak AJ. Anaemia in rheumatoid arthritis: the role of iron, vitamin B12, and folic acid deficiency, and erythropoietin responsiveness. Ann Rheum Dis. 1990;49:93–8.
319. Remacha AF, et al. Erythroid abnormalities in rheumatoid arthritis: the role of erythropoietin. J Rheumatol. 1992;19:1687–91.
320. Macdougall IC, Cooper A. The inflammatory response and epoetin sensitivity. Nephrol Dial Transplant. 2002;17:48–52.
321. Pixley JS, MacKintosh FR, Smith EA, Zanjani ED. Anemia of inflammation: role of T lymphocyte activating factor. Pathobiology. 1992;60:309–15.
322. Souweine B, et al. Serum erythropoietin and reticulocyte counts in inflammatory process. Ann Med Interne. 1995;146:8–12.
323. Jelkmann WE, Fandrey J, Frede S, Pagel H. Inhibition of erythropoietin production by cytokines. Implications for the anemia involved in inflammatory states. Ann N Y Acad Sci. 1994;718:300–9. discussion 309–311.
324. Jelkmann W, Pagel H, Wolff M, Fandrey J. Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. Life Sci. 1992;50:301–8.
325. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. Blood. 1992;79:1987–94.
326. Fandrey J, Jelkmann WE. Interleukin-1 and tumor necrosis factor-alpha inhibit erythropoietin production in vitro. Ann N Y Acad Sci. 1991;628:250–5.
327. Jelkmann W, Wolff M, Fandrey J. Modulation of the production of erythropoietin by cytokines: in vitro studies and their clinical implications. Contrib Nephrol. 1990;87:68–77.
328. Winter SS, Howard T, Ware RE. Regulation of expression of the human erythropoietin receptor gene. Blood Cells Mol Dis. 1996;22:214–24. discussion 224a.
329. Lu L, et al. Effects of recombinant human tumor necrosis factor alpha, recombinant human gamma-interferon, and prostaglandin E on colony formation of human hematopoietic progenitor cells stimulated by natural human pluripotent colony-stimulating factor, pluripoietin alpha, and recombinant erythropoietin in serum-free cultures. Cancer Res. 1986;46: 4357–61.
330. Yip R, Dallman PR. The roles of inflammation and iron deficiency as causes of anemia. Am J Clin Nutr. 1988;48:1295–300.
331. Gunnell J, Yeun JY, Depner TA, Kaysen GA. Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis [Online]. 1999;33:63–72.
332. Kim JK, et al. The predictive parameters of erythropoietin hyporesponsiveness in patients on continuous ambulatory peritoneal dialysis. Korean J Intern Med. 2001;16:110–7.
333. Barany P, Divino Filho JC, Bergstrom J. High C-reactive protein is a strong predictor of resistance to erythropoietin in hemodialysis patients. Am J Kidney Dis. 1997;29:565–8.
334. Kooistra MP, et al. Iron absorption in erythropoietin-treated haemodialysis patients: effects of iron availability, inflammation and aluminium. Nephrol Dial Transplant. 1998;13:82–8.
335. Ahsan N, Holman MJ, Gocke CD, Groff JA, Yang HC. Pure red cell aplasia due to parvovirus B19 infection in solid organ transplantation. Clin Transplant. 1997;11:265–70.
336. Bertoni E, et al. Severe aplastic anaemia due to B19 parvovirus infection in renal transplant recipient. Nephrol Dial Transplant. 1995;10:1462–3.
337. Bertoni E, et al. Aplastic anemia due to B19 parvovirus infection in cadaveric renal transplant recipients: an underestimated infectious disease in the immunocompromised host. J Nephrol. 1997;10:152–6.
338. Tonelli M, Blake PG, Muirhead N. Predictors of erythropoietin responsiveness in chronic hemodialysis patients. ASAIO J. 2001;47:82–5.
339. Coen G, et al. Parathyroidectomy in chronic renal failure: short- and long-term results on parathyroid function, blood pressure and anemia. Nephron. 2001;88:149–55.
340. Mandolfo S, et al. Parathyroidectomy and response to erythropoietin therapy in anaemic patients with chronic renal failure. Nephrol Dial Transplant. 1998;13:2708–9.
341. Rault R, Magnone M. The effect of parathyroidectomy on hematocrit and erythropoietin dose in patients on hemodialysis. ASAIO J. 1996;42:M901–3.
342. Barbour GL. Effect of parathyroidectomy on anemia in chronic renal failure. Arch Intern Med. 1979;139:889–91.
343. Zingraff J, et al. Anemia and secondary hyperparathyroidism. Arch Intern Med. 1978;138:1650–2.

344. Podjarny E, et al. Is anemia of chronic renal failure related to secondary hyperparathyroidism? Arch Intern Med. 1981;141:453–5.
345. Grutzmacher P, Radtke HW, Fassbinder W, Koch KM, Schoeppe W. Effect of secondary hyperparathyroidism on the anaemia of end-stage renal failure: in vivo and in vitro studies. Proceedings of the European Dialysis & Transplant Association 1983, vol. 20, p. 739–745.
346. Geary DF, et al. Hyperparathyroidism and anemia in chronic renal failure. Eur J Pediatr. 1982;139:296–8.
347. Kcomt J, Sotelo C, Raja R. Influence of adynamic bone disease on responsiveness to recombinant human erythropoietin in peritoneal dialysis patients. Adv Perit Dial. 2000;16:294–6.
348. Nazem AK, Mako J. The effect of calcitriol on renal anaemia in patients undergoing long-term dialysis. Int Urol Nephrol. 1997;29:119–27.
349. Goicoechea M, et al. Intravenous calcitriol improves anaemia and reduces the need for erythropoietin in haemodialysis patients. Nephron. 1998;78:23–7.
350. Massry SG. Pathogenesis of the anemia of uremia: role of secondary hyperparathyroidism. Kidney Int Suppl. 1983;16:S204–7.
351. Gallieni M, Corsi C, Brancaccio D. Hyperparathyroidism and anemia in renal failure. Am J Nephrol. 2000;20:89–96.
352. Foulks CJ, Mills GM, Wright LF. Parathyroid hormone and anaemia – an erythrocyte osmotic fragility study in primary and secondary hyperparathyroidism. Postgrad Med J. 1989;65:136–9.
353. Zachee P, Chew SL, Daelemans R, Lins RL. Erythropoietin resistance due to vitamin B12 deficiency. Case report and retrospective analysis of B12 levels after erythropoietin treatment. Am J Nephrol. 1992;12:188–91.
354. Sunder-Plassmann G, Horl WH. Novel aspects of erythropoietin response in renal failure patients. Nephrol Dial Transplant. 2001;16:40–4.
355. 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.
356. Graafland AD, Doorenbos CJ, van Saase JC. Enalapril-induced anemia in two kidney transplant recipients. Transpl Int. 1992;5:51–3.
357. Kuriyama R, et al. Angiotensin converting enzyme inhibitor induced anemia in a kidney transplant recipient. Transplant Proc. 1996;28:1635.
358. Le Meur Y, et al. Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: relationship with erythropoietin requirements. Am J Kidney Dis [Online]. 2001;38:510–7.
359. Eiselt J, Racek J, Opatrny Jr K. The effect of hemodialysis and acetate-free biofiltration on anemia. Int J Artif Organs. 2000;23:173–80.
360. Geerlings W, et al. Factors influencing anaemia in dialysis patients. A special survey by the EDTA-ERA Registry. Nephrol Dial Transplant. 1993;8: 585–9.
361. Losekann A, et al. Aluminium intoxication in the rat induces partial resistance to the effect of recombinant human erythropoietin. Nephrol Dial Transplant. 1990;5:258–63.
362. Fulton B, Jeffery EH. Heme oxygenase induction. A possible factor in aluminum-associated anemia. Biol Trace Elem Res. 1994;40:9–19.
363. Gonella M, Pratesi G, Calabrese G, Vagelli G, Mazzotta A. Improvement of anemia in patients on chronic dialysis treated by hemodiafiltration. Blood Purif. 1989;7:186–91.
364. Steuer RR, Leypoldt JK, Cheung AK, Senekjian HO, Conis JM. Reducing symptoms during hemodialysis by continuously monitoring the hematocrit. Am J Kidney Dis. 1996;27:525–32.
365. Coli L, et al. Evidence of profiled hemodialysis efficacy in the treatment of intradialytic hypotension. Int J Artif Organs. 1998;21:398–402.
366. 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 [see comments]. N Engl J Med. 1998;339:584–90.
367. Madore F, et al. Anemia in hemodialysis patients: variables affecting this outcome predictor. J Am Soc Nephrol. 1997;8:1921–9.
368. Casadevall N, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002;346:469–75.
369. Warady BA, et al. Iron therapy in the pediatric hemodialysis population. Pediatr Nephrol (Berlin). 2004;19:655–61.
370. Aggarwal HK, et al. Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. J Assoc Physicians India. 2003;51: 170–4.
371. Stoves J, Inglis H, Newstead CG. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. Nephrol Dial Transplant. 2001;16:967–74.
372. Pru C, Eaton J, Kjellstrand C. Vitamin C intoxication and hyperoxalemia in chronic hemodialysis patients. Nephron. 1985;39:112–6.
373. Boggs DR. Fate of a ferrous sulfate prescription. Am J Med. 1987;82:124–8.
374. Wingard RL, Parker RA, Ismail N, Hakim RM. Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. Am J Kidney Dis. 1995;25:433–9.
375. Nissenson AR, et al. Clinical evaluation of heme iron polypeptide: sustaining a response to rHuEPO in hemodialysis patients. Am J Kidney Dis. 2003;42:325–30.
376. Barraclough KA, et al. Rationale and design of the oral HEMe iron polypeptide Against Treatment with Oral Controlled Release Iron Tablets trial for the correction of anaemia in peritoneal dialysis patients (HEMATOCRIT trial). BMC Nephrol. 2009;10:20.

377. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. Am J Kidney Dis. 1995;26:41–6.
378. Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloib L. Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. Nephron. 1998;79:299–305.
379. Macdougall IC, et al. A randomized controlled study of iron supplementation in patients treated with erythropoietin. Kidney Int. 1996;50:1694–9.
380. Ruiz-Jaramillo Mde L, Guizar-Mendoza JM, Gutierrez-Navarro Mde J, Dubey-Ortega LA, Amador-Licona N. Intermittent versus maintenance iron therapy in children on hemodialysis: a randomized study. Pediatr Nephrol (Berlin). 2004;19: 77–81.
381. Warady BA, Zobrist RH, Wu J, Finan E. Sodium ferric gluconate complex therapy in anemic children on hemodialysis. Pediatr Nephrol (Berlin). 2005;20: 1320–7.
382. Bastani B, Rahman S, Gellens M. Lack of reaction to ferric gluconate in hemodialysis patients with a history of severe reaction to iron dextran. ASAIO J. 2002;48:404–6.
383. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. JAMA. 1980;243:1726–31.
384. Ifudu O. Parenteral iron: pharmacology and clinical use. Nephron. 1998;80:249–56.
385. Coyne DW, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. Kidney Int. 2003;63:217–24.
386. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol. 2004;76:74–8.
387. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. Am J Kidney Dis. 1999;33: 464–70.
388. Warady BA, Zobrist RH, Finan E. Sodium ferric gluconate complex maintenance therapy in children on hemodialysis. Pediatr Nephrol (Berlin). 2006;21: 553–60.
389. Charytan C, Qunibi W, Bailie GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract. 2005;100:c55–62.
390. Singh H, Reed J, Noble S, Cangiano JL, Van Wyck DB. Effect of intravenous iron sucrose in peritoneal dialysis patients who receive erythropoiesis-stimulating agents for anemia: a randomized, controlled trial. Clin J Am Soc Nephrol. 2006; 1:475–82.
391. Leijn E, Monnens LA, Cornelissen EA. Intravenous iron supplementation in children on hemodialysis. J Nephrol. 2004;17:423–6.
392. Morgan HE, Gautam M, Geary DF. Maintenance intravenous iron therapy in pediatric hemodialysis patients. Pediatr Nephrol (Berlin). 2001;16: 779–83.
393. Coyne DW. Ferumoxytol for treatment of iron deficiency anemia in patients with chronic kidney disease. Expert Opin Pharmacother. 2009;10:2563–8.
394. Provenzano R, et al. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4:386–93.
395. Singh A, et al. Safety of ferumoxytol in patients with anemia and CKD. Am J Kidney Dis. 2008;52: 907–15.
396. Spinowitz BS, et al. Ferumoxytol for treating iron deficiency anemia in CKD. J Am Soc Nephrol. 2008;19:1599–605.
397. Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH. Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. Am J Kidney Dis. 2001;37:564–72.
398. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol. 2005;16:3070–80.
399. Rambod M, Kovesdy CP, Kalantar-Zadeh K. Combined high serum ferritin and low iron saturation in hemodialysis patients: the role of inflammation. Clin J Am Soc Nephrol. 2008;3:1691–701.
400. Besarab A. Resolving the paradigm crisis in intravenous iron and erythropoietin management. Kidney Int Suppl. 2006;101:S13–8.
401. Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. Ann Intern Med. 1998;129:925–31.
402. Carmel R, Denson TA, Mussell B. Anemia. Textbook vs practice. JAMA. 1979;242:2295–7.
403. Abernathy KA, Meuleman JR. Appropriateness of iron prescribing: a retrospective study. Pharmacotherapy. 1996;16:473–6.
404. Shinton N. CRC Desk Reference for Hematology. 1st ed. Boca Raton, FL: CRC Press; 1998. p. 740.

Immune Function and Immunizations in Dialyzed Children

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Keywords
Chronic kidney disease • End-stage renal disease • Immune function • Dialyzed children • Immunization

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) 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 ESRD 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 ESRD [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 ESRD. 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 ESRD is sparse. The incidence of peritonitis and catheter-related infections in children are 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

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to the immune system dysfunction in children with CKD and ESRD. 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.

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 ESRD have produced conflicting results [12–18]. Lower numbers of memory B cells have been reported in children on dialysis, and children with pre-dialytic CKD have been reported to have alterations in memory T-cell subsets [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 the 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]. 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, 40, 41].

Phagocytic Cells and Receptors

Reduced chemotaxis, adhesion, migration, and phagocytosis characterize the dysfunction of neutrophils and monocytes demonstrated in patients on dialysis [27, 42–45]. Data on the characteristics and function of phagocytes in children with CKD are limited [46, 47]. Interestingly, one study demonstrated that treatment with recombinant human growth hormone enhanced the oxidative burst activity of neutrophils in uremic children [46]. Wasik and colleagues concluded that PD improves phagocytosis and intracellular killing of bacteria by peritoneal macrophages but not by peripheral blood neutrophils in ESRD patients [47]. In another study of pediatric patients with ESRD, 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 [48].

Limited information is available on the impact of CKD on IgG receptor (Fcγ(gamma)R) and complement receptor (CR) expression or function [49–53]. 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 [49, 50]. In children with pre-dialytic CKD and ESRD, studies have demonstrated a lower expression of Fcγ(gamma) RII (CD32) on peripheral blood monocytes and neutrophils compared to healthy children [40, 54–57]. 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 [40, 54–57].

Immunoglobulins

Low levels of IgG and/or subclasses have been described in patients on PD, attributed to peritoneal loss in most of the studies [58–69]. 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 [62, 63]. 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 [63]. Children receiving PD had the lowest serum Ig levels [63].

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 [64, 69]. In children, a study by Kuizon et al. found a significant relationship between IgG and the incidence of peritonitis [70]. 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 [63].

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 maximizing 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 immune globulin 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 may have reduced response to and/or reduced duration of antibody after immunization. In addition, pediatric dialysis patients may be at increased risk for infection from vaccine-preventable disease and therefore require immunizations not routinely provided to healthy children. Unfortunately, because the care of these children is so complex, delivery of routine well-child care, including immunizations, can be delayed or overlooked. In fact, data from the United States Renal Data System (USRDS) reveal that among prevalent pediatric ESRD patients, only one-third received seasonal influenza vaccine between 2004 and 2007, and fewer than 10% received vaccination against *Streptococcus pneumoniae* or hepatitis B [71]. In order to minimize the risk for vaccine-preventable disease in pediatric dialysis patients, it is imperative that all who care for these patients remain abreast of the recommended childhood immunization schedule, as well as alterations to this schedule required for children with CKD.

The recommended immunization schedule for healthy children in the United States is updated each year by the Center for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP), the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) [72, 73]. Because the schedule is updated annually, it is not published here, but can be found on the CDC and AAP websites (http://www.aap.org/healthtopics/immunizations.cfm; http://www.cdc.

gov/vaccines/). Immunization against diphtheria, tetanus, pertussis, *Hemophilus influenzae* type b, polio, measles, mumps, rubella, *Streptococcus pneumoniae*, varicella zoster, and Hepatitis B continue to be recommended by the AAP, ACIP, and AAFP for all healthy children [72, 73]. Recent modifications to this schedule include the recommendation that all infants receive the rotavirus vaccine, an attenuated live-virus vaccine, beginning at 6 weeks of age, with completion of the three-dose series by age 8 months [74]. Other recent changes to the standard schedule is the addition of the tetravalent-conjugated meningococcal vaccine, which is now recommended for all children between the age of 11 and 18 years and the hepatitis A vaccine which is recommended for all children at age 1 year with a second dose 6 months later [75, 76]. The final new addition to the schedule is immunization against human papillomavirus (HPV), which now includes recommendations that males receive the quadrivalent vaccine (HPV4) beginning at age 9 years [77]. Females may receive either HPV4 or the bivalent vaccine (HPV2) beginning at age 11 years [77].

In addition to the recommendations for healthy children, the CDC has developed a guideline for vaccinating patients with CKD, including those on dialysis, which is available on the CDC website [78]. In the following sections, available data concerning vaccine response in pediatric dialysis patients will be provided and any modification of the standard schedule that may be required for children on dialysis will be discussed.

Diphtheria, Tetanus, and Pertussis Vaccine (DTP)

Although studies in older children and young adults on dialysis suggest that seroconversion rates after DTP immunization are 69–88% compared to 93–100% in healthy children, a multicenter study performed in infants vaccinated while on dialysis revealed protective antibody titers to both diphtheria and tetanus toxoids in 7/8 patients (88%) [79–82]. Thus infants on dialysis should receive DTP immunizations according to according to the standard childhood schedule, but given the data in older children on dialysis, efforts should be made to ensure that booster immunizations against tetanus and diphtheria are provided.

Hemophilus 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 [83]. 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 [83]. 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 [84]. 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 [85]. Current recommendations specify that dialysis patients less than 20 years of age receive hepatitis B immunization according to the standard schedule, with the caveat that "higher doses might be more immunogenic" in pediatric HD patients [78, 81, 86]. The recommendations of the ACIP reflect the fact that, although response to hepatitis B vaccine has been extensively studied in the adult dialysis population, few studies have been performed in pediatric CKD patients. In one study, 62 children on dialysis or status post renal transplant received three doses of 5 μg (age < 10 years) or 10 μg (age > 10 years) of hepatitis B vaccine [84]. Antibody levels obtained 2 months after the final immunization were protective in 60/62 (97%) patients [84]. In a multicenter

study performed by the Southwest Pediatric Nephrology Study Group, 78 pediatric patients with CKD not yet on dialysis, on dialysis, or status post kidney transplant were given three immunizations of 20 μg HbsAg after which 91% of patients had a protective titer of ≥10 mIU/mL [87]. 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%) [87]. In addition, geometric mean antibody titers after three immunizations tended to be higher in patients with pre-dialysis CKD than in patients on dialysis or post-transplant, leading the authors to suggest that at least two immunizations be given prior to the point at which dialysis or transplant are necessary, whenever possible [87].

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) [81]. Antibody levels should then be measured annually and booster doses provided to patients whose antibody levels fall below protective [81].

Inactivated Polio Virus Vaccine

Since 1999, the AAP and ACIP recommendations have specified that only IPV vaccine, rather than the live-attenuated oral vaccine, be used for routine immunization in all children [88]. Although IPV vaccine should routinely be delivered to infants on dialysis, there are no studies documenting response to this vaccine in this patient population. A study performed in older children on dialysis measured antibody levels 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 [89]. 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. As such, MMR should be avoided in children on dialysis if they are receiving immunosuppressive therapy, including corticosteroids at a dose greater than 2 mg/kg body weight or 20 mg total daily or on alternate days for more than 14 days [90]. Once corticosteroids are discontinued, it is generally recommended that MMR vaccination be delayed for at least 1 month [90]. In addition, this live-viral vaccine is contraindicated in the immunosuppressed kidney transplant recipient [90].

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 [91]. Furthermore, only 3/10 (30%) had protective titers to all three viruses [91]. 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 [92]. 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 [92]. Finally, a 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 [84]. Although these data suggest that many pediatric patients on dialysis may respond well to MMR vaccine, because immunization post-transplant is contraindicated, antibody titers should be measured prior to proceeding to transplant, and repeat vaccination given to patients with negative titers [90].

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 kidney transplantation [93]. Because of the significant risk for morbidity and mortality from varicella zoster infection post-transplant, 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 [94, 95]. 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 [96, 97]. 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 [96, 97]. 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 kidney transplantation and to provide supplemental vaccination if positive antibody titers are not demonstrated.

Pneumococcal Vaccine

It has long been recommended that children on dialysis receive vaccination against *Streptococcus pneumoniae*, as these patients are considered high risk for the development of invasive pneumococcal infection [98, 99]. All children on dialysis should therefore be vaccinated with the heptavalent-conjugated pneumococcal vaccine (PCV7) as is recommended for healthy children. Recent studies have suggested that this vaccine produces adequate antibody response in children with CKD, including those on dialysis, and in solid organ transplant recipients [100, 101]. Because children on dialysis are considered high risk for pneumococcal disease, they should also receive supplemental immunization with the 23-valent polysaccharide vaccine (23PS) to expand serotype coverage [98]. The timing of the supplemental immunization with 23PS vaccine varies depending on the age of the patient and the number of previous immunizations with PCV7 [98]. Specific recommendations for immunizing high-risk children with PCV7 and 23PS vaccine can be found at the AAP and CDC websites. Revaccination with 23 PS should occur after 3 years in children less than 10 years of age at the time of first vaccination, and 5 years after the initial immunization in older children [98, 99]. Revaccination is important as several studies have suggested that although 23PS vaccine produces a reasonable antibody response in children on dialysis, there may be a rapid decline in antibody levels [84, 102, 103].

Hepatitis A, Meningococcal, Human Papillomavirus, and Rotavirus Vaccines

There are currently no data available on response to hepatitis A, meningococcal, HPV, or rotavirus vaccines in children on dialysis, although prospective studies of the response to HPV and the tetravalent-conjugated meningococcal vaccine in children with CKD, including dialysis patients, are currently underway (A Neu, personal communication). 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.

Influenza Vaccine

Previously recommended only for high-risk populations, annual vaccination against influenza is now recommended for all children over the age of 6 months [104]. High-risk populations continue to be a priority for immunization, and this group includes children on dialysis as well as their household contacts [105]. The composition of the influenza vaccine changes each year based on the strains of viruses likely to circulate in the upcoming year, and, therefore, this vaccine must be given annually, typically in the Fall [105]. 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 [105]. The influenza vaccine is available either as an inactivated vaccine or a live, attenuated vaccine (LAIV). However, the CDC currently recommends that persons with kidney dysfunction, including those on dialysis, not receive LAIV. Therefore, only the inactivated vaccine should be given to patients on dialysis [106].

Because of the significant risk for morbidity and mortality associated with influenza infection in pediatric patients with CKD, there have been several studies evaluating vaccine response in this population. The majority of these studies have focused on pediatric kidney transplant patients and although one study revealed a lower seroconversion rate than in healthy siblings, two other studies have demonstrated seroconversion rates that are similar between transplant patients and controls [107–109]. One of these studies also evaluated vaccine response in pediatric dialysis patients and revealed equivalent seroconversion rates between the study group and controls [108]. 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 [105].

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. More studies regarding the impact of uremia and the dialysis process on the immune system in children with CKD and ESRD are necessary. In the meantime, in an effort to minimize risk for vaccine-preventable disease, pediatric patients on dialysis should receive all of the 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-attenuated vaccines (Rotavirus vaccine, MMR, VZV) in dialysis patients treated with immunosuppressive medications. Because MMR and VZV vaccines are contraindicated post-transplant, every effort to provide immunization prior to the introduction of immunosuppressive medication post-transplantation should be made. Additional vaccination against *Streptococcus pneumoniae* and monitoring of protection against hepatitis B should be performed. Supplemental and/or augmented doses of hepatitis B vaccine should be given as indicated.

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 Jr K, 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, Buschenfelde KH Meyer zum, 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: evidence 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, Buschenfelde KH Meyer zum, 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 pre-dialysis 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. 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.

41. 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.
42. Descamps-Latscha B, Herbelin A. Long-term dialysis and cellular immunity: a critical survey. Kidney Int Suppl. 1993;41:S135–42.
43. 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.
44. 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.
45. Braun N. Expression of adhesion molecules and activation markers on lymphocytes and monocytes during hemodialysis. Blood Purif. 1997;15:61–76.
46. 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.
47. 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.
48. 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.
49. Nockher WA, Scherberich JE. Expanded CD14+ CD16+ monocyte subpopulation in patients with acute and chronic infections undergoing hemodialysis. Infect Immun. 1998;66:2782–90.
50. 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.
51. 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.
52. 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.
53. Halma C, Daha MR, Feitsma RI, et al. Does haemodialysis impair macrophage Fc receptor function? Nephrol Dial Transplant. 1992;7:618–22.
54. Bouts AHM. Fcγ receptor expression on phagocytic cells in children with CRF. Perit Dial Int. 2000; 20:112.
55. Bouts AHM, Davin JC, Monnens LA, et al. Complement receptors in blood and dialysate of children on peritoneal dialysis. Blood Purif. 2002;20:515.
56. 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.
57. 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.
58. Fivush BA, Case B, May MW, et al. Hypogammaglobulinemia in children undergoing continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1989;3:186–8.
59. Bunchman TE. Chronic dialysis in the infant less than 1 year of age. Pediatr Nephrol. 1995;9(Suppl):S18–22.
60. 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.
61. Katz A, Kashtan CE, Greenberg LJ, et al. Hypogammaglobulinemia in uremic infants receiving peritoneal dialysis. J Pediatr. 1990;117:258–61.
62. 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.
63. Bouts AHM, Davin JC, Krediet RT, et al. IgG and subclasses in children before and after starting peritoneal dialysis. Immunol Lett. 1997;56:333.
64. 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.
65. Descamps-Latscha B, Herbelin A, Nguyen AT, et al. Immune system dysregulation in uremia. Semin Nephrol. 1994;14:253–60.
66. Preud'homme JL, Hanson LA. IgG subclass deficiency. Immunodefic Rev. 1990;2:129–49.
67. 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.
68. Oxelius VA. IgG subclass levels in infancy and childhood. Acta Paediatr Scand. 1979;68:23–7.
69. Krediet RT, Koomen GC, Vlug A, et al. IgG subclasses in CAPD patients. Perit Dial Int. 1996;16:288–94.
70. 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.
71. U.S. Renal Data System, USRDS 2009 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, MD, 2009.
72. Committee of Infectious Diseases. Recommended childhood and adolescent immunization schedules United States, 2010. Pediatrics. 2010;125:195–6.

73. Centers for Disease Control and Prevention. Recommended immunization schedules for persons aged 0 through 18 years – United States, 2010. MMWR. 2010;58:1–4.
74. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2002;58(RR-02):1–28.
75. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2005;54(RR-07):1–21.
76. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2006;55(RR-07):1–23.
77. ACIP Provisional Recommendations for HPV Vaccine. http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm. Accessed 5 Jan 2010.
78. Guidelines for vaccinating kidney dialysis patients and patients with chronic kidney disease: Summarized from recommendations of the Advisory Committee on Immunization Practices. http://www.cdc.gov/vaccines/pubs/downloads/b_dialysis_guide-508.pdf. Accessed 5 Jan 2010.
79. 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.
80. 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.
81. Rangel MC, Coronado VG, Euler GL, et al. Vaccine recommendations for patients on chronic dialysis. Semin Dial. 2000;13:101–7.
82. 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.
83. Neu AM, Lederman HM, Warady BA, et al. *Haemophilus influenza* type b immunization in infants on peritoneal dialysis. Pediatr Nephrol. 1996;10:84–5.
84. Laube GF, Berger C, Goetschel P, et al. Immunization in children with chronic renal failure. Pediatr Nephrol. 2002;17L:638–42.
85. Centers for Disease Control and Prevention. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR. 2001;50(RR-05):1–46.
86. Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of Hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: immunization of infants, children, and adolescents. MMWR. 2005;54(RR-16):1–33.
87. 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.
88. 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.
89. 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.
90. 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. 1998;47(RR-08):1–58.
91. Schulman SL, Deforest A, Kaiser BA, et al. Response to measles-mumps-rubella vaccine in children on dialysis. Pediatr Nephrol. 1992;6:187–9.
92. 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.
93. 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.
94. Broyer M, Boudailliez B. Varicella vaccine in children with chronic renal insufficiency. Postgrad Med J. 1985;61(Suppl 4):103–6.
95. Zamora I, Simon JM, Da Silva ME, et al. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol. 1994;8:190–2.
96. 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. Pediatric Nephrol. 2003;18:33–8.
97. 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.
98. American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics. 2000;106:362–6.
99. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1997;46(RR-08):1–24.
100. 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.

101. Barton M, Wasfy S, Dipchand AI, et al. Seven-valent pneumococcal conjugate vaccine in pediatric solid organ transplant recipients. Pediatr Infect Dis J. 2009;28:688–92.
102. Fuchshuber A, Kuhnemund O, Keuth B, et al. Pneumococcal vaccine in children and young adults with chronic renal disease. Nephrol Dial Transplant. 1996;11:468–73.
103. 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.
104. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2008;57(RR-07):1–60.
105. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2002;51(RR-03):1–32.
106. Centers for Disease Control and Prevention. Prevention and Control of Influenza: recommendations of the Advisory Committee on Immunizations Practices (ACIP). MMWR. 2005;54(RR-8):1–40.
107. Edvardsson VO, Flynn JT, Deforest A, et al. Effective immunization against influenza in pediatric renal transplant recipients. Clin Transplant. 1996;10:556–60.
108. 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.
109. Mauch TJ, Crouch NA, Freese DK, et al. Antibody response of pediatric solid organ transplant recipients to immunization against influenza virus. J Pediatr. 1995;127:957–60.

Neurological Effects and Cognitive Development

29

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Pediatric dialysis • Neurological effects • Cognitive development • Brain development • End stage renal disease

Introduction

Children and adult survivors of childhood-onset end stage kidney disease (ESKD) 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 manifestations such as a lower intelligence quotient (IQ) and lower frequency of post-secondary education compared with the general population [2]. The mechanisms responsible for the brain dysfunction observed with ESKD have not been established. The goals of this chapter are to review the acute neurologic complications of dialysis and to explore potential mechanisms leading to brain dysfunction, summarize known neurocognitive and neurologic findings, and consider possible management strategies for cognitive dysfunction in children affected by ESKD.

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Acute Neurologic Complications of Dialysis

Dialysis is associated with neurologic complications that range from mild to severe. In the severely uremic patient undergoing initial hemodialysis therapy, investigations using magnetic resonance imaging (MRI) have documented that pre-dialysis cerebral edema may worsen after dialysis without evidence of cell toxicity. This finding was accompanied by variable nonspecific clinical manifestations of dizziness, headache, nausea, and vomiting after dialysis and stable serum sodium but significant diminution in blood urea nitrogen [3]. Dialysis disequilibrium syndrome is an uncommon complication at the end of hemodialysis or immediately following. The syndrome manifests as headache, nausea, muscle cramps and twitching, delirium, and seizures and typically spontaneously remits. The cause of disequilibrium syndrome is not clear. Postulated mechanisms include cerebral

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cellular osmolar imbalance caused by rapid urea clearance or intracellular acidemia with subsequent expansion of intracellular water and cerebral edema. Dialysis disequilibrium syndrome is now uncommon as efforts to prevent this condition are routinely employed, namely, limiting the urea clearance in initial dialysis sessions by reducing blood flow rate, dialysis time, dialyzer surface area and using sodium modeling or relatively high dialysate sodium to prevent significant fluid shifts during the initial sessions of hemodialysis in a uremic patient. Osmotic demyelination syndrome is a more severe manifestation of the fluid and osmolar shifts that accompany kidney failure. Patients with osmotic demyelination syndrome tend to have hyponatremia and uremia at the onset of dialysis. Dialysis may precipitously correct these abnormalities and result in acute demyelination in the pontine and extra-pontine regions [4]. The manifestations of this condition my include seizure activity and acute onset of neurologic changes such as dysarthria, dysphagia, and paraplegia reminiscent of a stroke. In patients with uremia, the osmotic demyelination syndrome may resolve partially or completely over the course of 1–2 weeks. As with dialysis disequilibrium syndrome, prevention of this condition with gradual correction of the osmolar, electrolyte, and fluid imbalances that accompany uremia is the optimal strategy. Hypoxic/ischemic stress occurs with dialysis-associated hypotension. This is likely complicated by chronic cerebral oxidative stress associated with uremia and dialysis therapy. The resulting CNS hypoperfusion may lead to acute or chronic neurologic manifestations of encephalopathy. On MRI, microinfarcts and ischemic and hemorrhagic cerebral vascular injury may be acute manifestations of this injury. In the chronic environment, cerebral atrophy may be the manifestation of dialysis-associated cerebral hypoperfusion. The impact of these acute neurologic challenges on the developing brain is incompletely understood but may play a causal role in the cognitive dysfunction observed in dialysis-dependent children.

Brain Development and Associated Neurocognitive and Neurological Function in ESKD

Brain Development

In general, brain development is quite rapid during early childhood and more subtle in late childhood and adolescence. Consequently, expectations for developmental attainment and general cognitive performance change as the child ages. This rapid neurodevelopmental growth trajectory places the developing brain at particular risk from injury or disease during infancy and childhood. Dennis [5] has suggested that the degree and severity of insult is likely related to when the insult occurs in the neurodevelopmental sequence and the available cognitive reserve of the individual. Studies of other childhood chronic health conditions present from birth or shortly after have found delays in language, motor skills, and overall developmental level [6–8]. In addition, children with early brain injury have shown deficits in academic achievement, cognitive, and motor functioning at the time of injury [9, 10], which persist long past the initial insult [11]. These deficits may be worse than brain insults obtained in later years [12]. Although studies of the longitudinal impact of ESKD in infancy and early childhood are sparse, one study found that developmental delays were greatest for infants who had kidney disease from birth [13]. Further research is needed to understand how ESKD affects the developing brain and whether or not factors, such as age of onset, prematurity, and disease severity, moderate future neurocognitive outcomes.

Neurocognitive Function and CKD

Over the past five decades, the cognitive function of small cohorts of children with ESKD 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. Even in the current era of ESKD management, however, cognitive function has continued to be shown to be at risk. A review of the contemporary studies over the past 15 years is provided in Table 29.1.

In infants and very young children, general assessments of neurodevelopment are based upon developmental levels (e.g., the developmental quotient or DQ), and in older children and adults the IQ is considered the general measure of cognition. In children with ESKD, mean DQ/IQ is approximately 15 points lower compared with normative populations. The nadir for IQ appears to correspond with dialysis-dependent ESKD and may partially improve with transplantation [25].

In ESKD, specific domains of cognition have also been affected including memory, academic achievement, attention, and executive function. Memory has been assessed in studies comparing children with CKD to a healthy population and between children with varying stages of CKD. Overall, the memory of children with CKD is impaired relative to the healthy control populations, and this impairment is greatest with dialysis-dependent ESKD. These abilities also have been noted to improve after kidney transplant [20].

Academic achievement skills, including reading and arithmetic, are also impaired in children with kidney failure. Three study cohorts examining the impact of CKD on academic achievement have been published. One study showed no difference between CKD and healthy controls, and two studies showed diminished academic achievement scores in children with ESKD relative to healthy sibling controls and to healthy population controls [16, 17].

Attention and executive functions have been identified as a more frequent problem in children with CKD compared with the general population. Attention appears to be most severely affected with dialysis-dependent ESKD and partially improves after transplantation [14, 20, 24]. Executive functions are considered higher-order brain functions which are highly multidimensional. In a single study of children with CKD compared with age-matched controls exploring this multidimensionality, children with CKD had particular difficulties in initiating and sustaining complex tasks within the executive function domain. The groups did not differ on the ability to stop or shift tasks, inhibition and set shifting, within executive function tasks [18].

We have a true paucity to absence of information regarding the impact of ESKD on language, fine motor, and gross motor skills. Similarly, we have relatively little data on adaptation or on the differential effect of cognitive function versus performance. This latter area of performance is an important concept which is often considered a potential strength of children who develop disabilities. How one compensates for a specific deficit is likely to have a significant impact on their overall daily activities and general adaptive functions.

Neuroanatomy and Electrical Conductance

In addition to neurocognitive function, the impact of ESKD has been demonstrated by various neuroimaging and electroencephalographic (EEG) procedures. From the neuroimaging literature, structural analyses via MRI and computerized tomography (CT) have documented chronic infarct lesions, ischemic watershed zone white matter lesions, and cerebral atrophy in children with ESKD [26, 27]. Electrical conduction dysfunction also has been reported, with EEG abnormalities being reported in 42% of a pediatric cohort with CKD from infancy; similar finding have been associated with lower kidney function and severe anemia in adults [28, 29]. Hurkx et al. [30] found no differences in auditory pathway nerve conduction between children with CKD and children undergoing peritoneal dialysis; however, high inter-peak latencies were found in the somatosensory cortex and were attributed to decreased cortical conduction via the thalamus. In addition to specific conduction abnormalities, children with CKD may be at risk for generalized conduction abnormalities which manifests as a seizure disorder reported in 0% [31] to 20% [32] of children with CKD. In a cohort of 51 children observed before and after transplant, 52% experienced one

Table 29.1 Cognitive functioning in children and adolescents with chronic kidney disease

Author	Study population				IQ/DQ	Attention/ executive functions	Memory	Academic achievement
	Control	Dialysis	Transplant	CKD II–IV				
Bawden et al. [14]	22	22[a]				ESRD < control	ESRD = control	ESRD = control
Crocker et al. [15]		15		9	Congenital = acquired		Congenital < acquired	Congenital = acquired
Brouhard et al. [16]	62	26	36		ESRD < controls			ESRD < controls
Duquette et al. [17]	41	15		30	CKD < controls			CKD < controls
Gipson et al. [18]	18	12		20	CKD < controls		CKD < controls	
Hulstijn-Dirkmaat et al. [19]		16		15	CKD < norms			
Mendley and Zelko [20]		9			Pre < post transplant	Pre < post transplant	Pre < post transplant	
Qvist et al. [21]			33		Mean IQ 87 < norm mean 100			
Warady et al. [22]			24		1(4%) below average development			
Duquette et al. [23]	15			15	CKD < control			
Slickers et al. [24]		ESRD = 14		Mild = 7 Severe = 8	ESRD < severe < mild	ESRD < severe < mild	ESRD < severe < mild	

[a]22 subjects include dialysis and non-dialysis patients awaiting transplant

or more seizures during dialysis-dependent care and 24% experienced one or more seizures after transplant [21]. Although this was considered a high-risk cohort, the greater frequency of seizures during dialysis dependency relative to transplant dependency may be generalizable.

Renal–Brain Connections in Children

Given the above findings from the available pediatric neurocognitive and neurological literature, there appears to be a 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/or brain development?

At its simplest level, chronic kidney disease (CKD) impacts the nervous system by not effectively filtering neurotoxic chemicals and metabolites from the bloodstream. In severe kidney failure, EEG analysis has demonstrated a progressive slowing of EEG patterns with escalating serum creatinine [29]. Over time, the circulation of harmful biochemicals through the brain and its periphery has the potential to significantly impact the structure and organization of the nervous system in children. Even early treatments for ESKD (e.g., aluminum phosphate binders) were found to have an adverse effect on the developing brain, and subsequently were eliminated from contemporary treatment protocols. Similarly, improved management of anemia in children with ESKD is thought to buffer the impact of kidney disease on the nervous system based, in part, on findings in adults with ESKD [33]. These findings, however, have not provided a clear mechanism for why kidney disease is associated with brain impairment in children.

Acquired Kidney Injury Versus Chronic Kidney Disease

Possible linkages between the kidney and brain have begun to be illuminated in the adult literature, and possible mechanisms have emerged that may have implications for pediatric kidney disease. For adult patients who sustain acute kidney injury (AKI), there is a greater susceptibility to encephalopathy, given the rapid encroachment of uremia, compared to those with CKD. Presenting symptoms in rapidly progressive AKI may include poor attention and concentration, motor clumsiness, cognitive fatigue, and seizures. These progressive clinical features may be related to changes in sodium and water imbalance [34], the acute accumulation of uremic toxins, subsequent neurotransmitter disruptions and inflammatory effects in the brain [35]. Nguyen et al. [36] further suggested that the amount of cerebral damage may be related to direct cerebral endothelial damage, systemic inflammation, and subsequent encephalopathy. Interestingly, animal studies by Liu et al. [37] and others [38] have found hippocampal inflammation and cell death following AKI. If these findings transfer to humans, then the appearance of attention, memory, and learning impairments in individuals with kidney disease would be expected. Additionally, it is important to note that this brain region is also sensitive to the effects of cerebral hypoxic-ischemic injury which may be present in individuals with AKI.

In contrast, the pathophysiology in CKD is different than what is seen in AKI. Here, the effects of uremia typically can be seen in the more severe forms of kidney disease, particularly in the presence of rapidly progressing kidney failure or severe hypertension. In conditions such as polycystic kidney disease, brain injury from intracranial brain hemorrhages may compound ESKD-induced central nervous system injury [39]. Brain dysfunction also can occur due to the various medications used, with brain dysfunction being associated with changes in drug clearance secondary to kidney failure. Although no specific metabolite has been identified as the major contributor to disruption of the neurotransmitter system, hormonal imbalances, demyelination, and associated brain impairment [39], the constellation of neurocognitive dysregulation in patients with kidney failure is known to nephrologists as uremic encephalopathy [40].

Vascular Integrity

Another potentially strong linkage from kidney disease to 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. Approximately, 14–18% of adult patients with CKD across the United States and Europe, respectively, have a medical history significant for transient ischemic attacks, carotid endarterectomy, and stroke [41]. The presence of hypertension, diabetes, and dyslipidemia, features seen in many adults with CKD, also are noted risk factors for cerebrovascular disease. Adults with some combination of these conditions manifest small vessel hypertensive disease and associated small lacunar brain infarctions detected during postmortem examination [42, 43]. Ikram et al. [44] found a high rate of moderate kidney impairment in a large geriatric sample, with lower kidney function being significantly related to less white matter in deep regions of the brain and more frequent white matter lesions.

Murray [45] and others have argued for a linkage between the kidney and the brain that is based on a model of accelerated vascular impairment. For example, Kobayashi et al. [46] studied the association between silent brain infarction (SBI) and CKD. Using a cross-sectional sample of 335 adults with CKD and 40 with essential hypertension, MRI revealed a 56.5% rate of SBI in the sample. Hypertensive nephrosclerosis had a strong association with SBI, with the odds of having an infarction increasing with severity of kidney disease as defined by eGFR. This study advocated for more intensive preventive management in adults with CKD, especially in the presence of hypertension.

Further, adults with ESKD have approximately a 3–9 times greater risk for stroke compared with the general population. Even adults with ESKD who do not have a significant history for stroke or transient ischemic attacks, approximately one-half of these individuals have an MRI-defined brain infarction and white matter lesions. For adults with mild to moderate renal insufficiency defined by Cystatin C levels, there is a 30–60% risk of stroke [47]. For adults with dialysis dependence, repeated hypotension during hemodialysis may contribute to a reduction in cerebral blood flow, possible cerebral swelling, irreversible brain ischemia, and subsequent infarcts in watershed regions of the brain [48, 49].

Kidney impairment also has been shown to be negatively related to the expected drop in nocturnal blood pressure, or dipping, and brain small vessel disease has been linked to diurnal variations in blood pressure. These types of associations point to a direct causal role of kidney disease brain dysfunction. Seliger and Longstreth [50] suggested two potential mechanisms. One related to the decrease in nitric oxide metabolites which regulate blood circulation in the small vessels in the brain. Decreased levels of nitric oxide have been linked to endothelial dysfunction of the connecting arteries, white matter lesions, and other small vessel disease in the brain [51]. A second mechanism suggested the presence of homocysteine and inflammation, which increase with kidney dysfunction, and these factors also have been linked to small vessel disease.

Summary

Vascular disease of both the kidney and brain is evident [44], but the exact mechanism or mechanisms remain to be identified. The adult nephrology literature has begun to provide some theories that may inform a neurodevelopmental model of brain dysfunction in children and adolescents with kidney disease; nonetheless, we are cognizant that the adult literature is just beginning to explore these relationships as well. The available literature indicates that many individuals with kidney disease are susceptible to cerebrovascular involvement, but what are the markers that might suggest that a child or adolescent has the same susceptibility? Connecting what is known about kidney–brain connections in the adult literature, with what is known about brain impairment in the child literature, could provide the field with a clearer view of how best to approach the brain functioning in children and adults with kidney disease.

Understanding these neurodevelopmental linkages in the kidney–brain connection will be critical with respect to determining specific risk factors in childhood, and perhaps examining long-term management and prevention strategies.

Management of Cognitive Dysfunction in Children with CKD

Given the chronic nature of CKD and the associated neurodevelopmental challenges, it is likely that children and adolescents with ESKD are in need of a variety of management strategies. Not only do the various medical complications that many of these children experience interfere with day-to-day functioning (e.g., frequent school absences, medication compliance issues, etc.), but they likely will experience frequent challenges in the school and preschool settings secondary to their cognitive dysfunction. Although there are not evidence-based educational management strategies or interventions explicitly linked to ESKD, there are a number of empirically based interventions that have a demonstrated track record in working with children with learning and developmental difficulties. These interventions likely will have good applicability to a pediatric CKD population.

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, and when fine-motor skills evolve into grasping a snack with the rake of a hand to scribbling with a crayon. Eventually adaptive skills and other important functions such as writing develop. This time period also is critical for the ongoing development of cognitive abilities, pre-academic skills, and increasingly complex social interactions [52]. As such, these 5 years of life are at least as important as any other 5 year span in an individual's life.

With the appearance of kidney disease during this time period, another risk factor now complicates this developmental period. In addition to the potential effects of kidney disease on brain development, there also may be concerns with respect to that child's involvement in the preschool setting. The importance of early intervention services for infants and preschoolers with CKD is supported by investigations showing that early impairment in this population persists into childhood. Previous work by Geary and Haka-Ikse [13] and, more recently, Coulthard and Crosier [53] has found that the developmental scores of infants and toddlers with CKD were relatively stable into early childhood with increased impairment being associated with earlier onset of disease.

The quality of neurodevelopmental outcomes may be dependent on the type and quality of the early intervention services that they receive. The accumulating evidence indicates that results of early efforts to remediate or attenuate children's deficits can be successful. To date, investigations of early intervention have focused on two major groups of children: those who exhibit developmental deficits as a result of environmental factors and those who are disabled as a result of biological factors. These two groups of children comprise the majority of the special education population in public school programs. A question that must be asked is: If these children had been identified and served earlier, could something have been done to reduce the need for special education placement or, at least, to reduce the severity of the children's problems?

Although more evidence exists to support the benefits of early intervention for children at environmental risk [54–56], research that supports services for young children with biological impairments also is growing. For example, Black et al. [57] 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, 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 early onset kidney disease remains to be determined.

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 [52]. There are specific evidence-based preschool curricula designed to promote skills across a broad range of developmental areas [58]. It is suspected that young children with CKD will respond positively to early intervention approaches and programs, but evidence-based findings are not yet available. In the meantime, it will be important for pediatric nephrologists to be aware of such programs in their communities so as to work with their families and local developmental experts in gaining the early intervention services that might be necessary for the child with CKD.

School Age

Despite many medical advances in pediatric nephrology, children with ESKD 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 revealed that 79–94% of children with ESKD attended regular education settings with or without remedial tutoring, while 13–15% received special education services not related to visual or hearing impairments [21, 22]. Proportions of children with CKD receiving additional educational support are approximately equal to national rates of enrollment in special education services among all disabilities (13% for the 2001–2002 school year [58]). More recently, preliminary findings from the NIH-funded CKiD project revealed that parents reported that school-age students with CKD were receiving special education or Section 504 services at a rate of about 37%; however, only about 40–70% of the children with CKD with various types of neurodevelopmental dysfunction were receiving the necessary services [59]. Additional research is needed to better understand the special education needs of children with CKD; however, there are a variety of evidence-based instructional strategies that likely are applicable to children with CKD.

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 as a critical component to reading intervention for children with reading recognition problems. Indeed, The National Reading Panel [60] over a decade ago showed the effects to be large in magnitude. Similarly, repeated reading interventions have been shown to improve reading fluency [61], while the development and use of strategies have been employed successfully to improve reading comprehension [62].

Less empirical work has been conducted in the areas of mathematics and written language; however, what is available does suggest that targeted interventions in these areas may be applicable to children with kidney disease who are struggling with learning issues. In the math area, Baker et al. [63] noted that peer tutoring and explicit teaching of arithmetic procedures and math concepts were successful in improving the overall math skills of students.

Similarly, in the area of written language, significant progress has been made for older school-age children with writing problems using metacognitive [64] and other self-regulated

strategies [65]. Most recently, Hooper et al. [66] documented the importance of examining the interaction between cognitive functioning and written language instruction for early elementary school children at risk for writing disorders, with a particular focus on language and executive functions. This latter study is important for children with ESKD given the reported memory and executive deficits that can be manifest in this population, which makes them at risk for written language disorders. These findings also raise the possibility that if such cognitive factors are not taken into account, they could be disruptive to even evidence-based interventions.

Adolescence and Adult Transition

Children with ESKD face many barriers during their transition through adolescence and 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 and the associated medical complications can prevent many adolescents from making this transition and facing these developmental challenges successfully [67]. However, the current survival rates for adolescents with ESKD of 80% at 10 years [68, 69] must be coupled with successful transition expectations.

To date, intervention research geared toward the medical and psychosocial barriers that impede transition to adulthood is almost nonexistent. Similarly, intervention research geared toward the cognitive barriers to transition are also absent. In spite of minimal response-to-intervention research with 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. [25] 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.

Summary

There are a variety of management strategies and interventions for the cognitive dysfunction that can be evident in children and adolescents with ESKD. Although there are no specific educational or cognitive treatment strategies that have been evaluated in the pediatric ESKD population, there is a firm, evidence-based foundation for many interventions in children that could be used for this population. The early intervention strategies for infants, toddlers, and preschool children clearly provide an immediate avenue for services for early onset kidney disease, while the areas of reading, math, and written language have specific strategies for addressing deficits in these academic content areas for children with CKD who also are struggling with core academic skills. Additionally, as children age, the issue of transition into the various needs of young adulthood – including management of their kidney disease – becomes a critical focus, although the evidence-based literature addressing transition is largely in its infancy. 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 CKD and his/her family from a life course perspective, with ongoing neurodevelopmental surveillance being a critical component of that approach.

Conclusions and Directions

This chapter outlined the neurodevelopmental challenges of children with ESKD which have implications on educational performance and achievement, acquisition of self-management skills during the adolescent to adult transitional phase, and ultimately vocational opportunities. Potential mechanisms have been proposed but require significant scientific inquiry to confirm or dispel these hypotheses. Regardless of the mechanism, children with neurodevelopmental challenges should have the opportunity for proven interventions to optimize their cognitive trajectory and opportunities for independence as adults. Using a multidisciplinary and scientifically

rigorous approach, we anticipate the coming decade to provide opportunity to progress from quantifying the developmental challenges to identifying effective interventions and to provide insight into the mechanisms of the cognitive dysfunction demonstrated in children with CKD.

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. Tarhan NC, Agildere AM, Benli US, Ozdemir FN, Aytekin C, Can U. Osmotic demyelination syndrome in end-stage renal disease after recent hemodialysis:MRI of the brain. Am J Roentgenol. 2004;182:809–14.
4. Chen CL, Lai PH, Chou KJ, Lee PT, Chung HM, Fang HC. A preliminary report of brain edema in patients with uremia at first hemodialysis: evaluation by diffusion-weighted MR imaging. Am J Neuroradiol. 2007; 28:68–71.
5. Dennis M. Developmental plasticity in children: the role of biological risk, development, time, and reserve. J Commun Disord. 2000;33:321–32.
6. Fleisher BE, Baum D, Brudos G, Burge M, Carson E, Constantinou J, et al. Infant heart transplantation at Stanford: growth and neurodevelopmental outcome. Pediatrics. 2002;109:1–7.
7. Hogan AM, Kirkham FJ, Prengler M, Telfer P, Lane R, Vargha-Khadem F, de Haan M. Br J Haematol. 2006;132:99–107.
8. Kramer JH, Crittenden MR, DeSantes K, Cowan MJ. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. Bone Marrow Transplant. 1997;19:607–13.
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:e616–23.
10. Wetherington CE, Hooper SR. Traumatic brain injury in the preschool period: implications for special educators. Exceptionality. 2006;14:155–70.
11. Anderson V, Brown S, Newitt H. What contributes to quality of life in adult survivors of childhood traumatic brain injury? J Neurotrauma. 2010;27:863–70.
12. AndersonV, Jacobs R, Spencer-Smith M, Coleman L, Anderson P, Williams J, Greenham M, Leventer R. Does early age at brain insult predict worse outcome? Neuropsychological implications. J Pediatr Psychol 2010;35:716–27.
13. Geary DF, Haka-Ikse K. Neurodevelopmental progress of young children with chronic renal disease. Pediatrics. 1989;84:68–72.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. Mendley SR, Zelko FA. Improvement in specific aspects of neurocognitive performance in children after renal transplantation. Kidney Int. 1999;56: 318–23.
21. 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.
22. Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol. 1999;13:759–65.
23. Duquette PJ, Hooper SR, Icard PF, Hower SJ, Mamak EG, WetheringtonCE, GipsonDS. Neurodevelopmental status and adaptive behaviors in preschool children with chronic kidney disease. J Spec Educ. 2008;43(1):45–51. doi:10.1177/0022466907313351.
24. 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.
25. Icard PF, Hower SJ, Kuchenreuther AR, Hooper SR, Gipson DS. The transition from childhood to adulthood with ESRD: educational and social challenges. Clin Nephrol. 2008;69:1–7.
26. Nichols SL, Press GA, Schneider JA, Trauner DA. Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. Pediatr Neurol. 1990;6: 379–81.

27. 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;8:44–51.
28. Elzouki A, Carroll J, Butinar D, Moosa A. Improved neurological outcome in children with chronic renal disease from infancy. Pediatr Nephrol. 1994;8:205–10.
29. 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.
30. 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.
31. Hamiwka LD, Midgley JP, Hamiwka LA. Seizures in children after kidney transplantation: has the risk changed and can we predict who is at greatest risk? Pediatr Transplant. 2008;12:527–30.
32. Awan AQ, Lewis MA, Postlethwaite RJ, Webb NJ. Seizures following renal transplantation in childhood. Pediatr Nephrol. 1999;13:275–7.
33. 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.
34. Arieff AI, Massry SG. Calcium metabolism of brain in acute renal failure: effects of uremia, hemodialysis, and parathyroid hormone. J Clin Invest. 1974;53: 387–92.
35. De Deyn PP, Vanholder R, D'Hooge R. Nitric oxide in uremia: effects of several potentially toxic guanidine compounds. Kidney Int Suppl. 2003;84:S25–8.
36. Nguyen DN, Spopen H, Su F, Schiettecatte J, Shi L, Hachimi-Idrissi S, Huyghens I. Elevated levels of S-100 beta protein and neuron-specific enolase associated with brain injury in patients with severe sepsis and septic shock. Crit Care Med. 2006;34:1967–74.
37. Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov J, Sun Z, Crow M, Ross CA, Mattson MP, Rabb H. Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol. 2008;19:1360–70.
38. Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry. 2007;12:656–70.
39. Davenport A. The brain and the kidney – organ cross talk and interactions. Blood Purif. 2008;26:526–36.
40. Brouns R, DeDeyn PP. Neurological complications in renal failure: a review. Clin Neurol Neurosurg. 2004; 107:1–16.
41. Goodkin DA, Bragg-Gresham JL, Koening KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and United States: the dialysis outcomes and practice patterns study (DOPPS). J Am Soc Nephrol. 2003;14:3270–7.
42. Lass P, Buscombe JR, Harber M, Davenport A, Hilson AJ. Cognitive impairment in patients with renal failure is associated with multiple-infarct dementia. Clin Nucl Med. 1999;24:561–5.
43. Van der Sande FM, Hermans MM, Leunissen KM, Kooman JP. Noncardiac consequences of hypertension in hemodialysis patients. Semin Dial. 2004;17: 304–6.
44. Ikram MA, Vernooij MW, Hofman A, Neissen WJ, van der Lugt A, Breteler MMB. Kidney function is related to cerebral small vessel disease. Stroke. 2008;39:55–61.
45. Murray AM. The brain and the kidney connection: a model of accelerated vascular cognitive impairment. Neurology. 2009;73:916–7.
46. Kobayashi M, Hirawa N, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, Andoh D, Toya Y, Yasuda G, Umemura S. Relationship between silent brain infarction and chronic kidney disease. Nephrol Dial Transplant. 2009;24:201–7.
47. Seliger SL, Longstreth WT, Katz R, Manolio T, Fried LF, Shlipak M, Stehman-Breen CO, Newman A, Sarnak M, Gillen DL, Bleyer A, Siscovick DS. Cystatin C and subclinical brain infarction. J Am Soc Nephrol. 2005;16:3721–7.
48. Davenport A. Ultrafiltration in diuretic resistant volume overload in nephritic syndrome and patients with ascites in chronic liver disease. Cardiology. 2001;96: 190–5.
49. Davenport A. Nitradialytic complications during hemodialysis. Hemodial Int. 2006;10:162–7.
50. Seliger SL, Longstreth WT. Lessons about brain vascular disease from another pulsating organ, the kidney. Stroke. 2008;39:5–6.
51. Hoth KF, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, Paul RH, Jefferson AL, Haley AP, Cohen RA. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. Stroke. 2007;38:308–12.
52. Hooper SR, Umansky W, editors. Young children with special needs. 5th ed. Columbus: Merrill; 2008.
53. 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.
54. Feldman MA, editor. Early intervention: the essential readings. Malden: Blackwell Publishing Ltd; 2004.
55. Vandell DL. Early child care: the known and the unknown. Merrill-Palmer Quarterly. 2004;50: 387–414.
56. Clarke K. Childhood, parenting and early intervention: a critical examination of the sure start national programme. Crit Soc Policy. 2006;26:699–721.
57. Black MM, Dubowitz H, Krishnakumar A, Starr Jr RH. Early intervention and recovery among children with failure to thrive: follow-up at age 8. Pediatrics. 2007;120(1):59–69.
58. U.S. Department of Education. Digest of education statistics. Washington, DC: National Center for Education Statistics; 2003–2004.

59. Hooper SR, Wentz A, Gipson DS, Mendley S, Gerson A, Lande M, Furth S, Warady B. Parent-reported school-based services for children with chronic kidney disease. Paper presented at the Annual Meeting of the Pediatric Academic Society, Honolulu, Hawaii, May 2008.
60. 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. Washington, DC: U.S. Government Printing Office; 2000. NIH Publication No. 00–4754.
61. Kuhn MR, Stahl SA. Fluency: a review of developmental and remedial practices. J Educ Psychol. 2003;95:3–21.
62. Hughes CA, Ruhl KL, Schumaker JB, Deshler DD. Effects of instruction in an assignment completion strategy on the homework performance of students with learning disabilities in general education classes. Learn Disabil Res. 2002;17:1–18.
63. Baker S, Gersten R, Lee D. A synthesis of empirical research on teaching mathematics to low-achieving students. Elem School J. 2002;103:51–73.
64. 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.
65. 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.
66. Hooper SR, Costa L-J, McBee M, Anderson K.L, Yerby DC, Childress A, Knuth SB. A written language intervention for at-risk second grade students: a randomized controlled trial of the Process Assessment of the Learner Lesson Plans at Tier 2. Manuscript submitted for publication, 2010.
67. 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.
68. Ferris ME, Gipson DS, Kimmel PL, Eggers PW. Trends in treatment and outcomes of survival of adolescents initiating endstage renal disease care in the United States of America. Pediatr Nephrol. 2006;21:1020–6.
69. 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.

Psychosocial Adjustment and Adherence of Children and Adolescents on Dialysis

30

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Keywords
Children • Dialysis • Adolescents • Pyschosocial adjustment • Child and parental adjustment

Introduction to Psychosocial Adjustment

A large body of literature has emerged over the past three decades examining the psychosocial functioning of children and adolescents undergoing dialysis. Advances in diagnosis, treatment, and disease outcomes have been associated with changes in psychosocial adjustment as children live longer with renal disease. Dialysis can significantly impact all domains of a child's life, including their emotional, behavioral, and social functioning. Studies examining adult outcomes (i.e., studies of adults who received dialysis in childhood and/or adolescence) suggest difficulties originating in childhood are maintained or even escalate as this population enters adulthood [1–4]. Therefore, understanding how to recognize and address psychosocial issues as early as possible is a necessary component of comprehensive patient care.

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In order to adequately understand child adjustment, one must also consider the family system in which the child resides. The time-consuming and complex nature of managing a dialysis treatment regimen requires involvement from and directly impacts members of the child's family. As such, the family system (i.e., parents, siblings, overall family functioning) is central to understanding, assessing, and managing psychosocial adjustment and medical treatments in the pediatric dialysis population. Therefore, in addition to a review of child psychosocial adjustment, literature related to parental, sibling, and overall family adjustment in pediatric dialysis will also be summarized. A discussion of the clinical implications and future directions for research and clinical care is presented at the end of the chapter.

Child Adjustment

While many children and adolescents are able to successfully cope with dialysis treatment, for other youth dialysis can be quite challenging. A number of stressors and disease-related consequences likely impact youth's adjustment as they undergo dialysis treatment. For example, delayed growth and puberty and physical changes associated with

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Table 30.1 Emotional, behavioral, and social difficulties experienced by children on dialysis

Emotional	• Depression/depressive symptoms • Anxiety
Behavioral	• Conduct problems • Hyperactivity
Social	• Difficulties with peers • Less likely to have a special friend • Young adults: More likely to live with parents, lack a close relationship with a significant other, and lack employment

dialysis are well documented in the larger literature (e.g., [5]). In addition, sometimes painful and/or intrusive medical procedures, medical appointments, hospitalizations, isolation from peers, and school absences likely contribute to children's individual psychosocial adjustment (e.g., [6, 7]). In fact, there is some evidence that children's adjustment may be related to treatment type (e.g., peritoneal dialysis versus hemodialysis); however, this research is mixed. Therefore, the following will focus on the emotional, behavioral, and social domains of psychosocial adjustment across dialysis modalities. Table 30.1 also summarizes difficulties commonly experienced by children and adolescents receiving dialysis.

Emotional Adjustment

A relatively large literature describes the increased risk for depression and subclinical depressive symptoms often experienced by youth receiving dialysis; however, actual symptom rates often vary across studies. For example, Simoni and colleagues described slightly elevated depressive symptoms in a sample of 23 patients on dialysis; however, they also noted that, overall, these youth obtained depression scores similar to those of healthy children [8]. In contrast, other researchers have described significantly higher rates of psychiatric disorders in children and adolescents receiving hemodialysis. Compared to 36.8% of children pre-dialysis, Bakr and colleagues found that 68.4% of youth receiving dialysis received a psychiatric diagnosis (e.g., depression, adjustment disorders with depressive symptoms) utilizing a semi-structured interview [9]. Further, in a mixed sample of adolescents and adults (15–63 years old), researchers suggested that the score obtained on a standardized measure of depressive symptoms was the most important predictor of survival, with increased depressive symptoms (score ≥ 25) leading to a decreased probability of survival from 85% to 25% at 2 years [10]. Some investigators have suggested that suicide may be one contributor to decreased survival rates for youth on dialysis noting that suicide was suspected in at least two deaths in their sample [4]. Given its possible relationship to survival and risk for later suicide, timely identification of depressive symptoms in youth undergoing dialysis is needed. Collectively, these data suggest that, for pediatric patients, assessment of depressive symptoms especially is warranted. However, depressive symptoms are not the only internalizing symptoms that these patients may experience during the course of treatment.

Other internalizing symptoms (i.e., anxiety) have also been documented in the pediatric dialysis literature. For example, increased rates of separation anxiety disorder, other anxiety disorders, and adjustment disorders with anxiety symptoms have each been documented relative to the healthy population. Compared to age- and sex-matched controls, separation anxiety disorder was significantly more common in children with end stage renal disease (ESRD), occurring in over 60% of the sample [11]. Similarly, parents have reported higher internalizing symptoms in children receiving dialysis compared to children pre-dialysis or healthy children on parent reports of child behaviors [12]. Although initial reactions to diagnosis vary, the dialysis treatment regimen can be especially stressful [13] and overall, the literature suggests that youth on dialysis are at increased risk for having difficulties with emotional adjustment.

Behavioral Adjustment

While much of the current literature examining child and adolescent psychosocial adjustment has focused on internalizing symptoms, a small body

of literature also suggests that youth on dialysis may be at risk for behavioral difficulties. Increased externalizing symptoms (i.e., aggressive and delinquent behaviors), especially in later childhood and adolescence, have been documented as children cope with dialysis treatment and related stressors. For example, parents reported levels of externalizing behaviors exceeding clinical cutoffs for over one quarter of children 9–15 years old on a well-validated parent report measure of child behaviors [12]. Even for those children starting dialysis as infants, parents described higher rates of externalizing behaviors (i.e., conduct problems, difficulties with peers, and hyperactivity) compared to the normative population [14]. Although not yet examined empirically, behavior problems may be due, in part, to the continued and substantial reliance of many youth on their parents for significant care and support (e.g., assistance with dialysis regimen, transportation to medical appointments) during a developmental period where youth are supposed to be seeking greater independence and engaging in their own self-exploration.

Social Adjustment

The demands of the dialysis treatment regimen and increased dependence on parental support also likely contribute to well-documented difficulties related to social functioning in children and adolescents. In a sample of 12 children (10–19 years) with ESRD receiving dialysis, not a single youth obtained a score equal to or exceeding the average score for social adjustment on a standardized measure [15]. Interestingly, transplantation often leads to improvements in social functioning, as youth are afforded greater freedom and are not dependent on dialysis [16], substantially decreasing the burden of care and interference in other activities (e.g., school, hobbies, sports). Compared to healthy and non-dialysis age and sex-matched controls, children and adolescents receiving dialysis were the least likely to have a special friend in a sample of youth aged 2–18 years [17]. Unfortunately, difficulties in social adjustment may persist into adulthood. Young adults who have received dialysis as children and/or adolescents are more likely to continue to live with their parents, lack close relationships with a significant other, lack employment, and attain lower educational achievement compared to their peers [2, 3, 7]. Physical changes (e.g., short stature, cushingoid appearance) related to the medication regimen and school difficulties [3, 18] may influence self-esteem and self-concept and compound social adjustment difficulties in this population. Taken together, these findings clearly demonstrate the adverse impact of pediatric dialysis on the social functioning of children and adolescents and emphasize the need to monitor and treat social problems in order to alleviate and/or prevent such difficulties in adulthood.

Parental Adjustment

Overall, the literature suggests that many families do fairly well while coping with the child's diagnosis and initiation of dialysis treatment (e.g., [15, 19]). However, current literature also suggests that, for some families, coping with dialysis presents significant challenges for the child's, parents', and family's overall psychological adjustment. A number of researchers have examined the emotional and practical impact of pediatric dialysis on parents. Similar to their children, a number of factors likely influence parent's adjustment while their child receives dialysis treatment. Family finances, parental marital adjustment, parental unemployment, parental isolation from social groups, difficulties related to time management, and other practical concerns related to caring for a chronically ill child may all affect parents' psychosocial functioning [5]. Given the multiple stressors facing parents, it is not surprising that pediatric dialysis often impacts parents' individual psychosocial functioning. While parental psychological functioning is important in and of itself, the impact that parent functioning can have on the emotional health on their children [17], makes family-centered care and increased attention to caregiver mental health of paramount importance [20].

Psychosocial Adjustment

Similar to the child adjustment literature, parents of children on dialysis are at risk for experiencing depression and anxiety. Compared to controls, both mothers and fathers have reported increased anxiety, depression, and stress symptoms [21] while caring for a child on dialysis. Similarly, other researchers have described that approximately 30% of parents report symptoms of depression and anxiety exceeding the clinical cutoff on standardized self-report measures of mood [22]. Not surprisingly, significant relationships between parent and child adjustment have also been documented; child psychological difficulties during pediatric dialysis are often more common when a family history of psychological difficulties is also present [17].

Practical Stressors

A number of factors likely influence parental adjustment, which may also contribute to the overall functioning of the family and the child's general adjustment. Parents of children awaiting renal transplantation must navigate a number of stressors on a daily basis [23]. Not surprisingly, financial-related stressors are frequently reported by parents as their child undergoes dialysis. Tsai and colleagues found that families of children receiving dialysis reported a lower family income and higher rates of unemployment compared to national normative information [24]. General caregiving stress may also contribute to a parents' subsequent emotional difficulties or changes in the marital relationship. For example, compared to parents of children not receiving dialysis, parents of children receiving dialysis were more likely to describe that their marriage was affected (65% versus 27%) by their child's medical diagnosis [25]. Taken together, these findings suggest that practical stressors impact both parental and child adjustment, as well as the general functioning of the family as a whole.

Family and Sibling Adjustment

Changes in family roles, greater responsibility for household chores, and/or patient care by siblings, differential attention by parents toward the patient, and lack of respite care are only a few of the factors likely to impact the overall adjustment of family and siblings of youth receiving dialysis. As the patient receiving dialysis treatment is part of a family unit, consideration of both the family and their sibling's adjustment must also be given in order to more fully understand psychosocial adjustment in this unique population.

Family Adjustment

Perhaps it is not surprising given what has been described related to child and parental psychosocial adjustment, pediatric dialysis can also have considerable repercussions for the general functioning of the family. Moreover, families experience significant disruption caused either by significant training and changes in the home environment required by peritoneal dialysis [26, 27] or the frequent and lengthy trips to dialysis unit required by hemodialysis. Indeed, 77% of parents described disruption in their family's life compared to 31% of parents of children not receiving dialysis [25]. In a sample of 36 adolescents receiving dialysis or undergoing transplant, researchers described that family environment and conflict were significantly related to child externalizing behaviors [28]. Family functioning may even be related to children's disease-related medical outcomes. Research by the same group also suggests that higher family conflict is related to a greater number of medications and that higher family cohesion is related to fewer hospitalizations [28]. Although this area of research is still in its early stages, such findings support a family-centered approach to the care of youth on dialysis where family functioning, not just child functioning, is routinely assessed and treated.

Sibling Adjustment

Overall, the majority of the literature related to sibling adjustment in pediatric dialysis suggests that siblings do fairly well. However, changes in roles (e.g., caregiving burden often placed on siblings) and the impact on the family related to caring for a child receiving dialysis treatment (e.g., financial burden, practical difficulties related to time management) can adversely impact siblings' psychosocial adjustment. Of note, in a small study of 15 siblings of children receiving dialysis or a transplant, almost half of siblings reported they were not able to share concerns with parents, almost 90% described disruption to their family's routine, and 80% reported being jealous or feeling left out [29]. Findings from this study are consistent with the broader pediatric chronic illness literature documenting differential attention by parents toward healthy siblings [30]. Thus, equal consideration also needs to be given to the psychosocial adjustment of siblings during the dialysis process.

Management and Treatment of Psychosocial Problems

While a full review is beyond the scope of the current chapter, a number of psychological treatments have proven efficacious in the broader pediatric chronic illness literature and can be expected to have applicability to the pediatric dialysis population in particular. For instance, cognitive behavioral therapy (CBT) is a highly effective psychological therapy for the treatment of depressive and anxiety symptoms (e.g., [31–33]), which could be beneficial for older children and adolescents, as well as parents, presenting to pediatric dialysis providers with depressive and/or anxiety symptoms (e.g., major depressive disorder, separation anxiety disorder). Behavioral Family Systems Therapy (BFST), a brief family systems–oriented therapy aimed at improving problem-solving skills (e.g., [34]), could help families to successfully maneuver around both practical difficulties (e.g., school absences, interruptions to the family schedule) and general difficulties with family functioning that can often contribute to poorer psychosocial functioning. When clinically significant psychosocial problems are identified, a trained mental health professional such as a psychologist should be incorporated into the patient's care in order to deliver the empirically supported treatment most suited to the patient's and family's needs.

Introduction to Adherence

The estimated rate of nonadherence to treatment regimens across pediatric chronic illness populations is 50% [35]. The prevalence of nonadherence is striking when one considers the serious consequences that can result from poor adherence. Lack of exposure to a given medical treatment as a result of nonadherence can result in increased morbidity and mortality (e.g., [36]), medication-related adverse events, and changes in quality of life [37, 38]. Changes in health care utilization and increased costs to medical institutions and the larger society have also been related to nonadherence [39–41]. Finally, poor adherence can influence healthcare provider clinical decision-making, potentially leading to increased dosages and/or discontinuation of medication believed to be ineffective [42, 43]. For these reasons, and others, estimating the prevalence of and understanding factors related to adherence in the pediatric dialysis population is critical to providing comprehensive patient care.

However, adherence to dialysis regimens in pediatric populations is vastly understudied. A number of factors hinder the advancement of adherence research in pediatric dialysis including, different types of dialysis that vary in the degree of patient self-management, multiple regimen components (e.g., diet, fluid intake, oral medication), and limited tools to assess adherence to the dialysis regimen. Therefore, the few studies that examine adherence to pediatric dialysis will be reviewed here as well as studies on adherence in other populations (i.e., adult dialysis, pediatric kidney transplant, and other pediatric populations) that can inform clinical and research endeavors until definitive research in the pediatric dialysis population is available.

Overview of Adherence

In 2003 the World Health Organization [44] defined adherence as, "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider." Notably, a number of other related terms have been used in conjunction or interchangeably with the term adherence including compliance [45] and newer terms such as persistence (i.e., the act of continuing the treatment for the prescribed duration; [46]) and concordance (i.e., negotiation between equals [provider and patient] with the aim of developing a therapeutic alliance; [47]). Here, the term adherence will be used due to the term's wide acceptance and emphasis on the patient's active role in his/her treatment as well as the importance of a collaborative physician–patient relationship.

Assessing rates of adherence to the pediatric dialysis regimen is particularly difficult to estimate due to the various treatment components (i.e., fluid intake, oral medication adherence, diet) and underdeveloped methods used to assess adherence. Unfortunately, the limited available research suggests that nonadherence is prevalent. Estimates of rates of nonadherence specific to the pediatric dialysis regimen range from 17% to 43% [8, 48, 49]. A study examining oral medication adherence in patients with CKD and in transplant recipients found that 29.4% of patients were nonadherent to their medication regimen (defined by prednisone concentrations in the blood of less than 20 ng/mL; [48]). Nonadherence to prescribed weight maintenance prescriptions have also been found to be prevalent, with 39% of the youth classified as nonadherent (i.e., gained above an investigator established 1.5 kg cutoff point) in one study [49]. In another sample of children on dialysis, serum phosphorus and calcium were within the recommended ranges, on average, only 39% and 43% of the time, respectively. Moreover, 17% of the children never had a normal serum phosphorus value and 26% never had a normal calcium value [8]. Although these findings are dramatic, the prior study did not specify which component of the treatment regimen they were assessing for nonadherence and serum phosphorus and calcium values are influenced by multiple treatment factors. Nonetheless, this and other studies conducted with the pediatric dialysis population confirm the prevalence of nonadherence and punctuate the need to regularly assess factors related to adherence in the pediatric dialysis population.

Factors Associated with Adherence

The prevalence and preventable nature of as well as the serious clinical consequences related to nonadherence make understanding factors related to nonadherence in this patient population of paramount importance. Unfortunately, virtually nothing is known about the factors that influence adherence and methods to promote adherence in children and adolescents who are on dialysis. Thus, the content of the following pages and Table 30.2 summarize several sociodemographic, medical, individual, and familial, and healthcare-specific factors that have been linked to adherence in pediatric transplant and chronic illness populations. Understanding these factors is critical to the development of targeted interventions to promote adherence in children receiving chronic dialysis.

Sociodemographic Factors

To our knowledge, only one study has examined sociodemographic factors in relation to adherence in the pediatric dialysis population [13]. Findings from this study are consistent with the larger pediatric adherence literature; older age, low family socioeconomic status (SES), and living in a single parent home are associated with poorer adherence in children on dialysis [13]. Declines in adherence during adolescence, a developmental period that is marked by a drive for autonomy, are widely and consistently documented in the broader adherence literature [50–52]. For youth on dialysis in particular, low SES could hinder adherence by potentially limiting access to

Table 30.2 General risk factors related to nonadherence

Sociodemographic	• Adolescent age • Living in a single parent home • Low socioeconomic status
Medical	• Longer duration of dialysis • Adverse treatment side effects
Individual	• Lack of disease-related knowledge • History of psychological or psychiatric problems
Family	• Ambiguous allocation of treatment responsibilities • Low parental involvement • High family conflict and/or poor communication • Additional significant family stressors (e.g., other family members with medical problems, employment problems, housing difficulties)

medication and impair the parent's ability to provide optimal supervision over dialysis delivery due to the demands that are often associated with low-wage jobs (i.e., working early morning or evening shifts when dialysis is often being initiated or completed). The identification of sociodemographic factors related to adherence in the pediatric dialysis population could assist clinicians and researchers in identifying who may be at risk for poor adherence and ways to most effectively assist patients and families.

Medical Factors

To our knowledge, only one published study documents the influence of medical predictors on adherence in the pediatric dialysis population. Brownbridge and colleagues [13] found that the duration of dialysis was associated with poorer adherence ($p < 0.05$). Replication of this finding as well as the examination of other medical factors that could be related to adherence should be investigated, including the type of illness underlying the need for dialysis, disease and dialysis duration, type of dialysis, and other treatment regimen characteristics. The influence of side effects on adherence to the dialysis treatment regimen also needs to be considered as side effects have been associated with poorer adherence in other pediatric populations [53, 54]. Side effects of treatment could have a substantial impact on adherence in this population as youth on dialysis experience numerous side effects from their treatments and other medications which can affect physiology, cognition, emotion, and behavior, all of which could subsequently affect a patient's willingness to consistently follow their treatment regimen.

Individual and Family Factors

Cognitive Functioning

To our knowledge, no studies have specifically investigated the relationship between intellectual functioning and dialysis adherence. However, based on literature demonstrating deleterious effects of poor kidney functioning on cognitive functioning [55], it stands to reason that persistent nonadherence would negatively impact cognitive development and functioning. It is also unclear what level of cognitive functioning is required to maintain good disease management. There is a critical need for research that determines how intelligence and executive functioning skills are related to adherence to a dialysis regimen, especially in the pediatric ESRD population in which many children and adolescents suffer cognitive effects [55] (also see Chap. 29).

Lack of Knowledge

The current consensus in the larger adherence literature is that disease- and regimen-related knowledge are necessary, but not sufficient alone to improve and maintain adherence to medical regimens [56–59]. The influence of disease and regimen knowledge needs to be examined in the

pediatric dialysis population in order to understand how to best train patients to effectively manage their regimens.

Psychological Functioning

As reviewed in the first half of the chapter, children and adolescents on dialysis are at greater risk for experiencing problems with psychological adjustment. Findings regarding the relationship between psychological distress and adherence is unequivocal, as those with poorer psychological functioning are at greater risk for poor adherence. Children and adolescents who report elevated levels of psychological distress including posttraumatic stress symptoms [60], depressive symptoms [13, 61, 62], and anxiety symptoms [13, 61] are at significantly greater risk for adherence problems. Among youth on dialysis, poor adjustment to diagnosis and dialysis is also significantly associated with nonadherence ($p < 0.01$; [13]). These findings attest to the importance of attending to the psychological as well as medical care of children and adolescents on dialysis.

Family Predictors

Family process variables are *critical and modifiable* factors that have been shown to influence adherence in multiple pediatric populations, including those with diabetes [63] and asthma [64]. Given the complexities of the treatments and the high stakes associated with completing treatments, families and caregivers play a critical role in dialysis treatments. For very young children (below age 6), the primary responsibility of ensuring adherence to the child's treatment regimen typically falls on the primary caregiver (i.e., parent). However, the allocation of regimen responsibilities for school-age children and adolescents and how the allocation of treatment responsibilities is related to adherence is not well understood. Allocation of treatment responsibility (ATR) and overlapping constructs, including parental involvement, child involvement, child autonomy, and family responsibility sharing, describe the degree to which each family member is involved in different aspects of a medical treatment regimen in order successfully complete a prescribed treatment regimen task. One regimen task, such as taking an oral medication, is comprised of multiple task components (i.e., obtaining the prescription, putting the pills in a pill box, and swallowing the pill). Each of these component tasks may be shared across multiple family members. Two primary patterns of ATR have been determined to be related to nonadherence in the pediatric population. First, more responsibility allocated to the parent and sustained parental involvement is related to increased adherence to pediatric treatment regimens [65–69]. In contrast, greater discrepancies between parent and child reports of who is responsible for specific aspects of a treatment regimen is related to poorer adherence [64, 70]. Clearly, more research is needed in order to determine how to most effectively allocate responsibilities for the treatment regimen to children and adolescents who receive chronic dialysis in a way that prepares them for the transition to adult care while maintaining optimal adherence.

The Impact of Treatment Adherence on Health and Psychosocial Outcomes

To our knowledge the impact of nonadherence has not been documented in children and adolescents on dialysis. In other pediatric nephrology populations, nonadherence has been associated with adverse health outcomes. In a small sample of children with nephrotic syndrome, nonadherence to oral steroid medications was related to the development of recurrent steroid-sensitive nephrotic syndrome [48]. This is consistent with studies in the pediatric kidney transplant population which show that nonadherence to oral medication regimens is related to poorer clinical outcomes, such as lower long-term graft survival rates [71–73]. Across studies, it is estimated that an average of 39% of late transplant losses are attributable to nonadherence [71–79]. Moreover, those who are nonadherent die at rates fourfold greater than more adherent recipients [80]. However, very little is known about how nonadherence impacts outcomes related to the dialysis

treatment regimen. Clearly the impact of severe and persistent refusal to do dialysis itself is apparent. However, the impact of less blatant forms of nonadherence on health outcomes is not well understood.

Interventions to Promote Adherence

The limited available information regarding adherence in the pediatric dialysis population makes it clear that interventions to improve adherence to multiple aspects of the dialysis treatment regimen are critically needed. A recent meta-analysis examining the effectiveness of adherence interventions in pediatric populations found that behavioral and multicomponent interventions are the most effective in changing adherence behaviors [81]. Although no intervention studies have been conducted with the pediatric dialysis population, interventions utilizing the Baxter Procard (i.e., computer chip that records dialysis machine usage) in the adult dialysis population have demonstrated substantial promise. Two studies have reported the use of the Procard as a tool to increase adherence [82, 83]. More recently, 42 adult patients received education about the Procard and used it to encouraged better adherence. Compared to historical rates, this group reported compliance rates of 95% or greater compared to the 43% prior to using the Procard [84]. The extent to which these interventions will be helpful in improving adherence in pediatric dialysis populations will need to be evaluated.

Adherence interventions developed for other pediatric chronic conditions range from fundamental education and simple self-management strategies to more complex, multifaceted interventions. Examples of adherence interventions are summarized in Table 30.3. Educational strategies typically provide factual information regarding the nature of the illness and its management, the mediations and treatments for the illness (including side effects), and the importance of following the treatment regimen. Periodic education as well as education at key points of treatment (e.g., when a new treatment is introduced or a treatment regimen is changed) is also important. Knowledge provided through education is necessary, but not necessarily sufficient, to promote regimen adherence [57–59, 85]. Therefore, when attempting to intervene on adherence problems, it is recommended that educational interventions be provided in conjunction with other intervention methods such as organizational and behavioral interventions.

Table 30.3 Examples of adherence interventions

Intervention type	Examples
Educational	• Education about health condition(s) • Education about treatment regimen • Education about self-management skills
Organizational	• Pill box • Have a designated location for medications in the home • Setting an alarm • Track appointments on calendars • Track medication schedules on calendars
Behavioral	• Daily logs (i.e., logging adherence, barriers, and facilitators of adherence) • Chaining (i.e., take medication when brushing teeth, eating breakfast, watching a certain show) • Reinforce adherence (or behaviors to increase adherence) • Reinforce the use of strategies to improve adherence (e.g., setting alarms, packing medications to have when away from home) • Reinforce open discussion of adherence-related issues • Encourage patient to seek adherence-specific and general social support • Identify and encourage appropriate parent involvement • Teach and assist patient in using problem-solving skills to overcome barriers to adherence

Note: When possible a trained mental health professional should be consulted and assist in the management and treatment of moderate to severe adherence problems

Organizational and self-management strategies are also helpful in improving adherence. Strategies known to promote better adherence include use of a pillbox, setting alarms, using calendars to track appointments, and minimizing scheduling conflicts. Behavioral approaches have also been shown to be effective in improving adherence and typically involve visual reminders (e.g., calendars, charts), self-monitoring (e.g., tracking medication dosing through a daily log), chaining of regimen tasks with previously established routines or behaviors (i.e., brushing teeth, eating breakfast), and contingency management strategies (rewards for the achievement of specific goals; [34]). Given the lack of available standardized and empirically supported treatments in the pediatric dialysis population, the involvement of a psychologist to develop individualized evidence-based treatment plans is recommended to address identified adherence problems [86].

Summary and Directions for Future Research

While many patients and families are able to successfully adapt to the pediatric dialysis treatment regimen, a sizable proportion of children do not. Children on dialysis are at greater risk for experiencing difficulties with emotional (depression, anxiety, etc.), behavioral (conduct problems, oppositional behavior), and social difficulties. This is true, not just for the patients themselves, but also for their parents and siblings. The psychosocial functioning of youth on dialysis is important not only for the implications that it has on the child's overall quality of life, but also the significant impact that it has on treatment adherence. Difficulties with treatment adherence are prevalent in the pediatric dialysis population and have consistently been related to individual and family functioning of the youth. Therefore, it is critical to provide patients with comprehensive family-centered care that addresses not only the medical, but also the psychological needs to effect the best possible outcomes for youth on dialysis.

Although there is a reasonable mass of evidence documenting difficulties with psychological functioning in youth on dialysis, there is still much that is not adequately understood. Longitudinal studies are needed to examine the multiple aspects of psychological adjustment that likely fluctuate over time. Such investigations may help clinicians target the most appropriate resources for patients and/or family members at the most appropriate times during treatment. For instance, youth on dialysis and their families may benefit from additional psychosocial support when there are changes in the patient's treatment regimen, when there are additional stressors unrelated to dialysis in the home, or when the youth and their family are managing the uncertainty of waiting for a transplant. Additional studies are also needed to compare psychosocial adjustment by treatment (i.e., dialysis) type. While a small number of investigators are currently pursuing this research question, the constantly evolving and improving dialysis regimens require continued investigation in this area. Such investigation is especially needed for those patients for whom more than one dialysis treatment type may be possible, not only to help guide clinical decision making, but also to help patients and families decide the most appropriate treatment choice for their individual family. Given its relationship to quality of life, adherence, and medical outcomes, the importance of psychosocial adjustment cannot be overstated, and continued research in this area is needed.

Treatment adherence is vastly understudied in the pediatric dialysis population, but there is little question that poor adherence dramatically and adversely impacts the health outcomes of youth on dialysis. Therefore, research on adherence in the pediatric dialysis population is critically needed to identify modifiable factors that adversely impact adherence, how to best measure adherence to each component of the dialysis treatment regimen, and effective interventions to optimize adherence.

Implications for Clinical Practice and Psychosocial Care

Taken together, the available literature of children undergoing dialysis suggests that routine, repeated, assessment of child, parent, and family

psychosocial functioning as well as treatment adherence is needed. To provide the necessary comprehensive care to youth on dialysis, multidisciplinary teams should include psychologists, social workers and other mental health professionals who are trained to assess and treat psychosocial issues. Such comprehensive assessment may then afford practitioners the ability to identify those families at risk for psychosocial difficulties thereby preventing the poor health outcomes as well as the ability to efficiently and appropriately target psychological resources.

References

1. Groothoff JW, Grootenhuis MA, Offringa M, Stronks K, Hutten GJ, Heymans HSA. Social consequences in adult life of end-stage renal disease in childhood. J Pediatr. 2005;146(4):512–7.
2. Morton MJS, Reynolds JM, Garralda ME, Postlethwaite RJ, Goh D. Psychiatric adjustment in end-stage renal disease: a follow up study of former paediatric patients. J Psychosom Res. 1994;38(4): 293–303.
3. Reynolds JM, Morton MJ, Garralda ME, Postlethwaite RJ, Goh D. Psychosocial adjustment of adult survivors of a paediatric dialysis and transplant programme. Arch Dis Child. 1993;68(1):104–10.
4. Roscoe JM, Smith LF, Williams EA, et al. Medical and social outcome in adolescents with end-stage renal failure. Kidney Int. 1991;40(5):948–53.
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. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. Am J Manag Care. 2003;9(2): 155–71.
7. Rosenkranz J, Bonzel K-E, Bulla M, et al. Psychosocial adaptation of children and adolescents with chronic renal failure. Pediatr Nephrol. 1992;6(5):459–63.
8. Simoni JM, Asarnow JR, Munford PR, Koprowski CM, Belin TR, Salusky IB. Psychological distress and treatment adherence among children on dialysis. Pediatr Nephrol. 1997;11(5):604–6.
9. Bakr A, Amr M, Sarhan A, et al. Psychiatric disorders in children with chronic renal failure. Pediatr Nephrol. 2007;22(1):128–31.
10. Shulman R, Price JD, Spinelli J. Biopsychosocial aspects of long-term survival on end-stage renal failure therapy. Psychol Med. 1989;19(4):945–54.
11. Fukunishi I, Kudo H. Psychiatric problems of pediatric end-stage renal failure. Gen Hosp Psychiatry. 1995;17(1):32–6.
12. 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(2):341–7.
13. Brownbridge G, Fielding DM. Psychosocial adjustment and adherence to dialysis treatment regimes. Pediatr Nephrol. 1994;8(6):744–9.
14. Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev. 2003;29(1):55–61.
15. Brem AS, Brem FS, McGrath M, Spirito A. Psychosocial characteristics and coping skills in children maintained on chronic dialysis. Pediatr Nephrol. 1988;2(4):460–5.
16. 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.
17. Garralda ME, Jameson RA, Reynolds JM, Postlethwaite RJ. Psychiatric adjustment in children with chronic renal failure. J Child Psychol Psychiatry. 1988;29:79–90.
18. Fukunishi I, Honda M. School adjustment of children with end-stage renal disease. Pediatr Nephrol. 1995; 9(5):553–7.
19. Reinhart JB, Kemph JP. Renal transplantation for children: another view. JAMA. 1988;260(22):3327–8.
20. Kazak AE, Simms S, Rourke MT. Family systems practice in pediatric psychology. Pediatr Psychol. 2002;27(2):133–43.
21. Snethen JA, Broome ME, Bartels J, Warady BA. Adolescents' perception of living with end stage renal disease. Pediatr Nurs. 2001;27(2):159.
22. 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.
23. 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.
24. 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.
25. 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.
26. Haffner JC, Schurman SJ. The technology dependent child. Pediatr Clin North Am. 2001;48(3):751–64.
27. 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.
28. 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.
29. Batte S, Watson A, Amess K. The effects of chronic renal failure on siblings. Pediatr Nephrol. 2006;21(2):246–50.

30. Quittner AL, Opipari LC. Differential treatment of siblings: interview and diary analyses comparing two family contexts. Child Dev. 1994;65(3):800–14.
31. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years (Part I). Focus. 1996;35:1427–39.
32. James A, Soler A, Weatherall R. Cognitive behavioural therapy for anxiety disorders in children and adolescents. Cochrane Database Syst Rev. 2005;4: CD004690.
33. Weersing VR, Brent DA. Cognitive behavioral therapy for depression in youth. Child Adolesc Psychiatr Clin N Am. 2006;15(4):939–57.
34. Wysocki T, Harris MA, Buckloh LM, et al. Effects of behavioral family systems therapy for diabetes on adolescents' family relationships, treatment adherence, and metabolic control. J Pediatr Psychol. 2006;31(9):928–38.
35. Rapoff MA. Adherence to pediatric medical regimens. New York: Springer; 1999.
36. Kennard BD, Stewart SM, Olvera R, et al. Nonadherence in adolescent oncology patients: preliminary data on psychological risk factors and relationships to outcome. J Clin Psychol Med Settings. 2004;11(1):31–9.
37. 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(3):289–99.
38. Ekberg H, Kyllonen L, Madsen S, Grave G, Solbu D, Holdaas H. Clinicians underestimate gastrointestinal symptoms and overestimate quality of life in renal transplant recipients: a multinational survey of nephrologists. Transplantation. 2007;84(8):1052–954.
39. Cloutier MM, Wakefield DB, Sangeloty-Higgins P, Delaronde S, Hall CB. Asthma guideline use by pediatricians in private practices and asthma morbidity. Pediatrics. 2006;118(5):1880–7.
40. Lewis CE, Rachelefsky G, Lewis MA, de la Sota A, Kaplan M. A randomized trial of A.C.T. (asthma care training) for kids. Pediatrics. 1984;74(4):478–86.
41. USGA Office. End-stage renal disease: characteristics of kidney transplant recipients, frequency of transplant failures, and cost to medicare. Washington, DC: United States Government Accountability Office; 2007. p. 1–27.
42. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. J Clin Epidemiol. 2001;54(12S1):57–60.
43. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40(9):794–811.
44. Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
45. Haynes RB, Sackett DL. Compliance with therapeutic regimens. Baltimore: Johns Hopkins University Press; 1976.
46. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44.
47. Rand CS. Patient adherence with COPD therapy. Eur Respir Rev. 2005;14(96):97–101.
48. 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.
49. Hudson J, Fielding D, Jones S, McKendrick T. Adherence to medical regime and related factors in youngsters on dialysis. Br J Clin Psychol. 1987;26(Pt 1):61–2.
50. Anderson BJ, Laffel LMB. Behavioral and psychosocial research with school-aged children with type 1 diabetes. Diabetes Spectrum. 1997;10:281–5.
51. Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2004;23(11):1035.
52. Zindani GN, Streetman DD, Streetman DS, Nasr SZ. Adherence to treatment in children and adolescent patients with cystic fibrosis. J Adolesc Health. 2006;38(1):13–7.
53. 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(7):1020–6.
54. Greenstein S, Siegal B. Compliance and noncompliance in patients with a functioning renal transplant: a multicenter study. Transplantation. 1998;66(12): 1718–26.
55. Bawden HN, Acott P, Carter J, et al. Neuropsychological functioning in end-stage renal disease. Br Med J. 2004;89(7):644.
56. La Greca AM. Issues in adherence with pediatric regimens. J Pediatr Psychol. 1990;15(4):423–36.
57. Tebbi CK, Cummings KM, Zevon MA, Smith L, Richards M, Mallon J. Compliance of pediatric and adolescent cancer patients. Cancer. 1986;58(5): 1179–84.
58. Modi AC, Quittner AL. Barriers to treatment adherence for children with cystic fibrosis and asthma: what gets in the way? J Pediatr Psychol. 2006;31(8): 846–58.
59. McQuaid EL, Kopel SJ, Klein RB, Fritz GK. Medication adherence in pediatric asthma: reasoning, responsibility, and behavior. J Pediatr Psychol. 2003; 28(5):323–33.
60. Shemesh E, Lurie S, Stuber ML, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics. 2000;105(2): e29.
61. Maikranz JM, Steele RG, Dreyer ML, Stratman AC, Bovaird JA. The relationship of hope and illness-related uncertainty to emotional adjustment and adherence among pediatric renal and liver transplant recipients. J Pediatr Psychol. 2007;32(5):571–81.
62. Shaw RJ, Palmer L, Blasey C, Sarwal M. A typology of non-adherence in pediatric renal transplant recipients. Pediatr Transplant. 2003;7(6):489–93.

63. Miller-Johnson S, Emery RE, Marvin RS, Clarke W, Lovinger R, Martin M. Parent-child relationships and the management of insulin-dependent diabetes mellitus. J Consult Clin Psychol. 1994;62(3):603–10.
64. Walders N, Drotar D, Kercsmar C. The allocation of family responsibility for asthma management tasks in African-American adolescents. J Asthma. 2000;37(1): 89–99.
65. Allen DA, Tennen H, McGrade BJ, Affleck G, Ratzan S. Parent and child perceptions of the management of juvenile diabetes. J Pediatr Psychol. 1983;8(2): 129–41.
66. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LM. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. Diabet Med. 2002;19(8): 635–42.
67. Boland EA, Grey M, Mezger J, Tamborlane WV. A summer vacation from diabetes: evidence from a clinical trial. Diabetes Educ. 1999;25(1):31–40.
68. 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.
69. La Greca AM, Auslander WF, Greco P, Spetter D, Fisher Jr EB, Santiago JV. I get by with a little help from my family and friends: adolescents' support for diabetes care. J Pediatr Psychol. 1995;20(4):449–76.
70. Martin S, Elliott-DeSorbo DK, Wolters PL, et al. Patient, caregiver and regimen characteristics associated with adherence to highly active antiretroviral therapy among HIV-infected children and adolescents. Pediatr Infect Dis J. 2007;26(1):61–7.
71. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant. 2005;9(3):381–90.
72. Ettenger RB, Rosenthal JT, Marik JL, et al. Improved cadaveric renal transplant outcome in children. Pediatr Nephrol. 1991;5(1):137–42.
73. Jarzembowski T, John E, Panaro F, et al. Impact of non-compliance on outcome after pediatric kidney transplantation: an analysis in racial subgroups. Pediatr Transplant. 2004;8(4):367–71.
74. Berber I, Tellioglu G, Yigit B, Turkmen F, Titiz MI, Altaca G. Pediatric renal transplantation: clinical analysis of 28 cases. Transplant Proc. 2006;38(2):430–1.
75. Michelon TF, Piovesan F, Pozza R, et al. Noncompliance as a cause of renal graft loss. Transplant Proc. 2002;34(7):2768–70.
76. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int Suppl. 2001;60(4):1565–70.
77. Vidhun JR, Sarwal MM. Corticosteroid avoidance in pediatric renal transplantation. Pediatr Nephrol. 2005;20(3):418–26.
78. Vlaminck H, Maes B, Evers G, et al. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. Am J Transplant. 2004;4(9):1509–13.
79. Warady BA, Mudge C, Wiser B, Wiser M, Rader B. Transplant allograft loss in the adolescent patient. Adv Ren Replace Ther. 1996;3(2):154–65.
80. De Geest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation. 1995;59(3):340–7.
81. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. J Pediatr Psychol. 2008;33(6):590–611.
82. Juergensen PH, Gorban-Brennan N, Finkelstein FO. Compliance with the dialysis regimen in chronic peritoneal dialysis patients: utility of the pro card and impact of patient education. Adv Perit Dial. 2004;20:90–2.
83. Neri L, Viglino G, Cappelletti A, Gandolfo C, Barbieri S. Compliance in automated peritoneal dialysis. Adv Perit Dial. 2002;18:72–4.
84. Lee AJ, Kho K, Chia KS et al. Simulating inadequate dialysis and its correction using an individualized patient-derived nomogram. Pediatr Nephrol. 2009;24:1–10.
85. La Greca AM, Follansbee D, Skyler JS. Developmental and behavioral aspects of diabetes management in youngsters. Child Health Care. 1990;19(3):132.
86. Spirito A, Kazak AE. Effective and emerging treatments in pediatric psychology. New York: Oxford University Press; 2006.

Part VI

Drugs and Dialysis

31 Drug Administration and Pharmacogenomics in Children Receiving Acute or Chronic Renal Replacement Therapy

Douglas L. Blowey and J. Steven Leeder

Keywords
Drug administration • Chronic renal replacement therapy • Acute renal replacement therapy • Children • Pharmacogenomics

Introduction

The prescription of a safe and effective dose of a medication for a child receiving dialysis is an arduous 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 associated with renal failure and the performance of dialysis can culminate in drug toxicity or inadequate treatment.

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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 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

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patch) and be present at the site of absorption in an aqueous solution. Most drugs are either weak acids or weak bases and in an aqueous solution exist as an ionized (charged) or nonionized (uncharged) moiety. The most common mechanism of drug absorption is passive diffusion of the nonionized drug moiety, a process influenced by the extent to which a drug is nonionized as 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]. Coadministration of drugs that reduce gastric acid (e.g., proton pump inhibitors, antiacids) shifts the equilibrium in favor of the poorly absorbed ionized moiety resulting in decreased ketoconazole absorption with the potential for subtherapeutic serum concentrations [3]. Less common mechanisms of drug absorption include convective transport, active transport, facilitated transport, ion-pair transport, and endocytosis.

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_o) and the fraction of the administered dose reaching the systemic circulation defines the volume of distribution (Vd):

$$\text{Vd} = \frac{\text{Dose} \times \text{Fraction absorbed}}{\text{Drug plasma concentration } (C_0)} \quad (31.1)$$

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 the vascular compartment contains most of the drug in the body. For example, digoxin binds more strongly to tissue sites outside the vascular space (e.g., muscle) than plasma proteins 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 protein binding or 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 (Equation 31.1) shows that the Vd determines the size of the loading dose.

$$\text{Loading dose (mg/kg)} = \text{Desired concentration (mg/L)} \times \text{Vd (L/kg)} \quad (31.2)$$

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.

$$Cl_{systemic} = Cl_{renal} + Cl_{hepatic} + Cl_{dialysis} + Cl_{other} \quad (31.3)$$

Drug elimination and metabolism usually require the drug to be present within the systemic circulation and drug partitioned outside the vascular space must return to the vascular space (redistribute) to be excreted or metabolized. Therefore, while dialysis may effectively clear a drug from 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 easily eliminated from the body; however, metabolites may be generated that have significant pharmacological activity [5, 6], toxic properties [7], and a disposition profile different from 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. Biotransformation reactions are classified as phase I or phase II reactions and usually the reactions occur sequentially. Phase I reactions introduce or expose a functional group on the parent drug and Phase II reactions couple the drug molecule to an endogenous substituent group (e.g., glucuronic acid, sulfate, glutathione). Although there are many different types of enzymes capable of carrying out Phase I reactions, the cytochromes P450 (CYP) are the most important class involved in the metabolism of therapeutic drugs. There is great interindividual variability in the biological activity of CYPs as a consequence of genetic, environmental, physiological, and developmental factors [8, 9].

The kidney is the most important organ for drug and drug metabolite elimination. Renal excretion of drugs involves glomerular filtration, tubular secretion, and tubular reabsorption. Unless limited by size or charge, drug and drug metabolites not bound to plasma proteins are 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 secretion of drugs. The classic example is the competitive inhibition of penicillin tubular secretion by probenecid [10]. Reabsorption is the passive diffusion of the nonionized drug from the filtrate 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 to enhance the elimination of salicylates in overdose situations [11]. Other pathways of drug excretion include biliary, salivary, mammary, sweat, lungs, and intestinal.

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 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 drug absorption, distribution, and metabolism [4, 12, 13] (Table 31.1).

The impact of renal failure on the disposition of a drug is largely determined by the relative contribution of renal drug clearance to the systemic drug clearance (Equation 31.3). When renal drug clearance accounts for more than 25% of the 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. 31.1). In contrast, modification of the dosing regimen is generally not required for drugs that are predominately eliminated by extrarenal pathways unless there are clinically significant changes in drug absorption, distribution, or metabolism (Table 31.1). Even though the disposition of the parent drug may be unchanged in renal failure, drugs undergoing extensive biotransformation may have

Table 31.1 Possible changes in drug disposition in 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

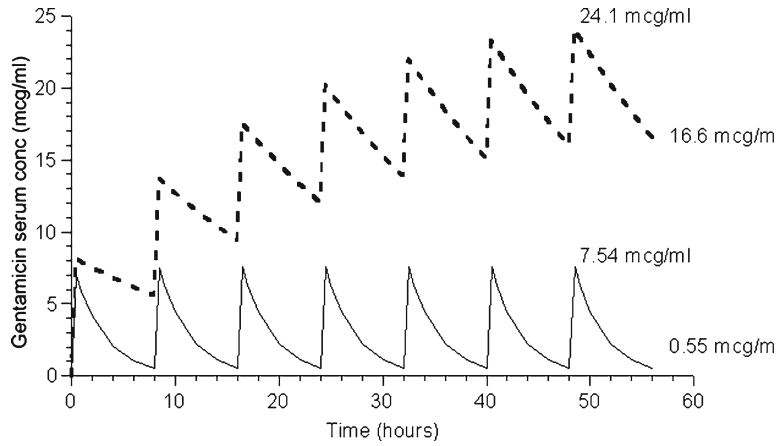

Fig. 31.1 Serum concentration – time profile for a child receiving intravenous gentamicin (2.5 mg/kg IV every 8 h). The solid line depicts the profile in a child with normal renal function. The dashed line depicts the gentamicin accumulation that occurs when dosing adjustments are not made in a child with a GFR measuring 15 mL/min/1.73 m^2

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 accumulates with repeated dosing and increases the risk of seizures in patients with renal failure [7]. There is also accumulating evidence that the biotransformation of parent drugs may also be altered in the presence of renal failure [14].

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 (Equation 31.3). In general, drug removal is considered clinically significant when >25% of the administered dose is removed by dialysis. Failure to recognize the extent of drug removal and provide supplemental dosing can result in under dosing and therapeutic compromise [15].

Drug elimination during dialysis occurs by 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 when the dialysis fluid drug concentration exceeds the serum concentration such as is observed with the intraperitoneal administration of antibiotics during the treatment of peritonitis. Convection is the movement of drug across the dialyzer membrane or peritoneal membrane that occurs with the flow of ultrafiltrate.

Dialysis removes only free drug from the body as drug bound to plasma proteins and other cellular constituents do not cross the dialyzer membrane or peritoneal membrane. The efficiency of drug removal 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 performed for a longer continuous period of time.

Hemodialysis

In hemodialysis, blood flows through a series of synthetic capillaries contained in a plastic shell (dialyzer) in a direction opposite dialysis fluid. As blood flows along the length of the capillaries, unbound solutes (e.g., drugs) diffuse across the membrane into the dialysis fluid that is then removed. Depending on the need for fluid removal, ultrafiltration and convective drug removal takes place, 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. A dialyzer with a larger surface area and a more porous membrane will increase drug clearance [14]. 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, 17].

Dialysis drug clearance (Cl_d) can be calculated by measuring the prefilter (arterial) and postfilter (venous) serum drug concentration and the rate of blood flow through the filter (Qb).

$$Cl_d = \left[\frac{(Ca - Cv)}{Ca}\right] \times Qb \qquad (31.4)$$

Equation (31.4) can be corrected for protein binding and hematocrit when appropriate [18]. The equation can be further adapted to account for drug removal that occurs with ultrafiltration by measuring the ultrafiltration rate (Qf).

$$Cl_d = \left[\frac{(Ca - Cv)}{Ca}\right] \times Qb + \left[\left(\frac{Cv}{Ca}\right) \times Qf\right] \qquad (31.5)$$

The drug clearance by hemodialysis is considered to be significant when the dialysis procedure accounts for more than 25% of systemic drug clearance.

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 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 hydrostatic pressure and convection. 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 hemodiafiltration (e.g., CVVHD) countercurrent dialysis fluid is present and the

majority of drug removal occurs by diffusion. During hemodiafiltration, the dialysis flow rate is the factor limiting solute (e.g., drug) removal and increasing the dialysis flow rate can enhance drug clearance [19]. Typical replacement fluid and dialysis flow rates during CRRT are 2,000 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 (Ca) and venous (Cv) concentrations is termed the sieving coefficient.

$$\text{Sieving coefficient} = \frac{\text{Ultrafiltrate drug concentration}}{(\text{Ca} + \text{Cv})/2} \tag{31.6}$$

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).

$$\text{Saturation coefficient} = \frac{\text{Ultrafiltrate} + \text{dialysate drug concentration}}{(\text{Ca} + \text{Cv})/2} \tag{31.7}$$

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_f) flow rates.

$$Cl_{CRRT} = \text{Si (or Sa)} \times (Q_d + Q_{uf}) \tag{31.8}$$

The drug clearance by CRRT is considered to be significant when the dialysis procedure accounts for more than 25% of systemic drug clearance.

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 time 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, or alternatively, multiple blood samples can be obtained and an area under the curve (measure of exposure) calculated.

$$Cl_{pd} = \frac{\text{Volume of dialysate} \times \text{Drug concentration}}{\text{Mid - dialysis Ca} \times \text{time}} \tag{31.9}$$

$$Cl_{pd} = \frac{\text{Volume of dialysate} \times \text{Drug concentration}}{AUC_{0-t}} \tag{31.10}$$

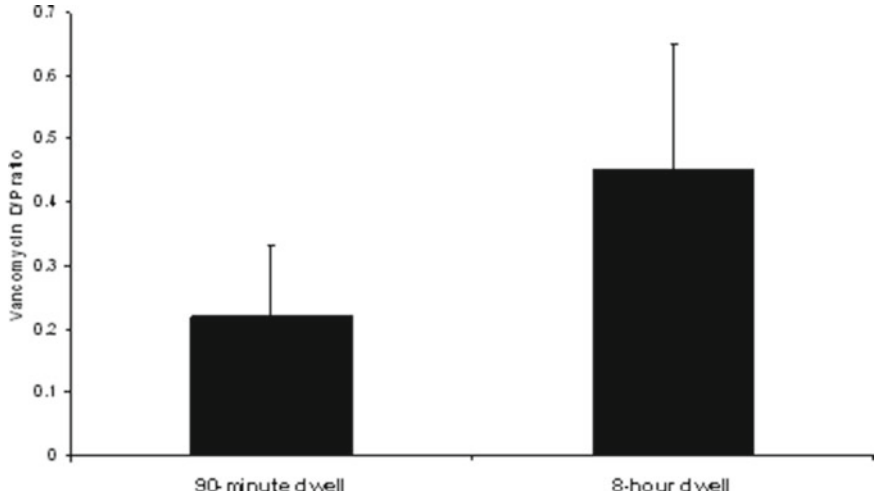

Fig. 31.2 Vancomycin dialysate-to-plasma (D/P) ratio in children who received an IV dose of vancomycin. The D/P ratio at 90 min measured 0.22 ± 0.11 and due to the time-dependent transfer of vancomycin from the blood to the dialysis fluid increased to 0.45 ± 0.2 at 8 h

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 obtained [20]. Treatment is initiated with an intraperitoneal loading dose that dwells for a 3–6 h period and is followed by continuous or intermittent maintenance therapy to complete the 14–21-day treatment course. During continuous 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 infection 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 antibiotic-free exchanges, antibiotic diffuses from the serum 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 dialysate to the serum concentration and the time allowed for drug diffusion (e.g., dwell time). The prolonged dwell time employed during continuous ambulatory peritoneal dialysis (CAPD) is sufficient time to achieve 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 adequate movement of drug into the peritoneum resulting in subtherapeutic peritoneal drug concentrations (Fig. 31.2). Whether therapeutic peritoneal antibiotic concen-

Table 31.2 Intraperitoneal dosing recommendations for children with peritonitis [22]

Drug	Loading dose (mg/L)	Continuous therapy dosage (mg/L)	Intermittent therapy dosage
Ampicillin		125	
Cefazolin	500	125	15 mg/kg QD
Cefepime	500	125	15 mg/kg QD
Ceftazidime	250	125	15 mg/kg QD
Clindamycin	300	150	
Gentamicin	8	4	
Teicoplanin	200	20	15 mg/kg Q 5–7 D
Tobramycin	8	4	
Vancomycin	1000	25	30 mg/kg Q 5–7 D

trations 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 [21]. Guidelines for the intraperitoneal dosing of common antibiotics are provided in Table 31.2.

The intraperitoneal administration of a drug is often 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 later 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 insure that there has been adequate drug absorption.

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 31.3), 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 and failure to account for the continued renal elimination of drug may result in insufficient drug dosing and therapeutic failure.

Table 31.3 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)
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:

$$Q = 1 - \left[\text{Fraction renal elimination} \times \left(1 - \frac{\text{Child's } Cl_{Cr} \text{ (mL/min/1.73 m}^2\text{)}}{\text{Normal } Cl_{Cr} \text{ (mL/min/1.73 m}^2\text{)}} \right) \right] \quad (31.11)$$

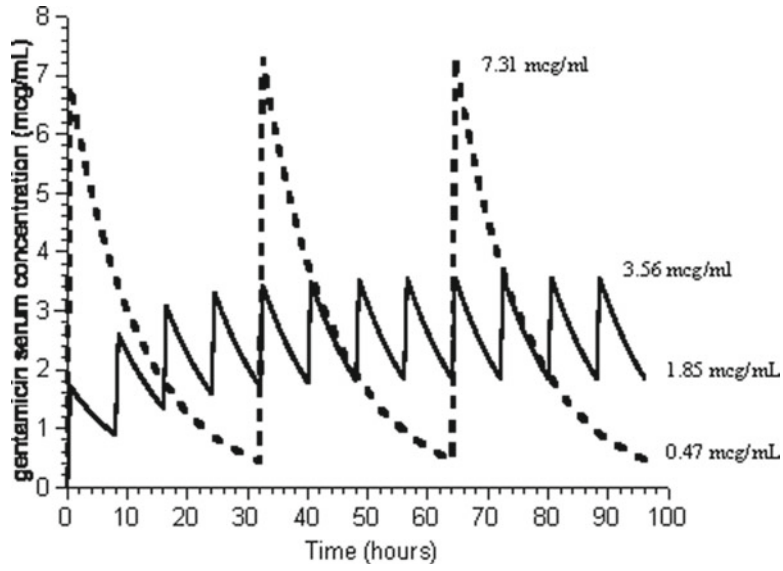

Fig. 31.3 Serum concentration – time profile for a child with a GFR = 15 mL/min/1.73 m^2. The dashed line depicts the profile when the dosing interval is adjusted to 2.5 mg/kg IV every 53 h. The solid line depicts the profile when the dosing interval is unchanged and the dosage amount is reduced (0.375 mg/kg IV every 8 h)

The 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, supplemental drug doses 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 gentamicin accumulates to toxic blood levels in renal failure if the dosing regimen is not modified (Fig. 31.1). Using (Equation 31.11), 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.

$$Q = 1 - \left[0.95 \times \left(1 - \frac{15\ \text{mL/min/1.73m}^2}{120\ \text{mL/min/1.73m}^2} \right) \right] = 0.15 \tag{31.12}$$

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, 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, the modified regimen is calculated to be 2.5 mg/kg administered IV every 53 h (8 h ÷ 0.15). As displayed in Fig. 31.3, both adjustments produce similar mean gentamicin serum levels but very different gentamicin serum concentration-time profiles. 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 with lower peak and higher trough concentrations. 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.

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 >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 31.4 lists some common drugs and notes whether adjustments are needed for renal failure and if supplemental doses are suggested during dialysis.

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 are capable of altering 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.

Table 31.4 Antibiotic, antiviral, antifungal agents

Drug	Adjustment for renal failure	Supplement for dialysis			Comments
		Hemodialysis	CRRT	Peritoneal dialysis	
Acyclovir [23–26]	Yes	Yes	No	No	Neurotoxicity
Amantadine [27–29]	Yes	No	No	No	
Amikacin [30–32]	Yes	Yes	Yes	Yes	TDM
Amoxicillin [164, 33]	Yes	Yes	Yes	No	
Amphotericin B [34, 35]	No	No	No	No	
Ampicillin [36–38]	Yes	Yes	Yes	No	
Azithromycin [29, 39]	No	No	No	No	
Cefaclor [40, 41]	Yes	Yes	?	No	
Cefazolin [15, 42]	Yes	Yes	Yes	Yes	
Cefepime [43–45]	Yes	Yes	Yes	No	Neurotoxicity
Cefixime [46, 47]	Yes	No	No	No	
Cefotaxime [36, 48, 49]	Yes	Yes	Yes	No	
Cefpodoxime [50–52]	Yes	Yes	?	No	
Cefprozil [53]	Yes	Yes	?	?	
Ceftazidime [36, 54–56]	Yes	Yes	Yes	No	
Ceftriaxone [19, 36, 57]	No	No	No	No	
Cefuroxime [36, 58, 59]	Yes	Yes	Yes	No	
Cephalexin [29]	Yes	Yes	?	No	
Ciprofloxacin [29, 60]	Yes	No	No	No	
Clindamycin [61]	No	No	No	No	
Co-trimoxazole [62, 63]	Yes	Yes	?	No	
Erythromycin [29, 36, 64]	Yes	No	No	No	
Famciclovir [65]	Yes	No	?	?	Dose after hemodialysis
Fluconazole [66, 67]	Yes	Yes	Yes	No	
Foscarnet [68]	Yes	Yes	?	?	Nephrotoxicity

(continued)

Table 31.4 (continued)

Drug	Adjustment for renal failure	Supplement for dialysis			Comments
		Hemodialysis	CRRT	Peritoneal dialysis	
Ganciclovir [69, 70]	Yes	Yes	Yes	?	Dose after hemodialysis
Gentamicin [38, 71, 72]	Yes	Yes	Yes	Yes	TDM
Imipenem/ Cilastin [36, 73, 74]	Yes	Yes	Yes	No	Seizures
Isoniazid [75, 76]	No	No	No	No	TDM dose after hemodialysis
Ketoconazole [77]	No	No	No	No	
Loracarbef	Yes	Yes	?	?	
Meropenem [78–80]	Yes	Yes	Yes	?	
Metronidazole [29, 36, 81]	Yes	No	No	No	Dose after hemodialysis
Oxacillin [82]	No	No	No	No	
Penicillin G [29]	Yes	Yes	Yes	No	
Pentamidine [83, 84]	No	No	No	No	
Piperacillin [85–87]	Yes	Yes	Yes	No	
Piperacillin/Tazo	Yes	Yes	?	No	
Rifampin [29, 75]	No	No	No	No	
Ticarcillin [88, 89]	Yes	Yes	Yes	Yes	
Tobramycin [90, 91]	Yes	Yes	Yes	Yes	TDM
Valacyclovir [92, 93]	Yes	No	No	No	Dose after hemodialysis neurotoxicity
Valganciclovir [94]	Yes	?	?	?	Not recommended in dialysis
Vancomycin [29, 165]	Yes	No	No	No	TDM
Anticonvulsants					
Carbamazepine [95, 96]	Yes	No	No	No	TDM
Gabapentin	Yes	No	No	No	Dose after hemodialysis
Lamotrigine [97, 98]	Yes	No	?	?	
Phenobarbital [29, 99]	Yes	Yes	Yes	Yes	
Phenytoin [29, 100] (Fosphenytoin)	No	No	No	No	↓ Protein binding TDM – free levels
Valproic acid [4, 101, 102]	No	No	No	No	↓ Protein binding
Cardiovascular agents					
Aliskerin	No	?	?	?	
Amlodipine [103, 104]	No	No	?	No	
Atenolol [105–107]	Yes	Yes	?	No	
Captopril [108–111]	Yes	Yes	Yes	No	
Clonidine [112, 113]	No	No	?	No	
Digoxin [12, 114–117]	Yes	No	No	No	↓ Vd (adjust loading dose) Avoid K^+ depletion
Enalapril [118, 119]	Yes	Yes	Yes	No	
Esmolol [120, 121]	No	No	No	No	
Fosinopril [122, 123]	Yes	No	No	No	
Labetalol [124, 125]	No	No	No	No	
Lisinopril	Yes	Yes	Yes	No	
Minoxidil [29, 126]	No	No	?	No	
Nifedipine [127, 128]	No	No	?	No	
Nadolol [129]	Yes	Yes	?	No	

(continued)

Table 31.4 (continued)

Drug	Adjustment for renal failure	Supplement for dialysis			Comments
		Hemodialysis	CRRT	Peritoneal dialysis	
Metoprolol [29]	No	Yes	?	?	Dose after hemodialysis
Prazosin [130]	No	No	?	No	
Propranolol [131–133]	No	No	No	No	
Immunosuppressive agents					
Daclizumab	No	?	?	?	
Azathioprine [29]	Yes	Yes	?	?	
Cyclosporine [134, 135]	No	No	No	No	TDM, nephrotoxicity
Mycophenolate [136–138]	No	No	No	No	TDM
Prednisone [139]	No	No	No	No	
Sirolimus	No	?	?	?	TDM
Tacrolimus [140]	No	No	No	No	TDM, nephrotoxicity
Miscellaneous					
Buspirone [141]	Yes	No	?	?	Active metabolites
Cetirizine [142]	Yes	No	?	?	
Codeine [29, 143]	Yes	?	?	?	Active metabolites
Diazepam [29]	No	No	?	?	Active metabolites
Enoxaparin [144]	Yes	?	?	?	TDM
Famotidine [145–147]	Yes	No	No	No	Active metabolites
Fentanyl [29, 148]	Yes	No	?	?	
Fluoxetine [148, 149]	No	No	No	No	
Hydromorphone	No	?	?	?	
Imipramine [29, 150]	No	No	?	No	
Lansoprazole [151, 152]	No	No	?	?	
Lithium [153]	Yes	Yes	?	No	TDM
Loratadine [154]	Yes	No	?	?	
Meperidine [7]	Yes	?	?	?	Seizures, metabolites not recommended
Methadone [29]	Yes	No	?	?	
Methylphenidate	No	?	?	?	
Midazolam [5]	Yes	?	?	?	Active metabolites
Montelukast	No	?	?	?	
Morphine [6, 29, 155]	Yes	No	?	?	
Omeprazole [156, 157]	No	No	?	?	
Ondansetron	No	?	?	?	
Oxycodone [29]	Yes	?	?	?	Active metabolites
Paroxetine [158]	Yes	?	?	?	
Ranitidine [159–161]	Yes	No	?	No	Dose after hemodialysis
Sufentanil	No	?	?	?	
Warfarin [29]	No	No	?	No	

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 renal failure, 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 non-functional 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. Secondly, genetic variation becomes increasingly important as the therapeutic index – the difference between concentrations associated with effect and those associated with toxicity – decreases. Warfarin is one medication where genetic information is becoming a very useful adjunct to initial dose selection.

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, CYP2D6 is one of the best-studied, clinically relevant pharmacogenetic polymorphisms [162]. The *CYP2D6* gene locus is highly polymorphic with more than 75 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. On the other hand, 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) were concordant with genotype at 2 weeks of age and throughout the following 12 months [163]. 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 relate 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 resperidone; 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 ACE inhibitors, 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 non-functional 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. However, a potential role for pharmacogenetics should be anticipated soon 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. Ritschel W, Kearns GL. Handbook of basic pharmacokinetics…Including clinical applications. 7th ed. Washington, DC: American Pharmaceutical Association; 2009.
2. Miyagawa CI. Hydrochloric acid given with ketoconazole through a jejunostomy tube. Clin Pharm. 1984;3:205–7.
3. Blum RA, D'Andrea DT, Florentino BM, Wilton JH, Hilligoss DM, Gardner MJ, Henry EB, Goldstein H, Schentag JJ. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med. 1991;114:755–7.
4. Bruni J, Wang LH, Marbury TC, Lee CS, Wilder BJ. Protein binding of valproic acid in uremic patients. Neurology. 1980;30:557–9.
5. Bauer TM, Ritz R, Haberthur C, Ha HR, Hunkeler W, Sleight AJ, Scollo-Lavizzari G, Haefeli WE. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet. 1995;346:145–7.
6. Ball M, McQuay HJ, Moore RA, Allen MC, Fisher A, Sear J. Renal failure and the use of morphine in intensive care. Lancet. 1985;1:784–6.
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;86:738–41.
8. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther. 2008;118:250–67.
9. Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem. 2008;392:1093–108.
10. Odugbemi T. An open evaluation study of sulbactam/ampicillin with or witohut probenecid in the treatment of gonococcal infections in Lagos. Drugs. 1988;35:89–91.
11. Prescott L, Balali-Mood M, Critchley J, Johnstone A, Proudfoot A. Diuresis or urinary alkalinisation for salicylate poisoning. Br Med J. 1982;285:1383–6.
12. Paulson MF, Welling PG. Calculation of serum digoxin levels in patients with normal and impaired renal function. J Clin Pharmacol. 1976;16:660–5.
13. Blowey DL, Kearns GL, Lalkin A. Special considerations in the prescribing of medications for the pediatric CAPD/CCPD patient. In: Fine RN, Alexander SR, Warady BA, editors. CAPD/CCPD in Children, chap 15. Boston: Kluwer Academic Publishers; 1998. p. 229–46.
14. Zhang Y, Zhang L, Abraham S, Apparaju S, Wu T-C, Strong S, Xiao S, Atkinson A, Thummel K, Leeder JS, Lee C, Burckart GJ, Lesko L, Huang S-M. Assessment of the impact of renal impairment on systemic exposure of new molecular entities – Evaluation of recent new drug applications. Clin Pharmacol Ther. 2009;85:305–11.
15. 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;32:410–4.
16. Zoer J, Schrander-van der Meer AM, Van Dorp WT. Dosage recommendation of vancomycin during haemodialysis with highly permeable membranes. Pharm World Sci. 1997;19:191–6.
17. DeSoi CA, Sahm DF, Umans JG. Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes. Am J Kidney Dis. 1992;20:354–60.
18. Blowey DL. Extracorpeal methods of drug removal. In: Ritschel W, Kearns GL, editors. Handbook of basic pharmacokinetics, chap 38. 7th ed. Washington, DC: American Pharmaceutical Association; 2009. p. 395–407.
19. Matzke GR, Frye RF, Joy MS, Palevsky PM. Determinants of ceftriaxone clearance by continuous venovenous hemofiltration and hemodialysis. Pharmacotherapy. 2000;20:635–43.
20. Warady BA, Schaefer F, Holloway M, Alexander S, Kandert M, Piraino B, Salusky I, Tranaeus A, Divino J,

Honda M, Mujais S, Verrina E. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int. 2000;20: 610–24.
21. Schaefer F, Klaus G, Muller-Wiefel DE, Mehls O, The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. J Am Soc Nephrol. 1999;10:136–45.
22. Li PK-T, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye W-C, Salzer W, Schaefer F, Struijk DG. ISPD guidelines/recommendations: peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int. 2010;30:393–423.
23. 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;20:69–76.
24. Laskin OL, Longstreth JA, Whelton A, Krasny HC, Keeney RE, Rocco L, Lietman PS. Effect of renal failure on the pharmacokinetics of acyclovir. Am J Med. 1982;73:197–201.
25. Stathoulopoulou F, Almond MK, Dhillon S, Raftery MJ. Clinical pharmacokinetics of oral acyclovir in patients on continuous ambulatory peritoneal dialysis. Nephron. 1996;74:337–41.
26. Wagstaff AJ, Faulds D, Goa KL. Aciclovir A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1994;47: 153–205.
27. Wu MJ, Ing TS, Soung LS, Daugirdas JT, Hano JE, Gandhi VC. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. Clin Nephrol. 1982;17:19–23.
28. Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep.. 2002;51:1–31.
29. Olyaei AJ, De Mattos A, Bennett W. Prescribing drugs in renal disease. In: Brenner B, editor. The Kidney, chap 61. Philadelphia: WB Saunders; 2000. p. 2606–53.
30. 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;8:85–95.
31. Lanao JM, Dominguez-Gil A, Tabernero JM, Macias JF. Influence of type of dialyzer on the pharmacokinetics of amikacin. Int J Clin Pharmacol Ther Toxicol. 1983;21:197–202.
32. Armendariz E, Chelluri L, Ptachcinski R. Pharmacokinetics of amikacin during continuous veno-venous hemofiltration. Crit Care Med. 1990; 18:675–6.
33. Oe PL, Simonian S, Verhoef J. Pharmacokinetics of the new penicillins. Amoxycillin and flucloxacillin in patients with terminal renal failure undergoing haemodialysis. Chemotherapy. 1973;19:279–88.
34. Muther RS, Bennett WM. Peritoneal clearance of amphotericin B and 5-fluorocytosine. West J Med. 1980;133:157–60.
35. Block ER, Bennett JE, Livoti LG, Klein Jr WJ, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. Studies in man. Ann Intern Med. 1974;80:613–7.
36. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. J Antimicrob Chemother. 1995;36: 773–80.
37. Jusko WJ, Lewis GP, Schmitt GW. Ampicillin and hetacillin pharmacokinetics in normal and anephric subjects. Clin Pharmacol Ther. 1973;14:90–9.
38. Golper TA, Pulliam J, Bennett WM. Removal of therapeutic drugs by continuous arteriovenous hemofiltration. Arch Intern Med. 1985;145: 1651–2.
39. Kent JR, Almond MK, Dhillon S. Azithromycin: an assessment of its pharmacokinetics and therapeutic potential in CAPD. Perit Dial Int. 2001;21: 372–7.
40. 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;14:281–3.
41. 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;5:465–70.
42. Manley HJ, Bailie GR, Asher RD, Eisele G, Frye RF. Pharmacokinetics of intermittent intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1999;19:65–70.
43. Cronqvist J, Nilsson-Ehle I, Oqvist B, Norrby SR. Pharmacokinetics of cefepime dihydrochloride arginine in subjects with renal impairment. Antimicrob Agents Chemother. 1992;36:2676–80.
44. Wong KM, Chan WK, Chan YH, Li CS. Cefepime-related neurotoxicity in a haemodialysis patient. Nephrol Dial Transplant. 1999;14:2265–6.
45. Barbhaiya RH, Knupp CA, Pfeffer M, Zaccardelli D, Dukes GM, Mattern W, Pittman KA, Hak LJ. Pharmacokinetics of cefepime in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1992;36:1387–91.
46. Faulkner RD, Yacobi A, Barone JS, Kaplan SA, Silber BM. Pharmacokinetic profile of cefixime in man. Pediatr Infect Dis J. 1987;6:963–70.
47. 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: 485–90.
48. Albin HC, Demotes-Mainard FM, Bouchet JL, Vincon GA, Martin-Dupont C. Pharmacokinetics of intravenous and intraperitoneal cefotaxime in chronic ambulatory peritoneal dialysis. Clin Pharmacol Ther. 1985;38:285–9.

49. Fillastre JP, Leroy A, Humbert G, Godin M. Pharmacokinetics of cefotaxime in subjects with normal and impaired renal function. J Antimicrob Chemother. 1980;6(Supply A):103–11.
50. Hoffler D, Koeppe P, Corcilius M, Przyklinik A. Cefpodoxime proxetil in patients with endstage renal failure on hemodialysis. Infection. 1990;18:157–62.
51. Borin MT, Hughes GS, Kelloway JS, Shapiro BE, Halstenson CE. Disposition of cefpodoxime proxetil in hemodialysis patients. J Clin Pharmacol. 1992;32: 1038–44.
52. Johnson CA, Ateshkadi A, Zimmerman SW, Hughes GS, Craig WA, Carey PM, Borin MT. Pharmacokinetics and ex vivo susceptibility of cefpodoxime proxetil in patients receiving continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1993;37:2650–5.
53. 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;31:362–71.
54. Welage LS, Schultz RW, Schentag JJ. Pharmacokinetics of ceftazidime in patients with renal insufficiency. Antimicrob Agents Chemother. 1984; 25:201–4.
55. Nikolaidis P, Tourkantonis A. Effect of hemodialysis on ceftazidime pharmacokinetics. Clin Nephrol. 1985;24:142–6.
56. Kinowski JM, de la Coussaye JE, Bressolle F, Fabre D, Saissi G, Bouvet O, Galtier M, Eledjam JJ. Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. Antimicrob Agents Chemother. 1993;37:464–73.
57. Losno GR, Santivanez V, Battilana CA. Single-dose pharmacokinetics of ceftriaxone in patients with end-stage renal disease and hemodialysis. Chemotherapy. 1988;34:261–6.
58. Weiss LG, Cars O, Danielson BG, Grahnen A, Wikstrom B. Pharmacokinetics of intravenous cefuroxime during intermittent and continuous arteriovenous hemofiltration. Clin Nephrol. 1988;30: 282–6.
59. Konishi K, Suzuki H, Hayashi M, Saruta T. Pharmacokinetics of cefuroxime axetil in patients with normal and impaired renal function. J Antimicrob Chemother. 1993;31:413–20.
60. 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;31:589–93.
61. 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;14:435–9.
62. Nissenson AR, Wilson C, Holazo A. Pharmacokinetics of intravenous trimethoprim-sulfamethoxazole during hemodialysis. Am J Nephrol. 1987;7:270–4.
63. Paap CM, Nahata MC. Clinical use of trimethoprim/sulfamethoxazole during renal dysfunction. DICP. 1989;23:646–54.
64. 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;24:460–4.
65. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. Clin Pharmacokinet. 1996;31:1–8.
66. Dudley MN. Clinical pharmacology of fluconazole. Pharmacotherapy. 1990;10:141S–5.
67. Nicolau DP, Crowe H, Nightingale CH, Quintiliani R. Effect of continuous arteriovenous hemodiafiltration on the pharmacokinetics of fluconazole. Pharmacotherapy. 1994;14:502–5.
68. Aweeka FT, Jacobson MA, Martin-Munley S, Hedman A, Schoenfeld P, Omachi R, Tsunoda S, Gambertoglio JG. Effect of renal disease and hemodialysis on foscarnet pharmacokinetics and dosing recommendations. J Acquir Immune Defic Syndr Hum Retrovirol. 1999;20:350–7.
69. Combarnous F, Fouque D, Bernard N, Boulieu R, Chossegros P, Laville M, Zech P. Pharmacokinetics of ganciclovir in a patient undergoing chronic haemodialysis. Eur J Clin Pharmacol. 1994;46:379–81.
70. Boulieu R, Bastien O, Bleyzac N. Pharmacokinetics of ganciclovir in heart transplant patients undergoing continuous venovenous hemodialysis. Ther Drug Monit. 1993;15:105–7.
71. Ernest D, Cutler DJ. Gentamicin clearance during continuous arteriovenous hemodiafiltration. Crit Care Med. 1992;20:586–9.
72. Hamann SR, Oeltgen PR, Shank Jr WA, Blouin RA, Natarajan L. Evaluation of gentamicin pharmacokinetics during peritoneal dialysis. Ther Drug Monit. 1982;4:297–300.
73. Somani P, Freimer EH, Gross ML, Higgins Jr JT. Pharmacokinetics of imipenem-cilastatin in patients with renal insufficiency undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother. 1988;32:530–4.
74. 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;18:183–93.
75. 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;159:1580–4.
76. Ellard GA. Chemotherapy of tuberculosis for patients with renal impairment. Nephron. 1993;64: 169–81.
77. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. Clin Pharmacokinet. 1988;14:13–34.
78. Tegeder I, Neumann F, Bremer F, Brune K, Lotsch J, Geisslinger G. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing

continuous venovenous hemofiltration. Clin Pharmacol Ther. 1999;65:50–7.
79. 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;28:632–7.
80. 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;37:229–33.
81. Somogyi AA, Kong CB, Gurr FW, Sabto J, Spicer WJ, McLean AJ. Metronidazole pharmacokinetics in patients with acute renal failure. J Antimicrob Chemother. 1984;13:183–9.
82. 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;94:257–61.
83. Conte Jr JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. J Infect Dis. 1991;163: 169–75.
84. Conte Jr JE, Upton RA, Lin ET. Pentamidine pharmacokinetics in patients with AIDS with impaired renal function. J Infect Dis. 1987;156:885–90.
85. Thompson MI, Russo ME, Matsen JM, Atkin-Thor E. Piperacillin pharmacokinetics in subjects with chronic renal failure. Antimicrob Agents Chemother. 1981;19:450–3.
86. Francke EL, Appel GB, Neu HC. Pharmacokinetics of intravenous piperacillin in patients undergoing chronic hemodialysis. Antimicrob Agents Chemother. 1979;16:788–91.
87. Debruyne D, Ryckelynck JP, Hurault DL, Moulin M. Pharmacokinetics of piperacillin in patients on peritoneal dialysis with and without peritonitis. J Pharm Sci. 1990;79:99–102.
88. Parry MF, Neu HC. Pharmacokinetics of ticarcillin in patients with abnormal renal function. J Infect Dis. 1976;133:46–9.
89. Wise R, Reeves DS, Parker AS. Administration of ticarcillin, a new antipseudomonal antibiotic, in patients undergoing dialysis. Antimicrob Agents Chemother. 1974;5:119–20.
90. Lockwood WR, Bower JD. Tobramycin and gentamicin concentrations in the serum of normal and anephric patients. Antimicrob Agents Chemother. 1973;3:125–9.
91. Zarowitz BJ, Anandan JV, Dumler F, Jayashankar J, Levin N. Continuous arteriovenous hemofiltration of aminoglycoside antibiotics in critically ill patients. J Clin Pharmacol. 1986;26:686–9.
92. Izzedine H, Mercadal L, Aymard G, Launay-Vacher V, Martinez V, Issad B, Deray G. Neurotoxicity of valacyclovir in peritoneal dialysis: a pharmacokinetic study. Am J Nephrol. 2001;21:162–4.
93. 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.
94. Vaudry W, Ettenger R, Jara P, et al. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. Am J Transplant. 2009;9:636–43.
95. Kandrotas RJ, Oles KS, Gal P, Love JM. Carbamazepine clearance in hemodialysis and hemoperfusion. DICP. 1989;23:137–40.
96. Lee CS, Wang LH, Marbury TC, Bruni J, Perchalski RJ. Hemodialysis clearance and total body elimination of carbamazepine during chronic hemodialysis. Clin Toxicol. 1980;17:429–38.
97. 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;19:25–32.
98. Garnett WR. Lamotrigine: pharmacokinetics. J Child Neurol. 1997;12(Supply 1):S10–5.
99. Porto I, John EG, Heilliczer J. Removal of phenobarbital during continuous cycling peritoneal dialysis in a child. Pharmacotherapy. 1997;17:832–5.
100. Czajka PA, Anderson WH, Christoph RA, Banner Jr W. A pharmacokinetic evaluation of peritoneal dialysis for phenytoin intoxication. J Clin Pharmacol. 1980;20:565–9.
101. Lapierre O, Dubreucq JL, Beauchemin MA, Vinet B. Valproic acid intoxication in a patient with bipolar disorder and chronic uremia. Can J Psychiatry. 1999;44:188.
102. 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;24:387–90.
103. Doyle GD, Donohue J, Carmody M, Laher M, Greb H, Volz M. Pharmacokinetics of amlodipine in renal impairment. Eur J Clin Pharmacol. 1989;36:205–8.
104. Laher MS, Kelly JG, Doyle GD, Carmody M, Donohoe JF, Greb H, Volz M. Pharmacokinetics of amlodipine in renal impairment. J Cardiovasc Pharmacol. 1988;12(Supply 7):S60–3.
105. Wan SH, Koda RT, Maronde RF. Pharmacokinetics, pharmacology of atenolol and effect of renal disease. Br J Clin Pharmacol. 1979;7:569–74.
106. Salahudeen AK, Wilkinson R, McAinsh J, Bateman DN. Atenolol pharmacokinetics in patients on continuous ambulatory peritoneal dialysis. Br J Clin Pharmacol. 1984;18:457–60.
107. Flouvat B, Decourt S, Aubert P, Potaux L, Domart M, Goupil A, Baglin A. Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. Br J Clin Pharmacol. 1980;9: 379–85.
108. Ferguson RK, Rotmensch HH, Vlasses PH. Clinical use of captopril. Illustrative cases. JAMA. 1982;247: 2117–9.
109. Sica DA, Gehr TW, Fernandez A. Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease. Drug Saf. 2000;22:350–60.

110. 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;44:324–8.
111. Duchin KL, Pierides AM, Heald A, Singhvi SM, Rommel AJ. Elimination kinetics of captopril in patients with renal failure. Kidney Int. 1984;25:942–7.
112. Lowenthal DT, Saris SD, Paran E, Cristal N. The use of transdermal clonidine in the hypertensive patient with chronic renal failure. Clin Nephrol. 1993; 39:37–43.
113. Rosansky SJ, Johnson KL, McConnell J. Use of transdermal clonidine in chronic hemodialysis patients. Clin Nephrol. 1993;39:32–6.
114. Doherty JE, Flanigan WJ, Perkins WH, Ackerman GL. Studies with tritiated digoxin in anephric human subjects. Circulation. 1967;35:298–303.
115. Iisalo E, Forsstrom J. Elimination of digoxin during maintenance haemodialysis. Ann Clin Res. 1974;6: 203–6.
116. Pancorbo S, Comty C. Digoxin pharmacokinetics in continuous peritoneal dialysis. Ann Intern Med. 1980;93:639.
117. Golper TA, Bennett WM. Drug removal by continuous arteriovenous haemofiltration. A review of the evidence in poisoned patients. Med Toxicol Adverse Drug Exp. 1988;3:341–9.
118. 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;20:420–7.
119. Mason NA. Angiotensin-converting enzyme inhibitors and renal function. DICP. 1990;24:496–505.
120. Lowenthal DT, Porter RS, Saris SD, Bies CM, Slegowski MB, Staudacher A. Clinical pharmacology, pharmacodynamics and interactions with esmolol. Am J Cardiol. 1985;56:14F–8.
121. 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;45:321–7.
122. Gehr TWB, Sica DA, Grasela DM, et al. The pharmacokinetcs and pharmacodynamics of fosinopril in haemodialysis patients. Eur J Clin Pharmacol. 1993;45:431–6.
123. Gehr TW, Sica DA, Grasela DM, et al. Fosinopril pharmacokineitcs and pharmacodynamics in chronic peritoneal dialysis patients. Eur J Clin Pharmacol. 1991;41:165–9.
124. Wood AJ, Ferry DG, Bailey RR. Elimination kinetics of labetalol in severe renal failure. Br J Clin Pharmacol. 1982;13:81S–6.
125. Halstenson CE, Opsahl JA, Pence TV, Luke DR, Sirgo MA, Plachetka JR, Abraham PA, Matzke GR. The disposition and dynamics of labetalol in patients on dialysis. Clin Pharmacol Ther. 1986;40:462–8.
126. Halstenson CE, Opsahl JA, Wright CE, Fleishaker JC, Andreadis NA, Sobieraj J, Matzke GR. Disposition of minoxidil in patients with various degrees of renal function. J Clin Pharmacol. 1989; 29:798–802.
127. Spital A, Scandling JD. Nifedipine in continuous ambulatory peritoneal dialysis. Arch Intern Med. 1983;143:2025.
128. 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;11:316–22.
129. Herrera J, Vukovich RA, Griffith DL. Elimination of nadolol by patients with renal impairment. Br J Clin Pharmacol. 1979;7(Supply 2):227S–31.
130. Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. West J Med. 1992; 156:633–8.
131. 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.
132. Lowenthal DT, Briggs WA, Gibson TP, Nelson H, Cirksena WJ. Pharmacokinetics of oral propranolol in chronic renal disease. Clin Pharmacol Ther. 1974;16:761–9.
133. Bianchetti G, Graziani G, Brancaccio D, Morganti A, Leonetti G, Manfrin M, Sega R, Gomeni R, Ponticelli C, Morselli PL. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin Pharmacokinet. 1976;1:373–84.
134. Follath F, Wenk M, Vozeh S, Thiel G, Brunner F, Loertscher R, Lemaire M, Nussbaumer K, Niederberger W, Wood A. Intravenous cyclosporine kinetics in renal failure. Clin Pharmacol Ther. 1983;34:638–43.
135. Venkataramanan R, Ptachcinski RJ, Burckart GJ, Yang SL, Starzl TE, Van Theil DH. The clearance of cyclosporine by hemodialysis. J Clin Pharmacol. 1984;24:528–31.
136. Filler G, Grygas R, Mai I, Stolpe HJ, Greiner C, Bauer S, Ehrich JH. Pharmacokinetics of tacrolimus (FK 506) in children and adolescents with renal transplants. Nephrol Dial Transplant. 1997;12: 1668–71.
137. MacPhee IA, Spreafico S, Bewick M, Davis C, Eastwood JB, Johnston A, Lee T, Holt DW. Pharmacokinetics of mycophenolate mofetil in patients with end-stage renal failure. Kidney Int. 2000;57:1164–8.
138. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet. 1998;34:429–55.
139. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet. 1990;19:126–46.
140. Venkataramanan R, Jain A, Warty VS, Abu-Elmagd K, Alessiani M, Lever J, Krajak A, Flowers J, Mehta S, Zuckerman S. Pharmacokinetics of FK 506 in transplant patients. Transplant Proc. 1991;23: 2736–40.

141. Gammans RE, Mayol RF, LaBudde JA. Metabolism and disposition of buspirone. Am J Med. 1986;80: 41–51.
142. 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;38:67–9.
143. Matzke GR, Chan GL, Abraham PA. Codeine dosage in renal failure. Clin Pharm. 1986;5:15–6.
144. Buckley MM, Sorkin EM. Enoxaparin. A review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. Drugs. 1992;44:465–97.
145. Lin JH, Chremos AN, Yeh KC, Antonello J, Hessey GA. Effects of age and chronic renal failure on the urinary excretion kinetics of famotidine in man. Eur J Clin Pharmacol. 1988;34:41–6.
146. Saima S, Echizen H, Yoshimoto K, Ishizaki T. Hemofiltrability of H2-receptor antagonist, famotidine, in renal failure patients. J Clin Pharmacol. 1990;30:159–62.
147. Gladziwa U, Klotz U, Krishna DR, Schmitt H, Glockner WM, Mann H. Pharmacokinetics and dynamics of famotidine in patients with renal failure. Br J Clin Pharmacol. 1988;26:315–21.
148. 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;36:138–44.
149. Lemberger L, Bergstrom RF, Wolen RL, Farid NA, Enas GG, Aronoff GR. Fluoxetine: clinical pharmacology and physiologic disposition. J Clin Psychiatry. 1985;46:14–9.
150. Bailey RR, Sharman JR, O'Rourke J, Buttimore AL. Haemodialysis and forced diuresis for tricyclic antidepressant poisoning. Br Med J. 1974;4:230–1.
151. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet. 1996;31:9–28.
152. Barradell LB, Faulds D, McTavish D. Lansoprazole. A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs. 1992;44:225–50.
153. Clericetti N, Beretta-Piccoli C. Lithium clearance in patients with chronic renal diseases. Clin Nephrol. 1991;36:281–9.
154. Matzke GR, Halstenson CE, Opsahl JA, Hilbert J, Perentesis G, Radwanski E, Zampaglione N. Pharmacokinetics of loratadine in patients with renal insufficiency. J Clin Pharmacol. 1990;30:364–71.
155. Portenoy RK, Foley KM, Stulman J, Khan E, Adelhardt J, Layman M, Cerbone DF, Inturrisi CE. 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: 13–9.
156. Naesdal J, Andersson T, Bodemar G, Larsson R, Regardh CG, Skanberg I, Walan A. Pharmacokinetics of [14 C]omeprazole in patients with impaired renal function. Clin Pharmacol Ther. 1986;40:344–51.
157. Howden CW, Payton CD, Meredith PA, Hughes DM, Macdougall AI, Reid JL, Forrest JA. Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. Eur J Clin Pharmacol. 1985;28:637–40.
158. 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.
159. McFadyen ML, Folb PI, Miller R, Keeton GR, Marks IN. Pharmacokinetics of ranitidine in patients with chronic renal failure. Eur J Clin Pharmacol. 1983;25:347–51.
160. Zech PY, Chau NP, Pozet N, Labeeuw M, Hadj-Aissa A. Ranitidine kinetics in chronic renal impairment. Clin Pharmacol Ther. 1983;34:667–72.
161. Gladziwa U, Krishna DR, Klotz U, Ittel TH, Schunkert H, Glockner WM, Mann H. Pharmacokinetics of ranitidine in patients undergoing haemofiltration. Eur J Clin Pharmacol. 1988;35: 427–30.
162. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. Pharmacogenomics J. 2005;5:6–13.
163. Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, James LP, Wilson JT, Kearns GL, Leeder JS. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther. 2007;81:510–6.
164. 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;14:654–9.
165. 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: 79–85.

Use of Contrast Agents in Children with Chronic Kidney Disease

32

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Keywords

Contrast Media • Contrast induced nephropathy • Nephrotoxicity • Gadolinium • Nephrogenic systemic fibrosis • Dialysis • Pediatric • Growth

Abbreviations

CIN	contrast-induced nephropathy
CT	computed tomography
ESRD	end-stage renal disease
GCCA	gadolinium-containing 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

Contrast media have been used in diagnostic imaging since the late 1800s and have evolved over the decades. 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, 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, or directly into a body cavity such as the gastrointestinal or urinary tract. However, like any other pharmaceutical agent, adverse events may occur.

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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 recent emergence of nephrogenic systemic fibrosis (NSF).

The purpose of this chapter is to give an overview of 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, and the emergence 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.

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. Positive contrast media are used more commonly and are radiopaque. Barium and iodine can attenuate X-rays 50–1,000 times more than soft tissues and are the main components in positive contrast media. Gadolinium-containing contrast agents (GCCA) 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 bronchography and will not be discussed in this chapter. The most commonly used iodinated contrast agents are water soluble. They are utilized for angiography, intravenous urography, CT, and conventional radiography since they can also be administered into the urinary 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 (Table 32.1). The derivatives are either monomeric or dimeric depending on whether they contain one or two benzene rings [1–3]. Furthermore, their water solubility is achieved in different ways. Ionic contrast media dissociates 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 [3, 4].

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) [1, 5]. These different characteristics are responsible for the diverse levels of toxicity between the agents.

Table 32.1 Characteristics of water-soluble iodine contrast media

Structure	Contrast media ratio	Osmolality (mOsm/kg)	Name
Ionic monomer	3/2 = 1.5	1,500–2,000	Acetrizoate Diatrizoate Iodamide Ioglicate Iothalamate Ioxithalamate Metrizoate
Ionic dimer	6/2 = 3	600	Ioxaglate
Nonionic monomer	3/1 = 3	500–700	Iohexol Iopamidol Iopentol Iopromide Ioversol Metrizamide
Nonionic dimer	6/1 = 6	300	Iodixanol Iotrolan

Renal Handling of Contrast Media

Overall, iodinated contrast media have a relatively small molecular weight, high water solubility, and minimal protein binding [1, 2, 6, 7]. 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 [8, 9].

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 [10–12]. 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 [2]. In the tubules, contrast media exert an osmotic force reducing the reabsorption of water and sodium [13, 14]. 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 [15]. 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 [16].

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 [17]. 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 [17]. 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 [18, 19].

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 [20, 21].

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 [22, 23]. In vitro, dimeric contrast media have a greater potential for cytotoxic effects on proximal renal tubular cells than monomeric contrast media [24].

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 [19].

All of the above-mentioned 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). Minor reactions are more common (incidence 5–15%), intermediate reactions occur in 1–2% and severe reactions in 0.2–0.06% when using HOCM and are less frequent when using LOCM [25]. The incidence of these reactions in ESRD is not known. 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 [26–29]. Younathan et al. studied 10 patients with ESRD on chronic hemodialysis (HD) who underwent 11 procedures requiring intravascular administration of LOCM [30]. 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 [31]. 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 [32]. 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 1,550 Da and their water solubility, low protein binding, and minimal intracellular penetration allows 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 32.2) [33–46]. 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.

Table 32.2 Hemodialysis removal of contrast media

Study	Contrast agent	Molecular weight (D)	Dialyzer	Contrast clearance (mL/min)	Contrast removal
Kierdorf et al. [33]	Iopromide	791		80	41% in 3 h
Waaler et al. [34]	Iohexol	821	Polycarbonate Cellulose Cuprophan	81 ± 15	72 ± 11% in 4 h
Moon et al. [35]	Iohexol	821	Cuprophan Polysulfone	70.4 ± 24.6	60–90% in 6 h
Bailie et al. [36]	Iodixanol	1,550	Cellulose Polysulfone	22.8–57.8 19.3–281.86	36.1% at 4 h 49.6% at 4 h
Ueda et al. [37]	Ioversol	807	Cellulose	114–129	82.5 ±5.1% at 4 h
Ueda et al. [38]	Iomeprol	777	Cellulose	131.4–133.3	81.4 ± 4.6% at 4 h
Johnsson et al. [39]	Iohexol	821	Cellulose		71% at 3 h 79% at 6 h
Matzkies et al. [40]	Iopromide	791	Haemophan Polyamide	108 ± 1.9 110 ± 1.4	62% at 3 h 58% at 3 h
Horiuchi et al. [41]	Iohexol	821	Cellulose		72.9% at 3 h
Matzkies et al. [42]	Iopromide	791	Cuprophan Polysulfone	87–121 147–162	57–63% at 2 h 60–68% at 2 h
Sterner et al. [43]	Iodixanol Iohexol	1,550 821	Low flux	58 ± 11 69 ± 16	
Schindler et al. [44]	Iopromide	791	Hemophan	82 ± 2.3	64% at 4 h
	Iomeprol	777	Polyamide	100 ± 2.2	74% at 4 h
Shinoda et al. [45]	Iomeprol Iopromide Ioxaglate	777 791 1,268	High flux		80.6 ± 6.3 at 4 h
Teraoka et al. [46]	Iopromide	791	Cuprammonium	57.6	

The mean reduction rate of iodine by HD increases with longer dialysis time reaching over 70% at 3 h in most studies [37–39, 41, 45]. The relationship between contrast media clearance and blood flow rate was addressed by only two investigators. Bailie et al. calculated the iodixanol clearance for cellulose and polysulfone membranes at blood flow rates of 300, 400, and 500 mL/min. These investigators found no correlation between iodixanol clearance and blood flow rate for either membrane [36]. Using an in vitro HD system, Teraoka et al. reported different results. 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 [42]. 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. Overall, most studies have reported that high-flux membranes were more efficient than low-flux membranes in the elimination of contrast media [36, 42, 44, 47]. 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 [40].

The post-dialysis rebound or redistribution of contrast media has been reported in only three studies [39, 42, 43]. One study found no significant rebound when measuring the iodine concentration 1 hour after treatment [42]. 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 [39]. Sterner et al. found similar results [43].

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 [48]. 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 [35]. 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 [49]. 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 [50]. 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 [51]. 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 [52]. 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 [53]. 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 [54]. 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 [55]. 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 [56]. 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 [57]. 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 [58, 59]. However, widespread ST-segment elevation, decrease in coronary flow velocity, and profound global left ventricular dysfunction was documented after administration of small doses of intracoronary carbon dioxide in swines [60].

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. [61]).

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. The GCCA 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 GCCA have a molecular weight ranging from 500 to 1,000 Da, are highly soluble in water, and have low binding to plasma proteins. Hence, after intravenous administration, GCCA 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 GCCA (0.26–0.28 L/kg body weight) [62].

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, GCCA 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 GCCA is negligible with less than 3% being excreted in the stool [62, 63].

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 [64] and only 36 adverse reactions in 21,000 patients in another study [65]. Only one mortality has been reported [65]. Two case reports described a spurious hypocalcemia after Gd administration [66, 67].

When compared to iodinated contrast media, GCCA 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% [68, 69]. The risk of nephrotoxicity has been reported to be much higher in patients with more advanced renal disease and after intra-arterial injection of GCCA [70–73]. The exact mechanism of nephrotoxicity of GCCA is not well known. However, GCCA 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 GCCA clearance is delayed in renal failure, these compounds are of low molecular weight, not protein bound, and have a small volume of distribution [74–76]. 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 [74]. 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 [75]. An average of 98.9% of the administered dose was removed after three HD treatments.

Ueda et al. evaluated the clearances of three different GCCA in an in vitro system using low-flux cellulose diacetate and higher-flux cellulose triacetate hemodializers [76]. The clearance of all three GCCA was significantly higher when using the cellulose triacetate dialyzer with larger pore size.

The clearance of GCCA 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 [77]. Hence, the clearance of GCCA 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 (Fig. 32.1) in patients with acute or chronic renal failure [79]. 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 [80]. As more patients were recognized, 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.

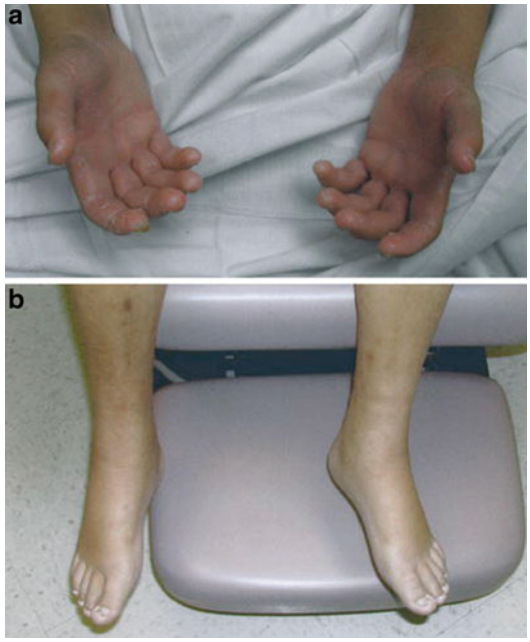

Fig. 32.1 (**a**) Indurated *yellow* plaques and sloughing on both palmar and dorsal surfaces of the hands with flexural contractures of the fingers. (**b**) Indurated plaques and non-pitting edema of the feet (Reproduced with permission from Jain et al. [78])

However, in 2005, multiple reports emerged of a strong association with prior Gd administration in patients who developed NSF disease 4–8 weeks later [81, 82]. Subsequently, Gd was detected in the skin lesions of some patients with NSF, increasing the likelihood that the association was causal [83, 84].

In renal failure, free Gd can potentially be liberated into tissue. Several GCCA are marketed (Table 32.3). 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, highly disproportionate to its estimated market share. The dose of GCCA administered may also play a role. GCCA were approved for use in MRI at a dose of 0.1 mmol/kg. However, in order to avoid the nephrotoxicity of iodinated HOCM, many radiologists started using high-dose GCCAS (0.3–0.9 mmol/kg) for magnetic resonance angiography [85]. Doses above 0.3 mmol/kg were never formally tested or approved by any regulatory agency in USA or Europe [86]. In the USA, the Food and Drug Administration (FDA) never approved any GCCA for use in children less than 2 years of age. In Europe, gadodiamide and gadopentate dimeglumine have been approved for children less than 2 years of age.

Of the several hundred NSF cases reported, only a few were seen in children (Table 32.4). No characteristics that were specific to children were noted. The youngest affected children were 8 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 GCCA use vary between the USA and Europe (Table 32.5). Both groups agree that GCCA risk of NSF is high when the GFR is known to be below 30 mL/min/1.73 m^2, but differ on the specifics of the recommendations, as shown in Table 32.5. The American College of Radiology recommends that a recent GFR assessment be reviewed prior to GCCA administration in high-risk patients, such as those with known prior renal disease, 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 [95]. 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 [96].

Table 32.3 Properties of gadolinium-containing contrast agents (GCCA) approved in Europe and perceived risk of NSF

Generic name	Trade name	Half-life (hours)	Kinetic stability	Structure	Charge	Perceived risk of NSF
Gadodiamide[a]	Omniscan	1.3	35 s	Linear	Nonionic	+++
Gadoversatamide[a]	OptiMARK	1.73	Not available	Linear	Nonionic	+
Gadopentate dimeglumine[a]	Magnevist	1.6	10 min	Linear	Ionic	+
Gadobenate dimeglumine[a]	MultiHance	1.2–2.0	Not available	Linear	Ionic	?
Gadoxetic acid	Primovist	Not available	Not available	Linear	Ionic	?
Gadofosveset trisodium	Vasovist	Not available	Not available	Linear	Ionic	?
Gadoteridol[a]	ProHance	1.57	3 h	Cyclic	Nonionic	?
Gadobutrol	Gadovist	Not available	24 h	Cyclic	Nonionic	?
Gadoterate meglumine	Dotarem	Not available	>1 month	Cyclic	Ionic	?

[a]Also approved in USA
+++ Highest risk, + Increased risk , ? unknown risk

Table 32.4 Pediatric cases of NSF

Publication, year	Number of cases	Patient age/sex/race	ESRD stage/ dialysis type	Gadolinium type	Outcome
Jain et al., 2003 [87]	2	8 Y/M/Caucasian 16 Y/F/Caucasian	PD HD	Not mentioned Not mentioned	Improvement Improvement
Jain et al., 2004 and Dharnidharka et al., 2006 [78, 88]	2	8 Y/M/Caucasian 19 Y/M/Caucasian	PD HD	Gadodiamide Gadodiamide	Died after 6 months Died after 1.5 years
Auron et al., 2006 [89]	2	13 Y/M/Caucasian[a] 20 Y/M/Not mentioned	PD CKD stage IV	Not mentioned Not mentioned	Partial resolution Still debilitated
DiCarlo et al., 2007 [90]	1	17 Y/M/Not mentioned	PD	Not mentioned	Near complete resolution
Krous et al., 2007 [91]	1	11 Y/M/Not available	Stage V	Not mentioned	Died
Sanchez-Ross et al., 2007 [92]	1	14 Y/F/Not mentioned	AKI	Not mentioned	Improved at 6 months
Sharma et al., 2008 [93]	1	14 Y/M/Hispanic	HD	Not mentioned	No responses to treatments; died 2 years later
Foss et al., 2009 [94]	1	9 Y/M/Not mentioned	CCPD, then HD	Gadodiamide	4 months: skin lesions same, mobility better

[a]Same patient as reported by Jain et al., 2003, reported again at age 13 to describe evolution of disease

Table 32.5 Current recommendations on use of GCCA

United States food and drug administration	European medicines agency
Considers all GCCA as increasing risk for NSF (class effect)	Separates out the GCCAs as below
No absolute contraindications for GCCA use; advises caution when GFR below 30 mL/min/1.73 m^2	Specifies that three GCCAs (gadodiamide, gadoverstamide, and gadopentate 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 GCCAs 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 GCCA, but prompt is not defined	Hemodialysis post-GCCA administration not specifically discussed

References

1. Almen T. Visipaque – a step forward. A historical review. Acta Radiol Suppl. 1995;399:2–18.
2. Katzberg RW. New and old contrast agents: physiology and nephrotoxicity. Urol Radiol. 1988;10:6–11.
3. McClennan BL. Ionic versus nonionic contrast media: safety, tolerance, and rationale for use. Urol Radiol. 1989;11:200–2.
4. Morris TW. X-ray contrast media: where are we now, and where are we going? Radiology. 1993;188: 11–6.
5. Almén T. Contrast agent design. Some aspects on the synthesis of water soluble contrast agents of low osmolality. J Theor Biol. 1969;24:216–26.
6. Dean PB, Kivisaari L, Kormano M. Contrast enhancement pharmacokinetics of six ionic and nonionic contrast media. Invest Radiol. 1983;18:368–74.
7. Eloy R, Corot C, Belleville J. Contrast media for angiography: physicochemical properties, pharmacokinetics and biocompatibility. Clin Mater. 1991;7: 89–197.
8. Rapoport SI, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood–brain barrier. Am J Physiol. 1972;223:323–31.
9. Rapoport SI, Levitan H. Neurotoxicity of X-ray contrast media. Relation to lipid solubility and blood–brain barrier permeability. Am J Roentgenol Radium Ther Nucl Med. 1974;122:186–93.
10. Blaufox MD, Sanderson DR, Tauxe WN, Wakim KG, Orvis AL, Owen Jr CA. Plasmatic diatrizoate-I-131 disappearance and glomerular filtration in the dog. Am J Physiol. 1963;204:536–40.
11. 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;35:513–24.
12. Mudge GH. The maximal urinary concentration of diatrizoate. Invest Radiol. 1980;15:S67–78.
13. 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. Invest Radiol. 1983;18:74–80.
14. 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. Invest Radiol. 1986; 21:64–70.
15. 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. Invest Radiol. 1990;25:46–51.
16. Nordby A, Tvedt KE, Halgunset J, Haugen OA. Intracellular penetration and accumulation of radiographic contrast media in the rat kidney. Scanning Microsc. 1990;4:651–64.
17. 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. Invest Radiol. 2001;36:309–16.
18. Katzberg RW. Contrast medium-induced nephrotoxicity: which pathway? Radiology. 2005;235:752–5.
19. Persson PB, Tepel M. Contrast medium-induced nephropathy: the pathophysiology. Kidney Int. 2006; 100(Suppl):S8–10.
20. 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;53:698–702.
21. 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;33:596–9.
22. Hardiek K, Katholi RE, Ramkumar V, Deitrick C. Proximal tubule cell response to radiographic contrast media. Am J Physiol Renal Physiol. 2001;280:F61–70.
23. Hizóh I, Sträter J, Schick CS, Kübler W, Haller C. Radiocontrast-induced DNA fragmentation of renal tubular cells in vitro: role of hypertonicity. Nephrol Dial Transplant. 1998;13:911–8.
24. 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;235:843–9.
25. Thomsen HS, Morcos SK. Radiographic contrast media. BJU Int. 2000;86:1–10.
26. Heydenreich G, Larsen PO. Iododerma after high dose urography in an oliguric patient. Br J Dermatol. 1977;97:567–9.
27. Goodfellow T, Holdstock GE, Brunton FJ, Bamforth J. Fatal acute vasculitis after high-dose urography with iohexol. Br J Radiol. 1986;59:620–1.
28. Je C. Iodide "mumps". N Engl J Med. 1961;264: 987–8.
29. Rivera M, Teruel JL, Castaño JC, Garcia Otero G, Ortuño J. Iodine-induced ialadenitis: report of 4 cases and review of the literature. Nephron. 1993;63:466–7.
30. 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: 969–71.
31. Hamani A, Petitclerc T, Jacobs C, Deray G. Is dialysis indicated immediately after administration of iodinated contrast agents in patients on haemodialysis? Nephrol Dial Transplant. 1998;13:1051–2.
32. Harasawa H, Yamazaki C, Masuko K. Side effects and pharmacokinetics of nonionic iodinated contrast medium in hemodialyzed patients. Nippon Igaku Hoshasen Gakkai Zasshi. 1990;50:1524–31.
33. 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.

34. 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;56:81–5.
35. Moon SS, Bäck 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;70:430–7.
36. Bailie GR, Eisele G, Sala J, Wu D. Determination of iodixanol hemodialysis clearance using a novel in vitro system. Clin Res Regul Aff. 1996;13:111–24.
37. Ueda J, Furukawa T, Takahashi S, Sakaguchi K. Elimination of ioversol by hemodialysis. Acta Radiol. 1996;37:826–9.
38. Ueda J, Furukawa T, Higashino K, Takahashi S, Araki Y, Sakaguchi K. Elimination of iomeprol by hemodialysis. Eur J Radiol. 1996;23:197–200.
39. Johnsson E, Attman PO, Samuelsson O, Haraldsson B. Improved clearance of iohexol with longer haemodialysis despite similar Kt/V for urea. Nephrol Dial Transplant. 1999;14:2407–12.
40. 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;40:220–3.
41. 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. Nippon Ika Daigaku Zasshi. 1999;66: 305–7.
42. 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;20:300–4.
43. Sterner G, Frennby B, Månsson S, Ohlsson A, Prütz KG, Almén T. Assessing residual renal function and efficiency of hemodialysis – an application for urographic contrast media. Nephron. 2000;85:324–33.
44. Schindler R, Stahl C, Venz S, Ludat K, Krause W, Frei U. Removal of contrast media by different extracorporeal treatments. Nephrol Dial Transplant. 2001;16: 1471–4.
45. Shinoda T, Hata T, Nakajima K, Yoshimoto H, Niwa A. Time-course of iodine elimination by hemodialysis in patients with renal failure after angiography. Ther Apher. 2002;6:437–42.
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 Transplant. 2005;20:754–9.
47. Rault RM. Hemodialysis for removal of iodinated contrast media. Int J Artif Organs. 2001;24:331–4.
48. Donnelly PK, Burwell N, McBurney A, Ward JW, Walls J, Watkin EM. Clearance of iopamidol, a nonionic contrast medium, by CAPD in patients with endstage renal failure. Br J Radiol. 1992;65:1108–13.
49. 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;19:380–5.
50. Lehnert T, Keller E, Gondolf K, Schäffner T, Pavenstädt H, Schollmeyer P. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant. 1998;13: 358–62.
51. Sterner G, Frennby B, Kurkus J, Nyman U. Does post-angiographic hemodialysis reduce the risk of contrast-medium nephropathy? Scand J Urol Nephrol. 2000;34:323–6.
52. Vogt B, Ferrari P, Schönholzer 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: 692–8.
53. 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;60:176–82.
54. 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;349:1333–40.
55. 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;119:155–62.
56. Hawkins Jr IF, 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: 149–54.
57. 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;16:269–74.
58. Shifrin EG, Plich MB, Verstandig AG, Gomori M. Cerebral angiography with gaseous carbon dioxide CO_2. J Cardiovasc Surg (Torino). 1990;31:603–6.
59. 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: 261–6.
60. Lambert CR, de Marchena EJ, Bikkina M, Arcement BK. Effects of intracoronary carbon dioxide on left ventricular function in swine. Clin Cardiol. 1996;19: 461–5.
61. Hawkins IF, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. Radiol Clin North Am. 2009;47:813–25.

62. 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: 4079–98.
63. 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. Invest Radiol. 1999;34:443–8.
64. 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: 1124–7.
65. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR Am J Roentgenol. 1996;167:847–9.
66. Prince MR, Erel HE, Lent RW, Blumenfeld J, Kent KC, Bush HL, Wang Y. Gadodiamide administration causes spurious hypocalcemia. Radiology. 2003;227: 639–46.
67. 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;128:1151–6.
68. 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:S179–82.
69. Arsenault TM, King BF, Marsh Jr JW, 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;71:1150–4.
70. Sam 2nd AD, 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;38:313–8.
71. 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 Transplant. 2004;19:2526–31.
72. Ergün I, Keven K, Uruç I, Ekmekçi Y, Canbakan B, Erden I, Karatan O. The safety of gadolinium in patients with stage 3 and 4 renal failure. Nephrol Dial Transplant. 2006;21:697–700.
73. 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 Transplant. 2008;23: 1233–40.
74. Rodby RA. Dialytic therapies to prevent NSF following gadolinium exposure in high-risk patients. Semin Dial. 2008;21:145–9.
75. Okada S, Katagiri K, Kumazaki T, Yokoyama H. Safety of gadolinium contrast agent in hemodialysis patients. Acta Radiol. 2001;42:339–41.
76. Saitoh T, Hayasaka K, Tanaka Y, Kuno T, Nagura Y. Dialyzability of gadodiamide in hemodialysis patients. Radiat Med. 2006;24:445–51.
77. 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;5:491–502.
78. Jain SM, Wesson S, Hassanein A, Canova E, Hoy M, Fennell RS, Dharnidharka VR. Nephrogenic fibrosing dermopathy in pediatric patients. Pediatr Nephrol. 2004;19:467–70.
79. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet. 2000;356: 1000–1.
80. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. Am J Dermatopathol. 2001;23:383–93.
81. Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant. 2006;11:1104–8.
82. 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;17:2359–62.
83. High WA, Ayers RA, Cowper SE. Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2007;56: 710–2.
84. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. J Am Acad Dermatol. 2007;56:27–30.
85. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? Semin Dial. 2008;21:129–34.
86. Penfield JG. Nephrogenic systemic fibrosis and the use of gadolinium-based contrast agents. Pediatr Nephrol. 2008;23:2121–9.
87. Jan F, Segal JM, Dyer J, LeBoit P, Siegfried E, Frieden IJ. Nephrogenic fibrosing dermopathy: two pediatric cases. J Pediatr. 2003;143:678–81.
88. Dharnidharka VR, Wesson SK, Fennell RS. Gadolinium and nephrogenic fibrosing dermopathy in pediatric patients. Pediatr Nephrol. 2007;22(9):1395.
89. Auron A, Shao L, Warady BA. Nephrogenic fibrosing dermopathy in children. Pediatr Nephrol. 2006;21: 1307–11.
90. DiCarlo JB, Gupta EA, Solomon AR. A pediatric case of nephrogenic fibrosing dermopathy: improvement after combination therapy. J Am Acad Dermatol. 2006;54:914–6.
91. Krous HF, Breisch E, Chadwick AE, Pinckney L, Malicki DM, Benador N. Nephrogenic systemic fibrosis with multiorgan involvement in a teenage male after lymphoma, Ewing's sarcoma, end-stage renal disease, and hemodialysis. Pediatr Dev Pathol. 2007; 10:395–402.

92. Sanchez-Ross M, Snyder R, Colome-Grimmer MI, Blumberg M, Huttenbach Y, Raimer S. Nephrogenic fibrosing dermopathy in a patient with systemic lupus erythematosus and acute lupus nephritis. Pediatr Dermatol. 2007;24:E36–9.
93. Sharma J, Mongia A, Schoenaman M, Chang S, D'Angelo A, Rao M. Nephrogenic fibrosing dermatopathy, cardiac calcification and pulmonary hypertension in an adolescent on chronic hemodialysis. Indian J Nephrol. 2008;18:70–3.
94. Foss C, Smith JK, Ortiz L, Hanevold C, Davis L. Gadolinium-associated nephrogenic systemic fibrosis in a 9-year-old boy. Pediatr Dermatol. 2009;26:579–82.
95. Karcaaltincaba M, Oguz B, Haliloglu M. Current status of contrast-induced nephropathy and nephrogenic systemic fibrosis in children. Pediatr Radiol. 2009;3:382–4.
96. Steen H, Schwenger V. Good MRI images: to Gad or not to Gad? Pediatr Nephrol. 2007;22:1239–42.

Part VII

Outcomes of Chronic Dialysis

Long-Term Outcome of Chronic Dialysis in Children

33

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Keywords
Chronic dialysis • Children • Long term outcomes • Pediatric dialysis

Introduction

As the prevalence of children on renal replacement therapy (RRT) increases worldwide and comprises at least 2% of any national dialysis or transplant programme, it is essential that paediatric nephrologists are able to advise families on the possible outcome for their child with end-stage renal disease (ESRD). Most children start dialysis with the expectation that a successful renal transplant is an achievable goal and will provide the best survival and quality of life. However, some will require long-term dialysis or may return intermittently to dialysis during the course of their chronic kidney disease (CKD) management. This chapter reviews the available outcome data for children on chronic dialysis along with data from the larger adult dialysis experience to inform our paediatric practise. The multiple factors that may influence outcome and particularly those which can potentially be modified are discussed.

Mortality in Children on Dialysis

Survival data for paediatric patients on chronic dialysis from both national registries and single centre studies provide us with essential information. In this chapter, data has been compiled from large national registries including the United States Renal Data System (USRDS), a compulsory registration system which includes children ≤19 years; the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which allows voluntary data reporting and includes children ≤21 years; the United Network for Organ Sharing (UNOS), which collects data on all patients registered for renal transplant in the USA; the European Renal Association – European Dialysis and Transplant Association (ERA – EDTA), a voluntary organisation which coordinates a national European registry for all patients; the Australia and New Zealand Dialysis and Transplant Association (ANZDATA), that is

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a comprehensive, compulsory database including children up to 20 years of age; and other national registries including the United Kingdom Renal Registry, the National Dutch Registry and the Italian Registry. Key points from these Registry reports are summarised below. Long-term outcome data from single centres are also included.

The USRDS in 2009 [1] reported an adjusted annual mortality rate for prevalent dialysis patients (age 0–19 years) in 2007 of 52.9/1,000 patient years at risk, compared to 61.3 in 2000 and 60.8 in 1990. In the 2008 NAPRTCS review, the survival of 2,867 patients aged 0–21 years on chronic dialysis without a history of previous transplantation and whose index dialysis course was the first for the patient was reported according to age at dialysis initiation [2]. At 36 months follow-up, patient survival was 65.4% if initiating dialysis at age <1 year and 69.1% at age 1–2 years. Three-year survival improved to 82.5% if dialysis began at age 2–5 years and 90.5% and 89% if at age 6–12 years and >12 years respectively (censored for transplantation or if lost to follow-up). Offering the longest longitudinal follow-up over four decades, ANZDATA has reported on the long-term survival of 1,634 children under 20 years of age when starting RRT between 1963 and 2002 and can therefore uniquely offer 20-year survival data. At 10 years survival was 79% and at 20 years, 66% [3].

Cardiopulmonary events and infection were cited as the most common causes of death by all registries, accounting for at 21% of deaths seen in all age groups by NAPRTCS, although with significantly more infections causing death in the youngest children [2]. The Dutch registry followed 381 children with (ESRD) including preemptively transplanted patients presenting between age 0–14 years between 1972 and 1992. Forty-one per cent of deaths were due to cardiovascular disease and 21% to infection [4]. In the 38 patients who died while on chronic dialysis, death was caused by cardiovascular disease in 45% and by infection, cessation of treatment and complications of treatment each in 13%. Similarly, ANZDATA reported that the most common cause of death on dialysis was cardiovascular disease (45%) with the second most common, infection (21%) [3]. Cardiovascular disease accounted for 57% of deaths in children on haemodialysis and 43% of those on peritoneal dialysis, compared to 30% in those with a functioning transplant, in whom malignancy was responsible for 14% of deaths [3].

Factors Influencing Outcome

Overall Mortality in Dialysis Patients Compared to Normal and Transplanted Children

Paediatric dialysis carries a significantly higher mortality than that for the age-adjusted population. In the Dutch registry cohort study in 2002 the mortality rate was 1.57/100 patient years on RRT. The standardised mortality rate1 for these children was 31, that is, the mortality rate for these children was more than 30 times higher than that seen in age- and gender-matched children [4]. Similarly, in the larger ANZDATA report, mortality rates among dialysed children were 30 times higher than for children without CKD [3]. Dialysis treatment was also associated with a mortality risk more than four times higher than for children who have been transplanted [3].

The UNOS report from 2002 listed a mortality rate of 21/1,000 patient years for paediatric dialysis patients and 2/1,000 patient years for transplanted paediatric patients [5]. A recent single centre report describing 25 years experience in the care of infants age <18 months when starting PD showed a significant survival advantage for the children who received a single functioning renal allograft. Those who had a failed transplant, whether they received a second transplant or remained on dialysis, had poorer survival compared to those treated with a single transplant or with dialysis alone [6].

The ERA-ERDTA registry has now reported 5-year survival data for 1,777 young adults who started RRT in childhood. The unadjusted 5-year survival from age 18 years was 95.1% (95% CI 93.9–96) with an average life expectancy of 63

years for young adults with a functioning graft and 38 years for those remaining on dialysis [7]. Comparable findings were reported by the USRDS in 2003 using prevalent ESRD mortality data. The prognosis for prevalent ESRD patients in the USA, age 20–24 years and 25–29 years who started RRT in their 20s was a remaining lifetime of 18.6 years and 16.4 years, respectively, if on dialysis and 40.3 and 35.6 years with a functioning graft [8].

Era of Dialysis

ANZDATA report a substantial improvement in the long-term survival of children and adolescents with CKD 5 with a mortality of 11/100 patient years between 1963 and 1972 and 1.8 per 100 patient years in those starting dialysis after 1993 [3]. The Dutch cohort reports a similar improvement in survival with survival rates of 81% and 79% at 5 and 10 years for children dialysed from 1972 to 1981 compared to 89% and 85%, respectively, in the 1982–1991 cohort which includes those with a functioning graft [4]. The continued improvement in survival with time may be underestimated, as younger children and those with significant non-renal comorbidity are taken onto dialysis programmes. This may explain the findings of the 2009 USRDS report [1] which shows no change in the 5-year survival of incident dialysis patients over the last decade reporting a 5-year survival of 68.7% in 1990 and 70.8% in 2002. For some cohorts, that is children age 10–14 years on haemodialysis, the probability of survival decreased between 1993–1997 and 1998–2002. The same lack of improvement in mortality has been recently reported for infants starting dialysis age <18 months from 1983–1995 to 1996–2008 in a single centre with an overall mortality of 54% during 25-years observation [6]. The authors also suggest that the statistics may be skewed by including smaller infants and more with comorbidities in recent years. However, Carey et al. reported that neonates who started dialysis between 1999 and 2005 compared to 1992 and 1998 had more favourable survival after 3 years and transitioned more rapidly to transplant [9].

Age at Start of Dialysis

All registries report a significantly higher mortality in infants starting dialysis. ANZDATA clearly identified younger age at the start as a risk factor with 5-year survival if under 1 year at the start of RRT of 73% compared to 86% for the whole population, and a fourfold increased risk of death compared to children age 15–19 years [3]. NAPRTCS report the poorest survival in children age less than a year at the start of dialysis with survival rates of 81.9%, 73.2% and 65.4% at 1, 2 and 3 years [2]. Further analysis of the NAPRTCS database from 1992 to 2005 has shown that survival among infants who initiated dialysis in the early neonatal period (age <1 month) was comparable to that of infants initiating dialysis in later infancy (age 1 month to 2 years): 24% of 193 infants <1 month and 20% of 505 infants >1 month–2 years died during the study period [9]. A single centre follow-up study from Minnesota of 23 infants dialysed in the neonatal period emphasises the significant morbidity and mortality in the first year of life with an overall 1 and 5 year survival of 52 and 48% [10]. A larger study of 52 infants aged <18 months when starting dialysis also reported the highest mortality within the first year of life (20/28 deaths: 71%) [6]. However, if the first year is discounted, the 5-year survival of the remaining 32 infants was 87%.

It must be kept in mind that treatment thresholds vary amongst different centres, making uniform comparisons of survival data difficult and reflecting the varying opinions amongst nephrologists towards offering RRT to the very young or those with comorbidity [11]. In the NAPRTCS report those age <5 years made up 25.5% of the overall cohort of paediatric dialysis patients; [2] only 9.3% of the paediatric cohort in the ANZDATA Registry were <5 years [3]. In a single centre study of 98 children on chronic dialysis since 1984, 21 were <1 year of age and 54 <5 years at initiation of dialysis. The overall patient survival was 83% at 20 years but the mortality rate was 2.7 times greater in children who required RRT under the age of 5 years [12] (see Fig. 33.1). The age at starting RRT does not seem to affect outcome if children survive to

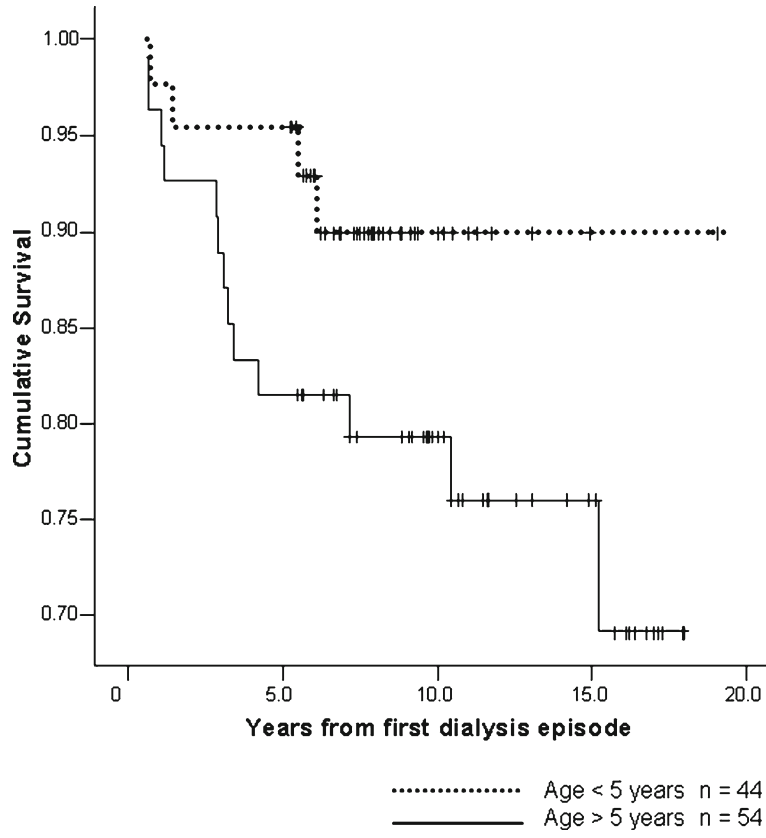

Fig. 33.1 Long-term survival in children on chronic dialysis according to age at initiation of dialysis

young adulthood [7]. Paediatric dialysis carries a significantly lower mortality compared to older age groups on dialysis. The 2009 USRDS data report an adjusted annual mortality rate for prevalent paediatric dialysis patients age 0–19 of 52.9/1,000 patient years at risk compared to 90/1,000 in young adults age 20–44. The mortality continues to increase with age to 156.2/1,000 in the 45–64 year olds and 253.1/1,000 in those aged 65–74 years [1].

Duration of Dialysis

In adults, the effect of length of time on dialysis (vintage) on mortality risk is complex and influenced by comorbidities and treatment factors. When adjusted for these factors, increasing vintage in all age groups is associated with increased mortality rate. The USRDS 2009 report shows 245.1 deaths/1,000 patient years at risk for patients of all ages on dialysis for >5 years, which is 20.6% more than the rate of 203.3/1,000 for patients on dialysis for <5 years. However, increased mortality with time on dialysis has declined since 2000 [1]. In contrast, the UK renal registry in 2008 reported for patients age >18 years that the risk of death does not differ significantly with increasing length of time on dialysis for most age groups, even with the follow-up period now increased to 10 years. An exception is those age >65 years after 7 years on dialysis [13]. This lack of a 'vintage' effect is partly related to the effect of having a survivor cohort who is healthier than those patients dying earlier after starting RRT. Dialysis vintage is considerably shorter in children compared to adults, with more children moving more quickly to transplantation. This makes detection of a vintage effect on survival more difficult in children. However, cardiovascular morbidity in children has been clearly associated with the length of time on dialysis [14].

Modality of Dialysis

The Italian registry reported on the survival of 458 children age less than 15 years who started chronic dialysis (295 CPD/163HD) with no preceding RRT between 1989 and 2000 [15]. Children age less than 5 years were almost exclusively managed on CPD and had a poorer 5-year survival than children age 5–15 on either CPD or HD, in whom survival was not significantly different. This confirms the findings of Wong et al. in 2002 who, using USRDS data, found no survival difference between dialysis modalities in paediatric patients [16]. The USRDS 5-year survival data of dialysis patients aged 0–9 years also shows no survival benefit for either modality [1]. Survival data for modality must be carefully interpreted as although some patients will elect HD as their primary choice of dialysis, it is often only offered when complications of PD occur and thus children on HD may be older, have greater comorbidity and a longer dialysis vintage than those on PD, making comparisons between the groups difficult.

Comorbidity

In recent years, patients with non-renal comorbidity such as multisystem involvement from inherited disorders, prematurity or CKD following overwhelming infection with multi-organ damage are increasingly offered RRT. Both renal (i.e. oligoanuria) and non-renal comorbidities (e.g. pulmonary hypoplasia, severe developmental delay) have been identified as significant risk factors for increased mortality in infants and young children [15, 17]. Smaller studies emphasise the increased mortality associated with comorbidity in children on both HD and PD [18–20]. The anuric infant is particularly difficult to manage, and anuria has been discussed as an important risk factor for survival [17]. Long-term dialysis outcome data from Great Ormond Street Hospital for Children showed that 30 children of a cohort of 98 on chronic dialysis had significant non-renal comorbidity including neurodevelopmental delay, syndromes with multisystem involvement, congenital cardiac disease, malignancy and inherited metabolic disorders. Of the 17 deaths reported, 76% were in those with associated comorbidities, a 7.5-fold greater risk of death in this group [12]. In a long-term follow-up study from Miami of 52 infants on dialysis, oligoanuria gave an odds ratio for death 41 times greater than that of infants with residual renal function. Major comorbidities (e.g. pulmonary hypoplasia or central nervous system disease) were also associated with an increased odds ratio for mortality of 4.4 [6]. Low birth weight (LBW) was not a significant risk factor in this group, although LBW has been identified by others as an independent risk factor for death in infants age <6 months with severe CKD (GFR < 20 mL/min/1.73 m^2) or requiring dialysis in first 2 years of life [21]. The effect of comorbidity on survival extends into adulthood as childhood survivors of dialysis with comorbidity have a significantly higher risk of death compared to those with only primary renal disease [7].

Primary Renal Disease

The 2006 USRDS report cites primary diagnosis as an independent determinant of mortality for paediatric patients on dialysis with glomerulonephritis and hereditary or congenital disease having a better 5-year survival than those with secondary glomerulonephritis or vasculitis. Autosomal recessive polycystic kidney disease has an odds ratio of 20 for mortality compared with other diagnoses in infants, but this may be due to the oliguria and pulmonary hypoplasia associated with this diagnosis [6]. Proteinuria secondary to focal segmental glomerulosclerosis requiring bilateral nephrectomies for effective management will increase mortality risk as children are rendered anuric. The poor transplant outcome associated with abnormal bladder function may be improved by prior augmentation cystoplasty, but there is as yet no data on the possible effects this may have on the potential for long-term PD in these children [22].

Demographics

Two studies have suggested but are not conclusive that African–American infants have a higher mortality rate. In a 2003 NAPRTCS study, African–American infants age 2–12 months at initiation of dialysis were three times more likely to die compared to Caucasian and Hispanic infants, although this significant difference was not observed if age at dialysis initiation was >2 years [23]. In a single centre long-term follow-up infant dialysis study, decreased survival of infants of African–American ethnicity compared to the predominantly Hispanic patients was also reported but was not felt to be due to the home or socioeconomic environment as the deaths occurred mainly in hospital with all patients receiving identical care [6].

As the age at initiation of dialysis and the presence of both renal and non-renal comorbidity are unavoidable risk factors, it is essential that those caring for children on dialysis are aware of the potentially modifiable factors that might improve long-term survival and the quality of life for their patients. Although a successful transplant is the goal for all paediatric ESRF patients with confirmed survival benefits, episodes of dialysis or long-term dialysis may be necessary. It is therefore essential to preserve dialysis access, maintain peritoneal membrane function, deliver adequate dialysis, prevent metabolic complications, and ensure adequate nutrition and growth. Cardiovascular risk factors and infectious complications must be minimised, and every support must be offered to ensure continuity of education for the best long-term outcome.

Treatment Factors and Interventions That May Influence Both Survival and Other Outcome Measures

Dialysis Access (see Also Chaps. 10 and 16)

The initial placement and subsequent conservation of either vascular or peritoneal access is critical for the young patient with CKD 5 in whom RRT is a lifelong undertaking. A NAPRTCS study in 2003 of 1992 incident dialysis in children showed that 70% were started on PD and the remaining 30% on HD with 96% of those <2 years starting on PD [23]. The NAPRTCS 2006 report shows that although HD is being increasingly used as the primary dialysis modality, approximately 64% of children continued to start dialysis on PD [24]. In the NAPRTCS 2003 study, although 68% terminated dialysis as they were transplanted, 20% changed dialysis modality over the 6-year study period. The majority of changes from HD to PD occurred within the first few months; in contrast the change from PD to HD occurred more slowly and was mainly attributable to recurrent infections [23]. There was a high rate of PD catheter revision (45%) mainly due to catheter malfunction. The access in use after 6 months in children on HD was almost exclusively tunnelled catheters in those age less than 6 years, while 57% of those older than 6 years of age were dialysed using an AV fistula or graft. HD access revision rates were very high with 919 revisions among the 584 initial placements, 31% of which were for creation of more permanent access. Both the National Kidney Foundation- Dialysis Outcomes Quality Initiative (NKF-DOQI) and the UK Renal Association now have paediatric clinical practise guidelines and offer recommendations for optimal dialysis access and its preservation [25, 26].

Vascular Access

Clinical practice guidelines clearly recommend that permanent access as either a native AV fistula or graft is preferred for most children on maintenance HD. If central venous catheters are used (i.e. in small or uncooperative children, where HD is initiated before a planned live related transplant or in patients in whom early transplantation is anticipated), catheter size should be matched to patient size to minimize vessel trauma but allow sufficient flow for adequate HD. External cuffed access should be placed in the internal jugular vein with the tip in the right atrium rather than the subclavian veins where the risk of stenosis is high. The right side is preferred as there is decreased risk of thrombosis and is usually contralateral to the non-dominant arm which

may eventually be needed for fistula formation. If possible all children with CKD stage 3–5 should avoid the use of the non-dominant arm for venepuncture and lines [25, 27]. An adult study has shown that HD with any type of venous catheter compared to a graft or fistula increases the risk of both all-cause and infection-related mortality [28]. Even in small paediatric patients, the use of fistulae or grafts is associated with equivalent access survival rates to adults and better survival than cuffed venous catheters [29]. In a 20-year retrospective review of 304 paediatric vascular access procedures, the median survival of arteriovenous fistulae is 3.1 years compared to 0.6 years for central venous access [30].

Peritoneal Dialysis Access and Preservation of Membrane Function

It has become clear that a meticulous approach to PD catheter insertion by a dedicated team is perhaps more critical than the specific type of catheter or implantation technique used [25, 31]. However, the 2006 NAPRTCS data showed that the time to the first episode of peritonitis is longer in children with two cuff catheters, swan-neck tunnels and for downward pointing exit sites [24]. Peritoneal membrane function is an independent predictor of patient survival with those with high transporter status and therefore decreased ultrafiltration capacity, demonstrating worse outcomes [32]. In a meta-analysis, Brimble showed an increased mortality risk of 21.9%, 45.7% and 77.3% in low-average, high-average and high transporters, respectively, compared to patients with low transporter status [33]. As alterations in peritoneal membrane transport appear to be related to peritonitis episodes rather than the duration of dialysis, every effort must be directed to reducing peritonitis rates including intensive training, flush before fill dialysis delivery systems, antibiotic prophylaxis for catheter insertion and prevention and early treatment of exit site infections [34]. Although there is no long-term data, the use of biocompatible PD solutions, that is normal pH, bicarbonate–lactate buffer and low glucose concentrations, particularly in children who are anticipated to have a long wait on PD may be advantageous. The use of icodextrin to increase fluid removal appears to be associated with less functional deterioration of the peritoneal membrane as the use of high glucose solutions is avoided [35] Encapsulating peritoneal sclerosis is the most serious complication of long-term PD, and there should be heightened awareness of the possibility of developing this potentially fatal complication in any child on PD for more than 5 years [36].

Dialysis Adequacy

Haemodialysis (see Also Chap. 18)

Although the optimal haemodialysis dose has not been defined in children, the Renal Association and NKF K/DOQI guidelines agree that children should receive at least the delivered dialysis dose as recommended for adults, that is either a urea reduction ratio (URR) >65% or an equilibrated Kt/V urea >1.2 delivered thrice weekly [25, 26]. The HEMO trial in adults showed no difference in survival between patients with a mean eKt/V of 1.16 and those achieving a Kt/V of 1.53 [37]. These findings are similar to a study in 613 adolescent HD patients in which hospitalisation risk was increased with a single pool Kt/V <1.2 compared to 1.2–1.4 but a spKt/V of >1.4 did not further improve outcome [38]. However, in a smaller study of 12 children receiving a carefully controlled dietary intake with a mean Kt/V of 2 and mean URR = 84.7%, catch up growth was demonstrated [39]. Increasing the frequency of HD sessions has been shown to significantly improve appetite and increase growth velocity in a small paediatric study, and may lead to a re-evaluation of dialysis adequacy in children [40]. Certainly in adults, short daily or nocturnal home or in-centre dialysis has been shown to improve well-being and cardiovascular outcome [41, 42]. By adding convective clearance to conventional haemodialysis, haemodiafiltration has been shown to be a superior dialysis modality in two large adult studies with significantly improved clearance of beta-2 microglobulin and 35% better survival [43, 44]. These findings may translate in the future to improved outcomes for children on dialysis.

Peritoneal Dialysis (see Also Chap. 11)

Current clinical opinion supports the recommendation that total solute clearance in paediatric patients receiving maintenance PD should meet or exceed the adult guidelines of a combined urinary and peritoneal Kt/V urea/week of 1.7–1.8 or a creatinine clearance of 50 L/week/1.73 m^2 BSA [25, 26]. In anuric adult patients, a minimum peritoneal Kt/V urea of 1.7 and an optimal target of 1.8 has been suggested by Lo et al. based on survival data [45]. A previous interventional study by the same group clearly demonstrated increased clinical problems including severe anaemia in patients with a total Kt/V urea of <1.7. No difference in survival was seen between patients with a Kt/V urea maintained above 2 and those between 1.7 and 2.0 when the difference in Kt/V urea was accounted for by increasing peritoneal clearance only [46]. The ADEMEX trial measured both peritoneal creatinine clearance and urea clearance as determinants of small-solute clearance and after adjusting for factors known to influence survival found no difference in 2-year survival between the control group and an intervention group with significantly greater clearances [47]. However, the Dutch NECOSAD study clearly identified an increase in the relative risk of death in anuric PD patients if Kt/V urea was <1.5/week and creatinine clearance <40 L/week/1.73 m^2 BSA [48].

While there are no comparable mortality data in children, the Network 1 Clinical Indicators Project reporting on clinical morbidity in paediatric dialysis patients found that in a small group of well-dialysed patients on either HD or PD, exceeding recommended adequacy guidelines did not influence morbidity [49]. Indeed, in children on PD a Kt/V urea of >2.75 was associated with increased peritoneal albumin losses which may have an adverse effect on nutrition and growth [50]. A similar finding has been reported from the 'Australian and New Zealand Dialysis and Transplant registry' of adults on PD with patient mortality significantly increased with a peritoneal Kt/V urea <1.45/week or 1.45–1.69/week, compared to the reference group with a Kt/V urea = 1.7–2.0. Higher Kt/V urea values (>2.0) also tended to be associated with increased mortality [51].

Residual Renal Function

Although the above studies have attempted to describe an optimal dialysis dose with reference to dialysis adequacy, it is clear from adult studies that residual renal function contributes significantly to patient survival [52]. The CANUSA trial [53] was important in defining adequacy of small-solute clearance, but re-evaluation of the data revealed that residual renal clearance was a more important factor for survival than peritoneal clearance and ultrafiltration [54]. This has been confirmed in adult HD and PD patients in the NECOSAD studies [48], and it is recommended that the dialysis prescription takes into account residual renal clearances. A smaller study in children suggests a correlation between renal solute clearance and growth, rather than peritoneal Kt/V urea [55]. Adult studies have shown that episodes of volume depletion, either unintentional or therapeutic, are associated with increased risk of loss of residual renal function [48, 56]. However, furosemide has been used successfully to achieve diuresis and improved fluid balance, without influencing residual renal function [57]. The use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB's) in adult PD patients suggests a positive effect on preserving residual renal function [58, 59]. In a 2008 study of over 300 prevalent adult PD patients, the use of ACEi or ARB's was associated with a 62% reduced risk of death independent of blood pressure control or other clinical or demographic variables [60]. Results of the ESCAPE trial evaluating the renoprotective effect of intensified blood pressure control using ramipril in children with CKD has shown that maintaining blood pressure at <50th percentile slows progression of renal disease and improves outcome. These findings may be relevant to preserving native renal function in paediatric dialysis patients [61]. A recent study in 134 adult

patients with CKD stage 4 has demonstrated that bicarbonate supplementation slows the rate of progression of renal failure and improves nutritional status, findings clearly applicable to children on dialysis [62].

Influence of Nutrition on Survival and Linear Growth

The prevention of malnutrition and associated hypoalbuminaemia is critical to improving long-term outcome and achieving optimal growth in paediatric dialysis patients. In a recent teaching article for Paediatric Nephrology, Rees and Shaw have discussed at length the importance of nutrition and growth in CKD patients [63]. Wong et al. found a significant association between hypoalbuminaemia and mortality in 1,723 patients age <18 years at initiation of dialysis with each −1 g/dL difference in serum albumin associated with a 54% higher risk of death after adjustment for glomerular causes and other known risk factors [16]. In a 2008 study of 675 adolescents on haemodialysis, those with an albumin >4.0 g/dL had fewer deaths per 100 patient years and fewer hospitalizations per time at risk with a 57% reduced risk of death on multivariate analysis [64]. Poor nutritional intake occurs early in CRF with deterioration in anthropometric indices as renal function deteriorates [65]. A low height SDS score at the start of dialysis is associated with an increased risk of death as shown by both Wong and Furth with a 14% increased risk of death with each decrease of 1 SD score for height [66] and a height SDS of <2.5 associated with a twofold higher risk of death [67]. Thus, early nutritional intervention is important for both long-term survival and linear growth.

Although the 2006 NAPRTCS registry data shows a decrease in height SDS on dialysis from −1.64 (SE 0.03) to −1.71 (0.04) at 1 year and −1.84 (0.05) at 2 years [24], we have demonstrated that an early and more intensive approach to feeding maintains or even improves height SDS [12, 18, 68]. In our experience, 89% of children presenting before age<2 years with CKD 4–5 who were subsequently dialysed, required enteral feeding. Their mean height SDS improved from −2.18 (SD 1.44) at 6 months to −1.74 (1.55) at 1 year and −1.51 (1.38) at 2 years and improved steadily to −0.87 (1.51) at 5 years [12, 18, 68]. None of these children were treated with recombinant human growth hormone (rhGH). In a further long-term analysis of the growth of survivors among 101 infants with severe CKD, those without comorbidity achieved a mean adult height within the normal range [21] (see Fig. 33.2a and b). The use of rhGH remains controversial and while some studies have shown that a combination of dialysis under adequacy control [69], careful attention to nutrition [21] and maintaining the PTH within the normal range [70] can promote normal growth, others support the use of rhGH in selected cases [71]. In the 2009, 25-year infant dialysis follow-up study, Hijazi et al. showed better growth in infants age <18 months starting dialysis between 1996 and 2008 compared to those starting between 1983 and 1995 (−1.4 ± 0.9 SDS vs. −3.0 ± 1.5). This is tentatively attributed to the increased use of growth hormone at an earlier age and better control of renal bone disease, but all were tube fed with more using gastrostomies in the latter era [6].

Psychosocial and Neurodevelopmental Outcome (see Also Chap. 29)

Young adult patients with childhood onset CKD 5, particularly those who have had a longer period of time on dialysis, are more likely to have cognitive and learning impairment than an age-matched population [72]. Bawden et al. have performed neuropsychological assessments in sibling pairs and shown that although the children with CKD 5 had mild deficits of IQ and fine motor coordination, encouragingly there were no differences in measures of academic achievement, memory, behaviour or self-esteem [73]. In the long-term study of infants age <18 months at the start of dialysis, 58% of the survivors (18/31) attended regular school, but 13 (42%) had significant neuropsychological impairment of which 9 (25% of

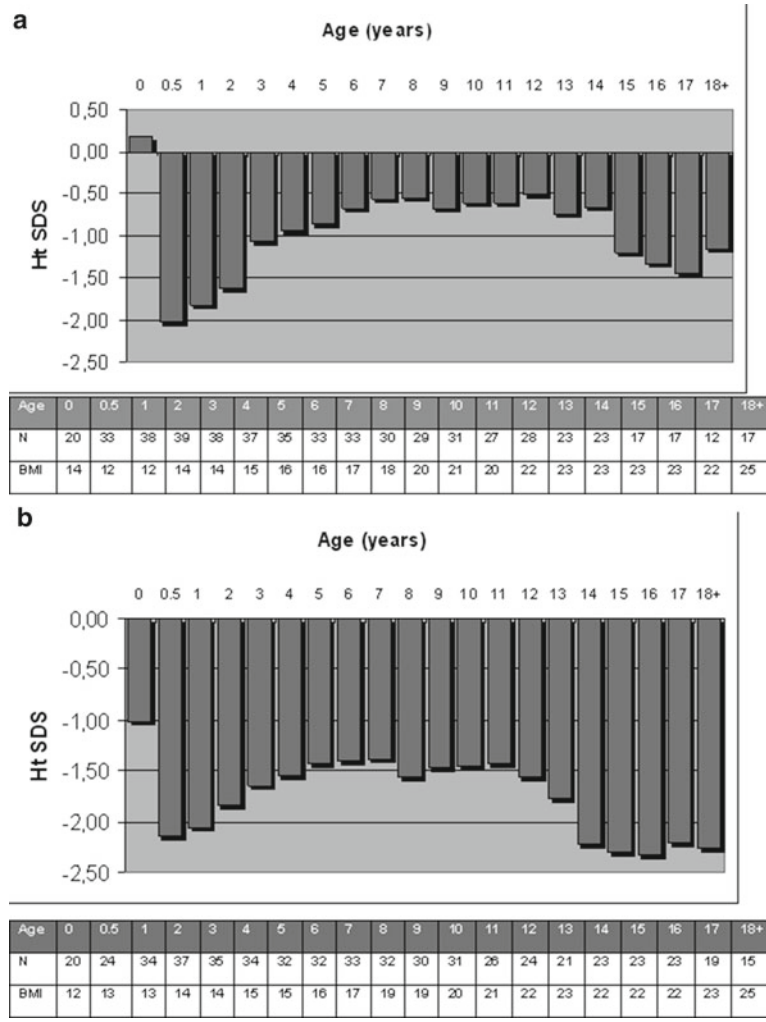

Fig. 33.2 Height SD score and body mass index in children with severe chronic kidney disease without (**a**) and with comorbidities (**b**) presenting age <6 months with GFR <20 mL/min/1.73 m^2 or requiring renal replacement therapy age <2 years

all survivors) required special education and 4 (13%) were severely impaired requiring residential care. There was no significant change in these outcomes in infants starting dialysis between 1983 and 1995 compared to 1996 and 2008. Hypotension on PD was a particularly severe complication resulting in blindness or partial sightedness in four patients and hemiparesis and facial palsy in one [6]. These complications due to ischaemic injury during CCPD have been previously reported and emphasise the continuous vigilance required to care for these infants [12, 18]. More recent studies using health-related quality of life (HRQOL) indices have shown that children with CKD have lower scores than healthy controls, but surprisingly, children on dialysis have higher scores than would be expected compared to transplant patients [74, 75]. In support of this, Groothoff et al. have shown that although survivors of prolonged dialysis during childhood are twice as likely to be unemployed than an age-matched population, taking into account the unavoidable physical problems, the overall subjective health perception of these young adults is surprisingly good [76]. It is interesting that parents of children who have been transplanted report a significantly better HRQOL compared to parents of children on dialysis, but the HRQOL of the transplanted patients themselves was comparable to those on dialysis except for the family

and peer interaction scale where the transplanted children scored higher [77]. It is clear that addressing the emotional, educational and social needs of children on dialysis and their carers by the provision of psychosocial and teaching support plays a crucial role in improving well-being and survival outcome, and must form an integral part of patient care.

Cardiovascular Risk Factors and Outcome (see Also Chaps. 21 and 26)

With improvements in RRT, cardiovascular disease is increasingly recognised as a life-limiting problem in young patients with CKD, with a 1,000-fold higher risk of cardiovascular death than in the healthy age-adjusted population [78]. Analysing the USRDS database, Parekh et al. reported that 311 of the 1,380 (22.5%) deaths in patients aged 0–30 years dialysed between 1990 and 1996 were from a cardiac cause [79]. Similarly, ANZDATA [3], the Dutch cohort [4] and both German [14] and Polish [80] single centre studies report cardiovascular disease as the single most common cause of death in their CKD patients. Chavers et al. presented the largest paediatric study on cardiovascular morbidity in children on dialysis from the Medicare database [81]. In 1,454 incident paediatric dialysis patients aged 0–19 years dialysed from 1991 to 1996, 452 (~31%) developed a cardiac-related event including arrhythmias (19.6%), valvular disease (11.7%), cardiomyopathy (9.6%) and death from cardiac arrest (3%). Unlike adults with CKD in whom coronary artery disease is the leading cause of death, cardiac arrest is the most commonly reported cause of death in children [79].

Both 'traditional' Framingham risk factors for cardiovascular disease as well as factors specific to the uraemic milieu contribute to the increased cardiovascular risk seen in children with CKD. However, traditional risk factors such as diabetes and dyslipidaemia cannot account for the greatly increased prevalence of cardiovascular disease in children with CKD [82] which presents a host of metabolic, mechanical and inflammatory damage-inducing agents such as mineral imbalance associated with secondary hyperparathyroidism [83, 84], inflammatory mediators [85, 86], oxidative stress [87, 88], hyperhomocysteinaemia [89, 90], hypoalbuminaemia [91], dyslipidaemia [92], anaemia [93] and chronic fluid overload [94, 95]. These factors acting individually or in concert result in endothelial dysfunction [89, 90, 96], arterial stiffness [97, 98] and calcification [99] which contribute to cardiac remodelling with left ventricular (LV) hypertrophy. Chronic volume overload is the most important factor contributing to uncontrolled hypertension in the dialysis population, with significantly higher BP in HD than PD patients reported in all series [79, 94, 100–102]. Hypertension remains the most important cardiovascular risk factor for young dialysis patients as underlined in a 2009 report of hypertension in 624 long-term HD patients aged 0–18 years. Hypertension was present in 79% of the patients with 62% on antihypertensive medication; of those treated, 74% still had uncontrolled hypertension [103]. In children and adults, the pulse pressure (= systolic – diastolic BP), which reflects the arterial wall compliance, has also been shown to be a significant risk factor for cardiovascular mortality [84, 104, 105].

Anaemia is a frequent finding in patients with CKD and following transplantation. Data from the UK renal registry (9th report) support this observation in the paediatric dialysis population with 47% of children on dialysis reported to have a Hb < 11 g/dL [106]. An observational study of 677 adolescent HD patients using data from the ESRD Clinical Performances Measures project clearly shows an association of a Hb of 11–12 g/dL vs. <10 g/dL decreasing mortality risk by 69% [107].

Long-standing exposure to the above risk factors leading to abnormal LV remodelling and left ventricular hypertrophy (LVH) has been reported in 30–80% of paediatric dialysis patients with a higher incidence in HD than PD patients [93]. Two distinct patterns of LV remodelling are seen in CKD patients – concentric LVH resulting from pressure overload as seen with hypertension and eccentric LVH that is related to volume overload, sodium retention and anaemia [95]. LVH leads to a decreased coronary reserve and arrhythmias [108],

which in turn are responsible for a disturbing 1,000-fold increase in cardiovascular mortality in CKD stage 5 patients [78].

Calcification of the arterial media or Monckeberg's sclerosis develops early in the course of CKD [109]. Studies in children with stage 2–4 CKD and on dialysis have shown that endothelial dysfunction [96], increased carotid artery intima media thickness [80, 84, 110] (a measure of structural changes in the vessel wall), increased pulse wave velocity [84, 105, 111] (a measure of stiffness or loss of compliance of the vessel) and presence of coronary and valvular calcification on CT scan [84, 111, 112] are present as early as the first decade of life. Secondary hyperparathyroidism, with an associated increase in calcium and phosphate levels [83] and renal bone disease [113] as well as its treatment with calcium-based phosphate binder [80, 114] and vitamin D [80, 84, 111] have also been implicated as major cardiovascular risk factors.

Adult studies have shown that approximately 65% of CKD patients have evidence of vascular calcification before starting dialysis, using calcium-based phosphate binders or receiving vitamin D therapy [115]. Vascular calcification is accelerated on dialysis [14, 80, 84, 110–112, 114]. Worsening hyperparathyroidism and renal bone disease [82, 113], the presence of 'damage-inducing' inflammatory mediators, oxidative stress and advanced glycation end-products [85, 86]coupled with a loss of the naturally occurring inhibitors of calcification (such as Fetuin-A) [116] all play a role in accelerating vascular calcification. Thus, time on dialysis is a strong independent predictor of vascular damage and calcification.

Summary

In summary, dialysis in children, and in particular infants and patients with comorbidity, carries an increased risk of mortality. Meticulous care directed towards reduction of modifiable risk factors is therefore of critical importance in children who have a lifetime of RRT ahead of them.

References

1. US Renal Data System. The Concise 2009 Annual Data Report: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, Bathesda, MD; 2009.
2. North American Pediatric Renal Trials and Collaborative Studies. NAPRTCS Annual Report: renal transplantation, dialysis, chronic renal insufficiency, 2008.
3. McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
4. 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(2):621–9.
5. UNOS. 2002 Annual report of the US scientific registry of transplant recipients and the organ procurement and transplantation network; transplant data 1992–2001: United Network for organ sharing, Rockville, MD; 2007.
6. 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.
7. Kramer A, Stel VS, Tizard J, et al. Characteristics and survival of young adults who started renal replacement therapy during childhood. Nephrol Dial Transplant. 2009;24(3):926–33.
8. ERA-EDTA Registry. ERA-EDTA Registry 2005 annual report. Amsterdam, the Netherlands: Academic Medical Center; 2005.
9. 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.
10. Rheault MN, Rajpal J, Chavers B, Nevins TE. Outcomes of infants <28 days old treated with peritoneal dialysis for end-stage renal disease. Pediatr Nephrol. 2009;24(10):2035–9.
11. Geary DF. Attitudes of pediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133(1):154–6.
12. 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.
13. Ansell D, Feehaly J, Fogarty D, Tomson C, Wiliams A, Warwick G. UK Renal Registry Report. Bristol, UK, 2008.
14. 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(1):100–5.

15. 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(1):82–90.
16. 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(2):630–7.
17. Wood EG, Hand M, Briscoe DM, et al. Risk factors for mortality in infants and young children on dialysis. Am J Kidney Dis. 2001;37(3):573–9.
18. 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.
19. Ellis EN, Pearson D, Champion B, Wood EG. Outcome of infants on chronic peritoneal dialysis. Adv Perit Dial. 1995;11:266–9.
20. 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.
21. 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.
22. Taghizadeh AK, Desai D, Ledermann SE, et al. Renal transplantation or bladder augmentation first? A comparison of complications and outcomes in children. BJU Int. 2007;100(6):1365–70.
23. Leonard MB, Donaldson LA, Ho M, Geary DF. A prospective cohort study of incident maintenance dialysis in children: an NAPRTC study. Kidney Int. 2003;63(2):744–55.
24. North American Pediatric Renal Trials and Collaborative Studies. NAPRTCS Annual Report: renal transplantation, dialysis, chronic renal insufficiency, 2006.
25. Renal Association. Treatment of adults and children with renal failure: standards and audit measures, 2002.
26. NKF-DOQI. NKF-DOQI: Clinical practice guidelines and clinical practice recommendations for pediatrics 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access, 2006.
27. Fischbach M, Edefonti A, Schroder C, Watson A. Hemodialysis in children: general practical guidelines. Pediatr Nephrol. 2005;20(8):1054–66.
28. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. Kidney Int. 2002;62(2):620–6.
29. 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(5): 1864–9.
30. 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(4):708–14.
31. White CT, Gowrishankar M, Feber J, Yiu V. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol. 2006;21(8):1059–66.
32. Rumpsfeld M, McDonald SP, Johnson DW. Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. J Am Soc Nephrol. 2006;17(1):271–8.
33. Brimble KS, Walker M, Margetts PJ, Kundhal KK, Rabbat CG. Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. J Am Soc Nephrol. 2006;17(9):2591–8.
34. Andreoli SP, Leiser J, Warady BA, Schlichting L, Brewer ED, Watkins SL. Adverse effect of peritonitis on peritoneal membrane function in children on dialysis. Pediatr Nephrol. 1999;13(1):1–6.
35. Davies SJ, Brown EA, Frandsen NE, et al. Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. Kidney Int. 2005;67(4):1609–15.
36. Honda M, Warady BA. Long-term peritoneal dialysis and encapsulating peritoneal sclerosis in children. Pediatr Nephrol. 2010;25(1):75–81.
37. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347(25):2010–9.
38. Gorman G, Furth S, Hwang W, et al. Clinical outcomes and dialysis adequacy in adolescent hemodialysis patients. Am J Kidney Dis. 2006;47(2):285–93.
39. Tom A, McCauley L, Bell L, et al. Growth during maintenance hemodialysis: impact of enhanced nutrition and clearance. J Pediatr. 1999;134(4):464–71.
40. Fischbach M, Terzic J, Menouer S, et al. Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol. 2006;21(11): 1746–52.
41. Pauly RP, Gill JS, Rose CL, et al. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. Nephrol Dial Transplant. 2009;24(9):2915–9.
42. Chan CT. Cardiovascular effects of home intensive hemodialysis. Adv Chronic Kidney Dis. 2009;16(3): 173–8.
43. Canaud B, Bragg-Gresham JL, Marshall MR, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int. 2006;69(11):2087–93.
44. Jirka T, Cesare S, Di Benedetto A, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int. 2006;70(8):1524. author reply 1524–1525.
45. Lo WK, Lui SL, Chan TM, et al. Minimal and optimal peritoneal Kt/V targets: results of an anuric peritoneal dialysis patient's survival analysis. Kidney Int. 2005;67(5):2032–8.
46. Lo WK, Ho YW, Li CS, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int. 2003; 64(2):649–56.

47. Paniagua R, Amato D, Vonesh E, 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.
48. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 2005;68(3):1199–205.
49. Brem AS, Lambert C, Hill C, Kitsen J, Shemin DG. Clinical morbidity in pediatric dialysis patients: data from the network 1 clinical indicators project. Pediatr Nephrol. 2001;16(11):854–7.
50. Brem AS, Lambert C, Hill C, Kitsen J, Shemin DG. Outcome data on pediatric dialysis patients from the end-stage renal disease clinical indicators project. Am J Kidney Dis. 2000;36(2):310–7.
51. Rumpsfeld M, McDonald SP, Johnson DW. Peritoneal small solute clearance is nonlinearly related to patient survival in the Australian and New Zealand peritoneal dialysis patient populations. Perit Dial Int. 2009;29(6):637–46.
52. Perl J, Bargman JM. The importance of residual kidney function for patients on dialysis: a critical review. Am J Kidney Dis. 2009;53(6):1068–81.
53. 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.
54. 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.
55. 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.
56. Konings CJ, Kooman JP, Gladziwa U, van der Sande FM, Leunissen KM. A decline in residual glomerular filtration during the use of icodextrin may be due to underhydration. Kidney Int. 2005;67(3):1190–1.
57. 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.
58. Li PK, Chow KM, Wong TY, Leung CB, Szeto CC. 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.
59. 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.
60. Fang W, Oreopoulos DG, Bargman JM. Use of ACE inhibitors or angiotensin receptor blockers and survival in patients on peritoneal dialysis. Nephrol Dial Transplant. 2008;23(11):3704–10.
61. The Escape Trial Group. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361(17%U http://content.nejm.org/cgi/content/abstract/361/17/1639%8 October 22, 2009):1639–50.
62. 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.
63. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702.
64. Amaral S, Hwang W, Fivush B, Neu A, Frankenfield D, Furth S. Serum albumin level and risk for mortality and hospitalization in adolescents on hemodialysis. Clin J Am Soc Nephrol. 2008;3(3):759–67.
65. 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.
66. Wong CS, Gipson DS, Gillen DL, et al. Anthropometric measures and risk of death in children with end-stage renal disease. Am J Kidney Dis. 2000;36(4):811–9.
67. 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.
68. 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.
69. Holtta T, Ronnholm K, Jalanko H, Holmberg C. Clinical outcome of pediatric patients on peritoneal dialysis under adequacy control. Pediatr Nephrol. 2000;14(10–11):889–97.
70. 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.
71. Seikaly MG, Salhab N, Warady BA, Stablein D. Use of rhGH in children with chronic kidney disease: lessons from NAPRTCS. Pediatr Nephrol. 2007;22(8):1195–204.
72. 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(5):380–5.
73. Bawden HN, Acott P, Carter J, et al. Neuropsychological functioning in end-stage renal disease. Arch Dis Child. 2004;89(7):644–7.
74. 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.
75. 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(7): 1899–905.

76. Groothoff JW, Grootenhuis MA, Offringa M, Stronks K, Hutten GJ, Heymans HS. Social consequences in adult life of end-stage renal disease in childhood. J Pediatr. 2005;146(4):512–7.
77. Goldstein SL, Rosburg NM, Warady BA, 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.
78. 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.
79. 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.
80. 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(5):1494–500.
81. Chavers BM, Li S, Collins AJ, Herzog CA. Cardiovascular disease in pediatric chronic dialysis patients. Kidney Int. 2002;62(2):648–53.
82. Goldsmith D, Ritz E, Covic A. Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? Kidney Int. 2004;66(4):1315–33.
83. 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.
84. Shroff RC, Donald AE, Hiorns MP, et al. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol. 2007;18(11):2996–3003.
85. Shanahan CM. Vascular calcification – a matter of damage limitation? Nephrol Dial Transplant. 2006;21(5):1166–9.
86. Shroff RC, Shanahan CM. The vascular biology of calcification. Semin Dial. 2007;20(2):103–9.
87. 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.
88. Nikolov I, Joki N, Drueke T, Massy Z. Beyond phosphate – role of uraemic toxins in cardiovascular calcification. Nephrol Dial Transplant. 2006;21(12):3354–7.
89. Bennett-Richards K, Kattenhorn M, Donald A, 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.
90. Bennett-Richards KJ, Kattenhorn M, Donald AE, et al. Oral L-arginine does not improve endothelial dysfunction in children with chronic renal failure. Kidney Int. 2002;62(4):1372–8.
91. Sarafidis PA, Bakris GL. Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. Nephrol Dial Transplant. 2006;21(9):2366–74.
92. Querfeld U, Salusky IB, Nelson P, Foley J, Fine RN. Hyperlipidemia in pediatric patients undergoing peritoneal dialysis. Pediatr Nephrol. 1988;2(4):447–52.
93. Mitsnefes MM. Cardiovascular morbidity and mortality in children with chronic kidney disease in North America: lessons from the USRDS and NAPRTCS databases. Perit Dial Int. 2005;25(Suppl 3):S120–2.
94. Mitsnefes MM. Hypertension in children and adolescents. Pediatr Clin North Am. 2006;53(3):493–512. viii.
95. Wilson AC, Mitsnefes MM. Cardiovascular disease in CKD in children: update on risk factors, risk assessment, and management. Am J Kidney Dis. 2009;54(2):345–60.
96. Kari JA, Donald AE, Vallance DT, et al. Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int. 1997;52(2):468–72.
97. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999;99(18):2434–9.
98. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18(9):1731–40.
99. Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. Am J Kidney Dis. 2004;43(3):572–9.
100. Lerner GR, Warady BA, Sullivan EK, Alexander SR. Chronic dialysis in children and adolescents. The 1996 annual report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 1999;13(5):404–17.
101. Leypoldt JK, Cheung AK, Delmez JA, et al. Relationship between volume status and blood pressure during chronic hemodialysis. Kidney Int. 2002;61(1):266–75.
102. Lingens N, Soergel M, Loirat C, Busch C, Lemmer B, Scharer K. Ambulatory blood pressure monitoring in paediatric patients treated by regular haemodialysis and peritoneal dialysis. Pediatr Nephrol. 1995;9(2):167–72.
103. Chavers BM, Solid CA, Daniels FX, et al. Hypertension in pediatric long-term hemodialysis patients in the United States. Clin J Am Soc Nephrol. 2009;4(8):1363–9.
104. Klassen PS, Lowrie EG, Reddan DN, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA. 2002;287(12):1548–55.
105. Covic A, Mardare N, Gusbeth-Tatomir P, et al. Increased arterial stiffness in children on haemodialysis. Nephrol Dial Transplant. 2006;21(3):729–35.
106. Verrier-Jones K, Reid C, Evans J, Webb N, Gilbert R, Lewis M. Aspects of anaemia management in

children with established renal failure. London: Royal College of Physicians and the Renal Association; 2006.
107. 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.
108. Paoletti E, Specchia C, Di Maio G, et al. The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. Nephrol Dial Transplant. 2004;19(7):1829–34.
109. Qunibi WY. Cardiovascular calcification in nondialyzed patients with chronic kidney disease. Semin Dial. 2007;20(2):134–8.
110. Mitsnefes MM, Kimball TR, Kartal J, 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.
111. Groothoff JW, Gruppen MP, Offringa M, et al. Increased arterial stiffness in young adults with end-stage renal disease since childhood. J Am Soc Nephrol. 2002;13(12):2953–61.
112. Civilibal M, Caliskan S, Adaletli I, et al. Coronary artery calcifications in children with end-stage renal disease. Pediatr Nephrol. 2006;21(10):1426–33.
113. Sanchez CP, Goodman WG, Ramirez JA, et al. Calcium-regulated parathyroid hormone secretion in adynamic renal osteodystrophy. Kidney Int. 1995;48(3):838–43.
114. 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(20):1478–83.
115. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005;68(4):1815–24.
116. Ketteler M, Bongartz P, Westenfeld R, et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet. 2003;361(9360):827–33.

Health-Related Quality of Life in Children on Dialysis

34

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Keywords
Health-related quality of life • Dialysis • Child • Adolescent

Introduction

Kidney dialysis remains a life-sustaining treatment for youth who have kidney failure. Optimum renal replacement therapy (RRT) results require strict adherence to dialysis prescription, to diet requirements/restrictions, and close follow-up with medical providers. While clinical markers of dialysis patient's health status (e.g., growth, infection rates, hospitalization, and survival) are necessary indicators of health outcomes, health care providers have become increasingly interested in patient and family perception of quality of life (QOL) as an adjunctive measure of treatment efficacy.

Many QOL experts point to the World Health Organization's 1958 definition of health as being an early catalyst for the expansion of the focus on mortality and morbidity to broader considerations of quality of life [1–3]. In the 6 decades since WHO distinctively defined health "as a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity" [4], data has been accumulated about the importance of patient perception of illness and health. Nevertheless, there still is not a unanimous acceptance in healthcare environments of the utility of systematic assessment of patient and family perception of quality of life. Unfortunately, in the case of youth with chronic kidney disease (CKD), even when there is acceptance of the multidimensional nature of health and illness and the value of assessing quality of life, limited health care resources prohibit widespread routine assessment.

In this chapter, we will describe the constructs of quality of life and health-related quality of life, review quality of life instruments that have been validated for use in pediatric dialysis populations, and summarize published literature on the impact of dialysis on the quality of life in children with kidney disease. Our aim is twofold. First, we hope to provide a foundation for clinicians and researchers to appreciate the utility and importance of health-related quality of life (HRQOL) assessment. Secondly, we hope to provide an up-to-date resource for choosing evaluation tools for use in research.

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Definition and Utility of Quality of Life and Health-Related Quality of Life

In a general sense, quality of life refers to one's sense of well-being and functional outcome within various domains of life. Over the past decade, the recognition that chronic health problems impact QOL and that both illness severity and treatment interventions may alter psychological, social, physical, and educational outcomes have lead to development of the construct of health-related quality of life (HRQOL) [5, 6]. Health-related quality of life refers to one's sense of well-being and functional outcome within various domains of life assuming that a disease and its treatment have impacted aspects of psychological, social, physical, educational, and/or vocational functioning. Measurement of health-related quality of life has been described as an attempt to quantify, in scientifically analyzable terms, the net consequence of a disease and its treatment on the patient's perception of his/her ability to live a useful and fulfilling life [7]. In a practical sense therefore, the measurement of QOL in children with medical problems results in an assessment of their HRQOL. The term HRQOL will be used throughout the remainder of this chapter to refer to the assessment of QOL of children with kidney disease.

By definition, HRQOL is something that must include assessment through direct inquiry. However, until recently, direct assessment of children's perceptions of their HRQOL has been hindered by the belief that children could not accurately report on their own well-being. This belief in turn, stalled the development of reliable pediatric assessment tools. Fortunately, in the past decade, several instruments that allow for the direct evaluation of children's HRQOL have been developed. These tools demonstrate that children do indeed have the ability to accurately report on their psychological, social, physical, and educational status [8, 9]. Discrepancies between caregiver and child perceptions within domains of HRQOL have lead to the recognition that differences in parent–child perceptions of well-being are as worthy of more in-depth assessment as are agreements of problem areas [6, 10, 11].

HRQOL is a multifaceted/multidimensional phenomenon and generally includes the following domains and components: (1) physical status and physical functioning, (2) psychological status and emotional functioning, (3) social interactions and social functioning, and (4) educational/vocational status and functioning. A growing number of HRQOL researchers also endorse the assessment of religious and/or spiritual status given the growing body of research that links spirituality to self-perceptions of well-being [2, 12, 13].

Health-related quality of life data has many potential uses. For example, it can be used to evaluate the impact of individual treatments or programs on individual patients or groups of patients. This type of application is sometimes referred to as a cost/utility analysis [14–16]. In addition, HRQOL data can be used to inform health policy [16–18]. Perhaps the most ambitious use of HRQOL data occurs when it is used to predict the future functional outcomes of people with an illness or condition [19, 20].

A conceptual definition of HRQOL is illustrated schematically in Fig. 34.1. The illustration highlights the interdependent nature of the domains, the importance of multidimensional assessment in understanding the full range of manifestations of health and illness, and the influences of variables that have been shown to mediate HRQOL.

Assessment of HRQOL in Patients with End-Stage Renal Disease

The charge by Medicare to assess the cost–utility of the various dialysis treatments provided for in the Medicare End-Stage Renal Disease program has led to the inclusion of an assessment of HRQOL in dialysis patients of age 18 years and older [21, 22]. This mandate appears to have been strongly influenced by the National Kidney Foundation's Clinical Practice Guidelines and Clinical Practice Recommendations for Hemodialysis (HD) and PERITONEAL DIALYSIS (PD) Adequacy originally published in 1997 and revised in 2006 [22].

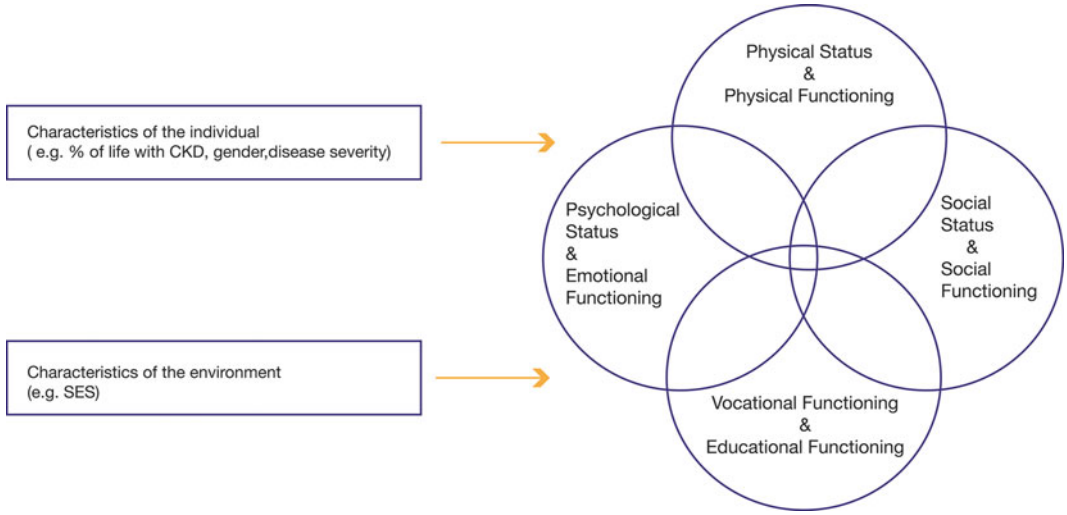

Fig. 34.1 Schematic definition of domains of health-related quality of life

Given improvements in dialysis treatment and decreased mortality, the 1997 NKF-DOQI guidelines recommended an expansion of the assessment of clinical outcomes to include both generic and disease- /treatment-specific measures of HRQOL [23]. Unfortunately, in 1997, none of the available survey instruments had been established as having the necessary reliability and validity in the ESRD population; so the DOQI work group advised that each dialysis facility serially evaluate HRQOL in patients over the age of 18 years using the tool of their choice. The workgroup further recommended that outcomes research using promising instruments be completed in order to establish a standardized HRQOL assessment that could be integrated into the routine care and evaluation of patients with ESRD [23].

The 1997 DOQI guidelines did not provide any recommendations for the assessment of HRQOL in children who were receiving dialysis. Similar to the situation for adults with ESRD, no instruments with sufficient psychometric authority were available to assess the HRQOL of youth with ESRD in 1997. Fortunately, the recognition of the value of assessing HRQOL in youth with chronic medical conditions has been a catalyst over the past decade for the development of reliable and valid tools to monitor the impact of disease and its treatment in children with CKD [24, 25].

Over the past 10 years, a number of HRQOL instruments have been validated for use in adults and children with ESRD and evidence has mounted regarding the association between HRQOL and both morbidity and mortality. The 2006 KDOQI update acknowledged the accumulation of valuable information regarding HRQOL outcomes and recommends that increased resources be allocated to incorporate the assessment of HRQOL into ongoing quality improvement efforts [26]. Moreover, the 2006 KDOQI Clinical Practice Update added a pediatric clinical practice guideline that echoed the adult recommendation for monitoring HRQOL as an important health outcome and referenced two instruments that have been validated for use in children on dialysis. Notwithstanding the 2006 KDOQI recommendation regarding the importance of evaluating HRQOL in pediatric ESRD patients, CMS did require its assessment in children in the 2008 Clinical Performance Measures Project, as it did in dialysis patients over the age of 18 years [22].

Quality of Life Studies in Children on Dialysis

Much of the early research assessing HRQOL in children on dialysis did not include validated multidimensional measures, but rather

used qualitative methods such as telephone interviews, investigator-designed questionnaires, and instruments that measure a single domain of HRQOL [25].

For example, in 1991, Roscoe et al. used a structured telephone interview to evaluate HRQOL. This study reported on the functional outcomes (defined by educational level, ability to care for oneself, employment, marital status, achievement of parenthood, and opinion of the caregiver on general adjustment) in 118 adolescents who were 11–19 years old when therapy for ESRD was initiated between 1966 and 1986 [27]. With a mean age of 22 years and a mean follow-up of 8 years, the authors found that almost 70% of patients were living with family members, and only 28.9% were living on their own or with a spouse. Thirteen percent of patients were neither enrolled in an educational program nor were employed. Furthermore, in over 73% of transplant recipients, functional outcome was defined subjectively by the caregiver as good or excellent. However, caregivers described good or excellent functional outcomes in only 45% of patients on dialysis. When the type of dialysis was considered, 25% of hemodialysis patients had good or excellent functional outcomes, compared to 75% of peritoneal dialysis patients.

The European Dialysis and Transplant Association registry reported similar results regarding HRQOL and functional health status assessment of individuals with a history of dialysis during childhood [28]. Of 617 patients who started RRT as children and were 21–35 years of age in 1986, 56% had completed secondary school and 16% were in a school for the handicapped. Also, 56% were employed but most (61%) lived with their parents. In comparison to the "healthy" population of the same age, employment was somewhat lower, and one third or more had some disability. Further information on the employment status of dialysis patients was presented in the single-center experience of 150 children transplanted between 1970 and 1993, as reported by Offner et al. [29]. Notably, 29% of patients on dialysis after graft failure were unemployed compared to 9% with functioning grafts.

Rosenkranz et al.'s large multicenter study (n = 479) published in 1992 comprising five pediatric nephrology centers in Germany reported similarly disappointing outcomes with regard to educational attainment and age-appropriate independence of adults with childhood onset kidney disease [30]. In 2005, Rosenkranz et al. used a HRQOL questionnaire validated for use in Germany to determine if their center's efforts over the previous two decades to improve HRQOL and functional outcomes of their patients had been successful. The study authors concluded that while some improvements could be attributed to their center's efforts, patients were still at a disadvantage compared to the general population with regard to educational attainment and vocational attainment [30].

In 1994, Morton et al. reported on the functional and psychological health of patients with onset of renal disease in childhood (mean age of renal disease onset was 8 years, range 0–16) and who had received RRT for an average duration of 10 years in the United Kingdom. Functional status and responses on several psychiatric inventories were compared in this group of 45 young adult survivors of ESRD (mean age at time of study was 24.8 years) to those of healthy age-matched controls of comparable socioeconomic status [31]. More of the renal patients were unemployed (31%) than were the healthy subjects (12%). Living with parents, lack of experience of close relationships, lack of educational qualifications, and unemployment were more common in the renal groups [31]. Interestingly, although the renal group described more psychological problems when they were less than 17 years old, they did not have evidence of significantly higher rates of psychiatric disorders in adulthood; they also had lower rates of use of drugs and alcohol compared to the age-matched controls [31].

The first published study to evaluate the health status of pediatric dialysis patients using a multidimensional, standardized, HRQOL questionnaire was published in 1994 by Kurtin et al. In this pilot study, a modified version of the parent-completed questionnaire, developed and validated in the Children's Health and Quality of Life Project,

was used with 20 English-reading adolescents maintained on chronic HEMODIALYSIS at the Children's Hospital of Los Angeles between April and June of 1992 [32]. The authors tested the discriminant validity of the items in the questionnaire and the association between health and family scale scores and compliance. Less-compliant adolescents consistently reported more pain and poorer general and mental health than more compliant adolescents, as well as lower family involvement. Data presented in Kurtin's report supported the use of a standardized questionnaire to evaluate HRQOL in children on dialysis [32].

In 1999, the first US multicenter longitudinal study of quality of life in children and adolescents with CKD was initiated by Furth et al. The study sought to expand on Kurtin's pilot research and validate two multidimensional generic quality of life measures (Child Health Questionnaire-Parent Form, CHQ-PF50, Child Health and Illness Profile-Adolescent Edition, CHIP-AE) for use in youth with various stages of kidney disease severity.

One of the published reports from this study demonstrated an association between anemia, defined by level of hematocrit, and HRQOL in pediatric patients with CKD [33]. The report was a cross-sectional analysis and included CHQ-PF50 surveys completed by parents of 113 CKD patients (mean age 14.4 ± 1.9 years) requiring dialysis (D), with a functioning kidney transplant (TX) or with advanced stage 2 or stage 3–5 CRI (chronic renal insufficiency) as defined by the NKF KDOQI. Seventy-five patients were found to be anemic as defined by a hematocrit ≤36%. In the domains of physical discomfort, limitations of activity, and overall satisfaction with health, patients with a lower hematocrit scored significantly lower than CKD patients with a hematocrit >36% [33].

Further cross-sectional analysis of data from Furth's study, this time looking at adolescent self-perceptions of HRQOL, revealed that the CHIP-AE distinguished between adolescents with kidney disease and healthy adolescents in a number of domains [34]. Using a case control design, analysis of study patients with kidney disease (mean age = 14; 39 CRI, 21 D and 53 TX) compared with two control groups of age: socioeconomic and sex-matched peers without kidney disease, and youth with CKD had lower overall satisfaction with health and more restriction in activity. Moreover, study patients receiving dialysis were less physically active and experienced more physical discomfort and limitations in activities than did study patients who had received a kidney transplant or study patients whose kidney disease had not advanced to ESRD [34].

A 4-year longitudinal analysis of the Furth et al. data using serially completed parent CHQ questionnaires of 78 youth with CKD found that height gain was associated with parent perceptions of improved physical and psychosocial functioning of their children and GFR decline was associated with parent perceptions of worse physical functioning [35].

The first studies to simultaneously evaluate both parent and youth perceptions of HRQOL were published in 2006 by Goldstein et al. and McKenna et al. using the Pediatric Quality of Life Inventory (PedsQL). Goldstein and his research team used a matched control design to evaluate 85 pediatric patients and 96 parents of children with ESRD receiving HD, PD, or TX to a matched group of healthy children [36]. The HRQOL of children with ESRD within the domains of physical, emotional, social, and school functioning were significantly lower compared to the healthy controls. Furthermore, the data suggested that dialysis patients had worse physical health than transplant patients [36]. McKenna et al.'s study population consisted of 64 pediatric patients with CKD (20 CRI, 17 D, 27 TX) [37]. Self-report HRQOL data of study participants and caregiver proxy HRQOL data was compared to published norms. Youth receiving dialysis had lower physical and school functioning scores in comparison to their healthy peers but similar emotional and social functioning scores [37]. In contrast, parent proxy HRQOL scores of youth receiving dialysis were lower than the normative group in all PedsQL domains [37].

Pediatric HRQOL Measures

As interest in assessing HRQOL has increased in the past decade, many research groups have become involved in efforts to develop tools to

evaluate this construct objectively and systematically. Two types of HRQOL measures have been developed: generic and condition-specific instruments. Generic instruments provide summary ratings of functioning within multiple life domains and allow for comparison of HRQOL across different patient groups. Condition-specific measures of HRQOL assess challenges associated with a particular illness and allow for a more specific assessment of the impact of a particular disease and its treatment on QOL. A number of excellent review articles are available that discuss the relative merits of generic and condition-specific HRQOL instruments [1, 38–42]. Table 34.1 lists a selection of generic HRQOL instruments that have been validated for use with pediatric dialysis patients. Also included in Table 34.1 is a description of a condition-specific instrument that has specifically been developed for children who have ESRD.

Below is a brief description of the purpose and content of the HRQOL survey tools listed in the aforementioned table. The reliability and validity evidence that exists to support clinical and research application of each tool is also presented. The development of clinically useful measurement tools is an iterative process. Clinicians and researchers must work together to determine how best to integrate the assessment of HRQOL into clinical practice and how best to use the information obtained to improve functional outcomes of children with ESRD.

Child Health and Illness Profile-Adolescent Edition

The Child Health and Illness Profile-Adolescent Edition (CHIP-AE) is a 153-item self-report instrument that assesses 6 domains of health status (discomfort, satisfaction, disorders, achievements, resilience, and risks) and takes about 20 min to complete [43, 44]. Reliability (test-retest and internal) and validity (criterion and construct) studies support its use as a generic health status assessment for youth aged 11–17 years [45]. In addition to the CHIP's usefulness in discriminating between healthy and ill adolescents [46], it has also been sensitive to age, gender, and socioeconomic influences [47, 48]. Use of the CHIP-AE was evaluated in a multicenter cross-sectional study in adolescents with CRI, on dialysis and post-transplant [34].

The Children's Health Questionnaire

The Children's Health Questionnaire (CHQ) is a generic HRQOL instrument that has both parent and child versions [49]. The child version is appropriate for administration to children aged 10–18 years and takes about 20 min to complete. The proxy version is appropriate for children aged 5–18 years. The CHQ measures 12 domains of health status (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 school work and other daily activities, self-esteem, mental health, behavior, family cohesion, and change in health). Internal consistency and concurrent validity have been demonstrated [49]. One advantage of this instrument is that the availability of both parent and youth forms allows for direct and simultaneous comparison of health status perceptions for parents and children. The child-completed CHQ has previously been used in a single-center study with children who have kidney disease and who were maintained on HD [32]. Use of the CHQ-PF50, a parent proxy of HRQOL, has also been evaluated in a multicenter cross-sectional study of health status in adolescents with CRI, on dialysis and post-transplant [33] as well as in a longitudinal study of adolescents with CKD [35].

The Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) is a 23-item generic HRQOL instrument that assesses 5 domains of health (Physical Functioning, Emotional Functioning, Psychosocial Functioning, Social Functioning, and School Functioning) in children and adolescents aged 2–25 years [50]. Internal reliability as well as construct and clinical validity have been demonstrated [51–53]. Parent and youth forms are available.

Table 34.1 Domains of multidimensional pediatric HRQOL measurement instruments

	CHQ-PF 50	CHQ-CF 87	CHIP-AE	PEDS-QL	PEDS-QL ESRD
Number of domains	13	13	6	4	7
Title of domains	Physical functioning, emotional/behavioral role functioning, physical role functioning, bodily pain, general behavior, mental health, self-esteem, general health perceptions, parental impact (emotional), parental impact (time), family activities, family cohesion	Physical functioning, emotional/behavioral role functioning, physical role functioning, bodily pain, general behavior, mental health, self-esteem, general health perceptions, parental impact (emotional), parental impact (time), family activities, family cohesion	Discomfort, disorders, satisfaction with health, achievement, risks, resilience	Physical functioning, emotional functioning, social functioning, school functioning	General fatigue, side effects of kidney disease, treatment problems, family and peer interactions, worry, perceived physical appearance, communication
Age range	5–18	10–18	11–17	2–25	5–25
Rating scale	4–6 point Likert scale	4–6 point Likert scale	3–5 point Likert scale	3–5 point Likert scale	3–5 point Likert scale
Number of items	50	87	107	23	34
Average completion time	20	20	30	10	10
Respondent	Proxy	Patient	Patient	Proxy or patient	Patient

CHQ-PF50 Child Health Questionnaire Parent Version
CHQ-CF87 Child Health Questionnaire Youth Version
CHIP-AE Child Health and Illness Profile-Adolescent Edition
PEDS-QL Pediatric Quality of Life Inventory, Core Scales
PEDS-QL ESRD Pediatric Quality of Life Inventory, End-Stage Renal Disease Module

The inventory takes approximately 5 min to complete. One of the most significant advantages of this instrument is its short length that allows for quick completion by patients and caregivers. Use of the PedsQL has been evaluated in a single-center study and multicenter study of QOL in children with CRI, on dialysis and post-transplant [36, 37]. The PedsQL has also been evaluated in a large multicenter study of children with mild to moderate CKD [54].

PedsQL ESRD Module

The 34-item PedsQL 3.0 ESRD Module developed by Goldstein et al. includes seven scales: (1) general fatigue, (2) side effects of kidney disease, (3) treatment problems, (4) family and peer interactions, (5) worry, (6) perceived physical appearance, and (7) communication. Parallel forms are available for parents of children between the ages of 2 and 18 years and for youth between the ages of 5 and 18 years. The format, instructions, Likert response scale and scoring method are similar to the PedsQL 4.0 Generic Core Scales with higher scores reflecting better HRQOL (fewer symptoms or problems) [55, 56]

Measuring HRQOL in Outpatient Nephrology Clinics

A variety of influences have increased interest in the potential utility of assessing health-related quality of life in pediatric nephrology clinical practices including: (1) pediatric research studies demonstrating the relationship between kidney disease severity and quality of life [33–35, 37, 55, 56], (2) the recent American Academy of Pediatrics recommendation that psychosocial assessments be performed at every well-child visit [57], (3) the belief that assessment of HRQOL could facilitate communication, uncovering patient problems and monitoring response to treatment [3], and (4) the recent CMS mandate to monitor HRQOL in adult patients with ESRD [22].

In spite of the fact that several HRQOL measures have received initial validation for use with pediatric patients with CKD, a number of questions about their use in clinical practice remain unanswered. For example, little research has been done to directly establish clinically meaningful cutoff scores in children with pre end-stage and end-stage kidney disease and to demonstrate test-retest reliability or responsiveness to change [20, 58, 59]. Given the status of current research in this field, there is little evidence base on which to recommend at what intervals these instruments should be administered in the outpatient setting, or what interventions can be made to improve HRQOL if scores are low. To this end, several multicenter research studies are currently underway which will begin to provide the necessary data for allowing the integration of HRQOL assessment into clinical practice [60].

Summary

Recent emphasis on patient-centered assessment of quality of life has been the result of an understanding that patients and their families can best assess the global effects that chronic disease and its medical management have on health. In this chapter, we have reviewed existing generic health status measures for children and adolescents, and summarized current studies evaluating their use in pediatric dialysis patients. Clinically, these tools can be used to assess patient health status over time in response to therapy. In research, these instruments can be used to measure the effectiveness of different medical practices on the health outcomes of children and adolescents with kidney disease. Future research encompassing measures of quality of life in pediatric dialysis is needed to assist health professionals in making more informed clinical decisions, using patient-centered assessments in conjunction with traditional medical and clinical endpoints to judge the “success” of therapy.

References

1. Pal DK. Quality of life assessment in children: a review of conceptual and methodological issues in multidimensional health status measures. J Epidemiol Community Health. 1996;50:391–6.
2. Spilker B, Revicki DA. Taxonomy of quality of life. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 25–32.
3. Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr. 2001;22:248–56.
4. World Health Organization. Constitution of the world health organization basic document. Geneva, Switzerland: World Health Organization; 1948.
5. Patrick DL, Erikson P. Health status and health care evaluation and resource allocation. New York: Oxford University; 1993.
6. Erling A. Methodological consideration in the assessment of health-related quality of life in children. Acta Paediatr Suppl. 1999;428:106–7.
7. Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: definitions and conceptual issues. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 11–23.
8. 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 PdsQL 4.0 generic core scales. Health Qual Life Outcomes. 2007;5:43.
9. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr. 2004;4:371–6.
10. Rosenbaum RL, Saigal S. Measuring health-related quality of life in pediatric populations: conceptual issues. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 785–91.
11. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes. 2006;4:58–62.
12. Cotton S, Grossoehme D, Rosenthal SL, McGrady ME, Roberts YH, Hines J, Yi MS, Tsevat J. Religious/spiritual coping in adolescents with sickle cell disease: a pilot study. J Pediatr Hematol Oncol. 2009;31:313–8.
13. Ashing-Giwa KT. The contexual model of HRQoL: a paradigm for expanding the HRQoL framework. Qual Life Res. 2005;14:297–307.
14. Torrance GW. Designing and conducting cost-utility analyses. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 1105–12.
15. Carcao M, Ungar WJ, Feldman BM. Cost-utility analysis in evaluating prophylaxis in haemophilia. Haemophilia. 2004;10:50–7.
16. Hansen RA, Chin H, Blalock S, Joy MS. Predialysis chronic kidney disease: evaluation of quality of life in clinic patients receiving comprehensive anemia care. Res Social Adm Pharm. 2009;5:143–53.
17. Patrick DL, Erikson P. Applications of health status assessment to health policy. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 717–28.
18. Koltowska-Haggstrom M, Mattsson AF, Shalet SM. Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations. Eur J Endocrinol. 2009;161:S51–64.
19. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK. Health-related quality of life as a predictor of mortality and hospitalization: the dialysis outcomes and practice patterns study (DOPPS). Kidney Int. 2003;64:339–49.
20. Huang IC, Thompson LA, Chi Y, Knapp CA, Revicki DA, Seid M, Shenkman EA. The linkage between pediatric quality of life and health conditions: establishing clinically meaningful cutoff scores for the PedsQL. Value Health. 2009;12:773–80.
21. Cagney KA, Wu AW, Fink NE, Jenckes MW, Meyer KB, Bass EB, Powe NR. Formal literature review of quality-of-life instruments used in end-stage renal disease. Am J Kidney Dis. 2000;36:327–36.
22. CMS. CPM Project Overview. 2008. www.cms.hhs.gov/cpmproject.
23. National Kidney Foundation. NKF DOQI: dialysis outcomes quality initiative. Am J Kidney Dis. 1997;30(3, Suppl 2):S97.
24. Tagge EP, Campbell DA, Dafoe DC, Merion RM, Sedman AB, Keslsch RC, Mollen E, Rocher LL, Tucotte JG. Pediatric renal transplantation with an emphasis on the prognosis of patients with chronic renal insufficiency since infancy. Surgery. 1987;102:692–8.
25. Furth SL, Gerson AC, Neu AM, Fivush BA. The impact of dialysis and transplantation on children. Adv Ren Replace Ther. 2001;8:206–13.
26. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for 2006: updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis. 2006;48:S1–322.
27. Roscoe JM, Smith LF, Williams EA, Stein M, Morton AR, Balfe JW, Arbus GS. Medical and social outcome in adolescents with end-stage renal failure. Kidney Int. 1991;40:948–53.
28. Ehrich JHH, Rizzoni G, Broyer M, Brunner FP, Brynger H, Fassbinder W, Geerlings W, Selwood NH, Tufveson G, Wing AJ. Rehabilitation of young adults during renal replacement therapy in Europe. 2.

Schooling, employment, and social situation. Nephrol Dial Transplant. 1992;7:579–86.
29. Offner G, Latta K, Hoyer PF. Kidney transplanted children come of age. Kidney Int. 1999;55:1509–7.
30. Rosenkranz J, Bonzel K-E, Bulla M, Michalk D, Offner G, Reichwald-Klugger E, Scharer K. Psychosocial adaptation of children and adolescents with chronic renal failure. Pediatr Nephrol. 1992;6: 459–63.
31. Morton MJS, Reynolds JM, Garralda ME, Postlethwalte RJ, Goh D. Psychiatric adjustment in end-stage renal disease: a follow up study of former paediatric patients. J Psychosom Res. 1994;38:296–303.
32. 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.
33. Gerson AC, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush BA, Furth S. Anemia and health-related quality of life in adolescents with chronic kidney disease. Am J Kidney Dis. 2004;44:1017–23.
34. Gerson AC, Fivush BA, Pham N, Fiorenza J, Robertson J, Weiss R, Chandra M, Trachtman R, Riley A, Furth SL. Assessing health status and health care utilization in adolescents with chronic kidney disease. J Am Soc Nephrol. 2005;16:1427–32.
35. 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.
36. 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.
37. McKenna AM, Keating LE, Vigneaux A, Stevens S, Williams A, Geary DF. Quality of life in children with chronic kidney disease–patient and caregiver assessments. Nephrol Dial Tranplant. 2006;21:1899–905.
38. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. Pharmacoeconomics. 1999;16: 605–25.
39. Eiser C, Jenney M. Measuring quality of life. Arch Dis Child. 2007;92:348–50.
40. Marra CA, Levine M, McKerrow R, Carleton BC. Overview of health-related quality-of-life measures for pediatric patients: application in the assessment of pharmacotherapeutic and pharmacoeconomic outcomes. Pharmacotherapy. 1996;16:879–88.
41. Landgraf JM, Abetz LN. Measuring health outcomes in pediatric populations: issues in psyhometrics and application. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996. p. 793–802.
42. Palermo TM, Long AC, Lewandowski AS, Drotrar 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.
43. Starfield B, Riley AW, Green B, Ensminger M, Ryan SA, Kelleher K, Kim-Harris S, Johnston D, Vogel K. The adolescent child health and illness profile: a population-based measure of health. Med Care. 1995;33: 553–66.
44. Starfield B, Riley AW, Green BF, Ensminger ME, Forrest CB, Robertson J, Ryan S, Harris SK. Manual for the child health and illness profile: adolescent edition tm. Baltimore, MD: The Johns Hopkins University; 2000.
45. Starfield B, Riley A. Profiling health and illness in children and adolescents. In: Drotar D, editor. Measuring health-related quality of life in children and adolescents: implications for research and practice. Mahwah: Lawrence Erlbaum Associates; 1998. p. 85–104.
46. Starfield BS, Forrest CB, Ryan SA, Riley AW, Ensminger ME, Green BF. Health status of well verses ill adolescents. Arch Pediatr Adolesc Med. 1996;150: 1249–56.
47. Starfield B, Robertson J, Riley AW. Social class gradients and health in childhood. Ambul Pediatr. 2002;2: 238–46.
48. Starfield B, Riley AW, Witt WP, Robertson J. Social class gradients in health during adolescence. J Epidemiol Community Health. 2002;56:354–61.
49. Landgraf JM, Abetz LN, Ware JE. The CHQ user's manual. 2 Printingth ed. Boston: Health Act; 1996.
50. Varni JW, Limbers CA. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. J Health Psychol. 2009;14(4):611–22.
51. Varni JW, Seid M, Knight TS, Uzark K, Szer IS. The PedsQL 4.0 generic core scales: sensitivity, responsiveness, and impact on clinical decision-making. J Behav Med. 2002;25:175–93.
52. Varni JW, Limbers CA, Newman DA, Seid M. Longitudinal factorial invariance of the PedsQL 4.0 generic core scales child self-report version: one year prospective evidence from the California State Children's Health Insurance Program (SCHIP). Qual Life Res. 2008;17:1153–62.
53. Varni JW, Burwinkle TM, Rapoll MA, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3:329–41.
54. 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.
55. 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. Am J Kidney Dis. 2008;51:285–97.

56. Goldstein SL, Rosburg NM, Warady BA, Seikaly M, McDonald R, Limbers C, Varni JW. Pediatric end stage renal disease health-related quality of life differs by modality: a PedsQL ESRD analysis. Pediatr Nephrol. 2009;24:1553–60.
57. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine and Bright Futures Steering Committee. Recommendations for preventive pediatric health care. Pediatrics. 2007; 120:1376.
58. Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. Health Qual Life Outcomes. 2006;4:1–5.
59. Drotar D. Validating measures of pediatric health status, functional status, and health-related quality of life: key methodological challenges and strategies. Ambul Pediatr. 2004;4:358–64.
60. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, Wong C, Munoz A, Warady BA. Design and methods in the chronic kidney disease in children (CKiD) prospective cohort study. Clin J Am Soc Nephrol. 2006;1:1006–15.

Transitioning the Adolescent Dialysis Patient to Adult Care

35

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Keywords
Dialysis transition • Pediatric dialysis • Adolescent dialysis • Adolescent renal disease

Introduction

There have been dramatic improvements in survival rates for a range of childhood illnesses during the last quarter century, including end-stage kidney disease (ESKD) [1–3]. In the United States alone, over 500,000 adolescents with chronic medical conditions transfer to adult-focused care every year [4]. Health-care transition (HCT) refers to a purposeful, planned process in which adolescent and young adult patients assume progressively increasing responsibility for their health condition management. The goal, highlighted in a number of consensus statements [5–7], is to maximize lifelong functioning and potential through the provision of high quality, developmentally appropriate uninterrupted health services, as the patient moves from pediatric to adult-focused care. An effective transition process is key to optimizing quality of life and survival for youth with serious ongoing medical conditions.

The Transitioning of Youth with Kidney Disease

Although specific information is not available on the number of transitioning dialysis and renal transplant patients, the magnitude of the population at risk can be approximated by extrapolating numbers from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). This is the only major registry that groups dialysis and transplant patient information into the transition age range of 15–24 years. Combining their data [8] with population statistics [9–11], one can estimate that there are at least 7,000 prevalent adolescent/emerging-adult dialysis patients and 11,000 renal transplant recipients in the combined regions of the European Union, North America, Australia, and New Zealand.

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The Vulnerability of Adolescent Renal Patients

The impact of CKD on adolescents and emerging adults can be enormous, and they are at particular risk for severe, irreversible complications of unsuccessful transition. For those on dialysis, life expectancy is approximately 25% that of the age-matched general population and 40% that of their transplant recipient peers [12].

Cardiovascular disease is a leading cause of their morbidity and mortality. Amongst ESKD patients aged 15–19 years, cardiovascular event rates are nearly 1,000-fold higher than those of their age-matched peers, and the mortality rate for those aged 25–34 years is similar to that of 75-year-olds in the general population [13, 14]. For adolescents and young adults with pediatric onset CKD, risk factors associated with the high cardiovascular mortality rate begin early, with calcium–phosphate imbalance, hypertension, fluid overload, and anemia all contributing.

Health-care goals for youth with CKD/ESKD include maximizing their potential for both longevity and quality of life, minimizing health complications, enhancing their capacity to live as independently and self-sufficiently as possible, and optimizing their chances to experience the same educational opportunities, employment possibilities, and social relationships as their peers [15]. Minimizing complications frequently requires close adherence to complex, restrictive, and burdensome medical regimens, particularly for those on dialysis. At a time in their lives when their peers are experiencing new freedoms and liberties, youth on dialysis are bound to a strict routine of care with little margin for acting out or error. They rely on technology for their continued health and survival [16]. Skipping medication, poor adherence to fluid restriction, and missed dialysis treatments can lead to irreversible injury and the risk of sudden death.

The complicated lives of adolescents on dialysis are often made more challenging by the need for transition. Little has been published on the transition of adolescent dialysis patients to adult-focused care, yet they are in danger of being lost in a system where they are vastly outnumbered. In the United States the median age of dialysis patients is 64 years, with adolescent and emerging adult patients comprising only 3% of the entire US dialysis population [12].

This chapter will begin with an overview of medical and psychosocial factors that can influence the transition journey and will outline specific recommendations for its assessment and implementation.

The Health-Care Transition Journey

There is widespread consensus that preparation for health-care *transition* should begin early, to foster progressively autonomous care; recommendations vary from shortly after diagnosis to between 10 and 14 years of age [5]. Suggestions for the preferred age of *transfer* to adult care range from 16 to 21 years [17, 18]; however, it is generally agreed that the timing should be flexible and personalized [19–21].

Young adulthood (20–29 years) can be a challenging period for many youth, even in the absence of chronic disease. It is associated with a peak incidence of risk taking behaviors, and a high rate of accidental death. In the developed world, the mortality rate of 19–24 year olds is four times higher than that of 10–14 year olds, while that of 15–19 year olds is between the two [22]. Rates of substance use and abuse, mental disorders including suicide, and sexual health risks are all greater in young adults than in adolescents [23]. The burden of a serious health disorder is an additional stressor; youth with chronic health conditions may have higher rates of risk behaviors compared to their healthy peers [24] and they are particularly vulnerable to serious medical complications [15, 21, 25, 26]. Socioeconomic factors such as loss of health coverage or lack of employment can add to the challenge and result in unmet health-care needs [27].

Providing effective HCT services can be complex and fraught with challenges. These will be explored in relation to the patient, the family, and health-care teams.

Participants in the Journey

The Patient

Not all pediatric-onset CKD patients are "created equal." ESKD beginning during infancy or early childhood is commonly caused by congenital abnormalities of the kidneys and urinary tract; when onset is during later childhood or adolescence, ESKD is more frequently due to glomerular conditions and/or inflammatory states [28]. Patients with congenital abnormalities are more likely to endure repeated hospitalizations and/or medical interventions, often require surgical procedures for urologic or nutritional problems (e.g., gastrostomy tube placement and/or fundoplication) and are more likely to suffer from orthopedic abnormalities and impaired growth [29]. All of these factors may impair their ability to socialize, consistently attend school, and/or participate in extracurricular activities. Additionally, the short stature that frequently accompanies CKD may lead to low self-esteem and lasting effects on their overall quality of life as adults [30–32].

When CKD or ESKD begins later in childhood or in adolescence, therapies for hypertension and inflammatory states are often required. Although these patients often have some portion of a typical childhood and better chances for normal growth and psychosocial development, the impact of medications (e.g., steroids and/or immunosuppressants) that may change their appearance and affect their psyche cannot be understated, and may subsequently influence HCT.

Neurocognitive dysfunction may occur in some CKD patients and can be associated with factors such as early age of renal failure onset [33–38] and the comorbidities of anemia, hypertension, and malnutrition [39–44]. These neurocognitive deficits may affect IQ, academic achievement, attention, language, visual-spatial abilities, memory, and executive functions [45] and can significantly influence their capacity to pursue educational opportunities, obtain employment, and achieve independence.

Adolescent and Emerging Adulthood Factors

Adolescence is characterized by changes in physical, psychological, and social development and is associated with increased emotional lability and vulnerability [46]. This developmental phase is not magically completed by the 18th birthday, the age when many youth with chronic illness must transfer to adult care. Arnett has used the term "emerging adulthood" to describe the period between 18 and 25 years, in recognition of the ongoing maturation and social development [47]. Cognitive abilities are normally well developed by the mid-teenage years; however, emotional regulation, reflective judgment, and social maturity lag behind [48]. Sensation-seeking activities peak during emerging adulthood, along with an exaggerated response to certain types of "rewards." [46] Emotional and social factors may override more rational cognitive functions, leading to potentially dangerous risk taking [48]. These influences continue at least into the mid twenties [49]. The complex interrelated skills of logical reasoning, reflective judgment, and emotional regulation evolve well into adulthood [50]. Transition to adult care coincides with this period of heightened emotional reactivity sensation seeking and risk taking .Yet, more than ever, this is a time when a stable infrastructure of support and an understanding of the normal developmental phase of emerging adulthood are needed.

A young person who makes a poor decision in a highly charged emotional context, may well "know better" and have different decision making in the absence of such influence [15]. Heightened responsiveness to rewards and relative immaturity of behavioral control, particularly in socially or emotionally roused settings, may lead adolescents to invest more in activities with immediate rather than long-term gains, and help explain their risky decision making and emotional reactivity [15, 49, 50].

Advances in neuroimaging, particularly structural and functional magnetic resonance imaging, have led to a greater understanding of the neurobiological basis for these phenomena. Developmental changes in brain structure continue into the third decade of life [49]. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned [51]. The subcortical limbic regions, important for emotion and reward seeking, mature relatively early, whereas the prefrontal cortex and associated areas, responsible

for "executive brain functions" such as foresight, planning, evaluation of risk and reward, and the capacity to dissociate decision making and strong emotion are among the last to reach adult level. In addition, functional connectivity between these two regions is delayed [46, 52]. Thus, there is some biological basis for the emotional extremes and lack of mature executive planning that can be seen during adolescence and early adulthood [15].

Adolescent Motivation, Engagement, Adherence, and Disease Self-Management

Motivation is a key element in adherence to a therapeutic regimen and disease self-management. Many factors influence the motivation of adolescents, including their short and long-term goals, their intrinsic sense of control, and the way they view themselves in the present and future [53]. Most young people do not experience the notion of "future" beyond the age of 30 [54], which may in part explain their short-term decision making, risk taking, and variable adherence to therapy.

Among the many concepts of motivation, the "self-determination theory" is particularly relevant to adolescents with chronic illness who are transitioning to adult-focused care. It encourages self-responsibility for their therapeutic regimen and engagement with their health-care team. Its application has been well studied in areas such as education, health behaviors of adults, and child rearing. [55–59].

The self-determination theory (SDT) emphasizes three basic psychological needs: autonomy, competence, and relatedness [55, 60]. Autonomy involves experiencing a sense of choice and willingness, rather than being controlled or pressured. Competence describes a feeling of self-confidence or self-efficacy, while relatedness is a sense of belonging, of having connection with others, of shared values and interests, and friendships. Aspects of self-determination theory that are especially pertinent to both parenting and working with adolescents are (1) providing a rationale and explanation for behavioral requests, (2) recognizing their feelings and perspectives, (3) offering choices and encouraging initiative, and (4) minimizing the use of controlling techniques.

In accordance with SDT, engaging adolescents in their health care can be enhanced by clear and consistent goals, a perception of fairness, and participation and collaboration in decision making with the responsible adults in their lives (parents and health-care staff) [61]. In turn, it is important to critically evaluate the prescribed treatment regimen in terms of its complexity, tolerability, and impact on the adolescent's quality of life. Making unreasonable demands will set the patient up for failure. This is particularly relevant for dialysis-dependent adolescents; their medical regimen is complex and non-adherence may seriously impair their future health and quality of life.

Teaching disease self-management skills must also take into account the individual patient's cognitive ability and personality; it requires participation and coordination of multiple team members (patient, caregiver, and multidisciplinary health providers within both the institution and the community). Adherence among adolescents can be compromised by both poor understanding and poor consequence recognition, leading to inconsistent commitment to the treatment regimen. A collaborative relationship between the patient and health-care team, with open and nonjudgmental dialogue, is essential. An approach that incorporates an understanding of adolescent development with self-determination theory motivational techniques [60] can help young people develop a sense of personal choice and autonomy in their behavior, rather than feeling controlled, pressured, or coerced. Other means of enhancing adherence include integrating more specific behavioral approaches (e.g., use of wrist watch alarms, cell phone/text messaging), life coaching, and motivational interviewing [62, 63]. A central tenet of SDT is the need for relatedness; consistent with this, social support strategies (e.g., patient support groups) and acceptance from peers can very positively influence disease self-management and adherence to the therapeutic regimen [64].

Techniques that may help improve adherence for adolescents and young adults and that are integral to successful transition are summarized in Table 35.1.

Table 35.1 Strategies to improve adherence among adolescents and young adults

Communication
A trusting, collaborative relationship that encourages dialogue between the youth and health professional
Education
Stepwise learning regarding the treatment, including purpose, names, dose, schedule, and side effects of prescribed medications
Enhance with booklets, pamphlets, videos, humor, and nonverbal materials (e.g., medication labels and cartoon diagrams)
Assess comprehension
Behavioral strategies
Simplifying the medication regimen
Tailoring the medication schedule to individual patient's lifestyle
Prescribing more "forgiving" medications with longer half lives
Recording of medication intake on calendars or pocket computers
Use of dose container aids
Use of wristwatch or mobile phone alarms
Linking of medication to daily routine cues such as meals, brushing teeth, shaving, etc.
Structured clinical and social network support
System for open communication with clinic or dialysis staff, such as internet, e-mail, and phone
Health-care provider continuity
Peer group support and mentoring
A clinic or dialysis environment that is welcoming to young adults and adolescents
Relevant educational and age appropriate reading material and diversional activities (computer, internet, etc.)
Youth friendly decor

Source: Adapted from Bell et al. [5]

Education

Successful transition of youth on dialysis to the adult world is far more than a coordinated change of health-care providers. Maximizing opportunities for education, vocational training, and employment are also key. Workforce integration is important not only for self-esteem but also for health and social benefits.

Much success in adult life depends on educational achievement [65]. Many patients with pediatric-onset CKD do well both academically and socially. However, a higher than average proportion of patients have problems with school achievement. Upon reaching adulthood, their unemployment rate is higher and the jobs at which they work generally require fewer skills than those of their age-matched peers [32, 66, 67]. Contributing elements include both school absenteeism and neurocognitive factors. Children and adolescents with advanced CKD may miss school frequently because of hospitalizations, regular clinic visits, fatigue, general malaise, or long hours of dialysis; in turn, they may lose out on key learning opportunities and mastery of core skills, leading to difficulty in academic areas that build on prerequisite knowledge [15]. This effect is present even after controlling for learning difficulties [68]. Equally critical, long periods of absence from school can lead young people to be less confident, for psychosocial reasons, about returning to school. It may be difficult for them to pick up on friendships that are perceived to, or that actually have "moved on." [15]

To help address these issues, areas to explore include (1) educational intervention programs (e.g., tutoring, teaching of coping skills, peer-mediated support), (2) school-reintegration programs for those who have missed prolonged periods of school [68], and (3) greater coordination between hospital and school settings, such as sensitizing teachers of children with CKD or those on dialysis to the potential effects of their illness and its treatment [15]. The patient's need for privacy and confidentiality must however be respected; he/she should be involved with decisions regarding information to be shared. Most importantly, a well-timed intervention is key because students who show low levels of engagement with school at the beginning of adolescence are more likely to drop out [69].

Health-Related Quality of Life (HRQOL) in Adolescence and Young Adulthood

Studies of adolescent dialysis patients' HRQOL are limited by small sample sizes, in part reflecting a goal of transplantation for almost all children with ESKD. Furthermore, differing measurement instruments hamper comparisons among studies. Two recent reports show a generally lower HRQOL for adolescents on dialysis compared with those transplanted; factors contributing were fatigue and limitations of family peer interactions [66, 70]. An earlier study found no major HRQOL differences between dialysis and transplant

patients [71]; however, HRQOL was worse for both dialysis patients and transplant recipients than for the age-matched general population. Of note, the adolescents' self-rating of their HRQOL was generally better than their parents' proxy reports [70, 71], perhaps reflecting their adaptation to chronic illness from an early age.

A major goal of transition is to help facilitate optimal functioning, independence, and HRQOL in adulthood. This is an area in need of considerable effort. A study from the Netherlands [67] compared the social independence and employment achievement of adults who had experienced childhood-onset ESKD with those of the age-matched general population. Approximately, 20% of the patients assessed were on dialysis. Findings were that adults with childhood-onset CKD were more likely to be living with their parents, less likely to have a partner, and more likely to be unemployed; dialysis duration of more than 8 years and onset of renal replacement therapy between 1972 and 1982 were associated with greater parental dependency. The patients' unemployment rate was 19%, twice the age-related norm, but only half that of young adult patients with adult onset ESKD [67]. Nonetheless, many of the pediatric "graduates" were only employed part-time and they tended to work in jobs with lower educational requirements. An earlier study found impaired self-esteem amongst adult survivors of pediatric ESKD and lower likelihoods of independent living, close interpersonal relationships, and employment [72]. Lower self-esteem was linked to earlier CKD onset and to educational and social dysfunction [72].

The perspective of qualitative research is particularly useful in helping to understand quality of life issues. One of its features is in depth exploration of the meanings people attribute to their experiences [73]. In a recent systematic review of qualitative studies on adolescent experiences following organ transplantation, Tong and colleagues synthesized HRQOL data from over 300 adolescent transplant recipients [74]. These young people experienced a sense of domination by their medical regimens, lowered self-esteem, resentment about feeling different, negative reaction from peers, a loss of a sense of belonging, anxiety about graft rejection/graft failure, and uncertainty about life expectancy [74]. Although they generally wished to set long-term academic and vocational goals, maintaining schoolwork was often a challenge. Extensive school absenteeism caused some to fall behind, and many felt stressed and overwhelmed as they struggled to achieve satisfactory grades [74]. Nonetheless, they were thankful for a "second chance at life" and new or restored vitality.

In preparing our patients for transition to adult-focused care, we should make every effort to help optimize their HRQOL, in both the present and future. We need to facilitate achievement of their educational and vocational potential and attainment of a sense of responsibility and control over their health; we also must work with them to minimize comorbid sequelae, such as growth impairment, metabolic bone disease, and cardiovascular disease [75, 76]. It is also essential to further delineate, and where possible correct, factors contributing to neurocognitive dysfunction [38, 77].

The Patient/Family Unit

Guiding Parents to Promote Independence and Self-Efficacy

The roles of the parents and family are critically important in preparing their child with ESKD for the road ahead, and helping their adolescent successfully transition to adult-focused care. Parents of children on dialysis may be reluctant to set limits or push their child to carry out age appropriate tasks. The pediatric team needs to encourage them to promote their child's independence and growing capacity for personal, family, and social responsibility [78]. This might include dialogue around participation in developmentally and medically appropriate chores at home, after-school activities, and summer jobs. Parents may need guidance to progressively involve their child with ESKD in his/her own medical care. Examples include graded responsibility for medication preparation, adherence, appointment scheduling and calling for prescription refills, and empowering them to see clinicians by themselves for part of each consultation [15]. Parents can be viewed as transitioning from total caregivers or "CEO's of care" to "managers," "supervisors" and then "consultants," as their children become progressively

more autonomous [5, 17]. These models of parenting are consistent with those embodied in self-determination theory [56].

It is equally important for parents to support their child/adolescent's development in a social context [79]. Group therapy and peer support may assist in improvement of self-esteem, interpersonal skills, and social networks [78]. Encouraging adolescents on dialysis to get involved in activities with peers is fundamental [79]; it may be helpful for the nephrology team to provide specific guidance and reassurance to the parents and patient about medically appropriate activities that will not pose unacceptable risks. Summer camps that focus on transition-related activities can provide excellent opportunities to increase social networks and help children and adolescents develop self-management skills [80].

The Burden of Care

CKD and ESKD can place tremendous emotional, physical, and financial stresses on the patient and family. Parents of chronically ill children have higher marital distress and decreased marital harmony, compared to parents of healthy children [81, 82]. Patients' siblings may miss out on activities and emotional support because the parents are immersed in the care of the child with CKD [83]. Compared with their healthy peers, children with CKD are at greater risk for behavioral and psychological difficulties including attention deficit-hyperactivity disorders, conduct disturbances, internalization of problems, phobias, anxiety, depressive symptoms, social isolation, and withdrawal [84, 85]. Each of these factors may hinder successful transition to adult-focused health care.

High family cohesiveness, expressivity and adjustment, and low family conflict correlate with fewer child behavior problems and lower internalizing symptoms, suggesting that a well-adjusted supportive family can help the child with chronic illness cope more successfully [86, 87]. Parental modeling of healthy lifestyle is central to health-promoting behaviors [88].

Health-care team members should be encouraged to provide culturally sensitive patient/parent support and education at a literacy level that recognizes the multicultural context of many CKD patients. A trans-disciplinary approach and compassionate awareness of all these issues are fundamental in helping the patient and family cope and move forward.

The Health-Care Teams

Effective transition requires committed health-care teams, coordinated interdisciplinary planning, and multilevel system support. To a large extent, the tasks related to transition need to be accomplished during the period of pediatric care. However, youth with chronic disease are particularly vulnerable during "emerging adulthood," a stage when most will have transferred to adult-focused care. Consequently, the adult health-care team's awareness and understanding of adolescent and young adult development and transition issues are essential and appropriate resources are required. In addition, health-care system support and facilitation of the process are crucial.

During the period of pediatric care, key transition elements include effective interdisciplinary communication, family/patient support and coaching, a clinical transition coordinator, a transition organizational and planning document, and preparation of a succinct but comprehensive medical/surgical patient summary for the new health-care providers. A simplified personal health synopsis should also be put together for the patient (meaningful for his/her level of understanding) [15]. An assessment of preparedness is also critical; an example of such a tool undergoing validation is described in the section below on Health Care Transition Programs and Tools. Table 35.2 outlines major Pediatric Team issues and tasks.

On the adult health-care side, ideally there should be a transfer liaison person and nurse coordinator, as well as a social worker skilled in working with adolescents and young adults. Adult team members may need to learn about renal diseases seen mainly in the pediatric age group, particularly conditions that were previously fatal in childhood. It is also important for them to acquire information about the developmental phases of late adolescence and emerging adulthood. Optimally, consideration should be given to creating a clinical and dialysis environment that is welcoming for youth and emerging

Table 35.2 Issues and tasks in transition for the pediatric nephrology team

Designated transition coordinator
Written health-care transition plan for each patient and their family
Checklist of critical tasks and milestones to achieve throughout childhood and adolescence and prior to transfer
Preparation of parents Guidance on age appropriate developmental tasks and the progressive responsibility of their child and adolescent for his/her own health care and social functioning
Promotion of educational and vocational planning throughout childhood and adolescence
Guidance for patient and family regarding health and drug insurance, well prior to transfer
Standardized assessment of readiness for transfer Communication of this assessment and areas in need of attention to adult providers at time of transfer
Up-to-date health passport for each patient
Developmentally challenged adolescents Adapted tasks and transition schedule Guardianship and consent issues addressed significantly in advance of 18th birthday Provision of their own meaningful medical summary adapted to their level of functioning
Collaboration with adult nephrology team regarding their expectations, dialysis or clinic setup, and protocols
Communication and education of primary care provider regarding care beyond the norm for the young adult with chronic kidney disease

Source: Adapted from Bell et al. [5]

Table 35.3 Issues and tasks in transition for the adult nephrology team

Partnership with pediatric team for bidirectional information exchange on practices, protocols, treatment plans
Education on developmental stages of adolescents, the impact of chronic disease on timing of these stages, and on management of congenital and childhood-onset chronic diseases in adulthood
Adult nephrology site optimal resources Transfer liaison person, nurse coordinator, dedicated social worker Young adult designated dialysis or clinic area and/or clinic day

Source: Adapted from Bell et al. [5]

adults, with age appropriate reading material (including health-care information) and internet access. These concepts are summarized in Table 35.3. Health-care system factors are also essential to facilitate the process; key components are outlined in Table 35.4.

Table 35.4 Systems issues in transition

Primary and preventive health care Partnerships with primary care providers and referral of patients to them well in advance of transfer
Mechanisms for joint meetings of adult and pediatric teams
Process and procedures for follow-up of outcomes of adolescent patients after transfer to adult care for both quality assurance and care improvement
Educational tools Self-learning: web based, DVD, podcasts, printed manuals Continuing education conferences Component of residency/fellowship training (both adult and pediatric)
Timing of transfer Complement or coincide with other age-related milestones (finishing high school, going to college or university, moving out of parental home, beginning to work) Flexibility to take into consideration individual patient readiness, medical, social, and emotional stability

Source: Adapted from Bell et al. [5]

Communication Factors

Effective communication and collaboration at multiple levels are essential for the success of a transition program. Those involved include the patient, the family, the pediatric and adult multidisciplinary team members, educators, and community resource persons.

Communication Between Health-Care Providers and Adolescents

The quality of communication between clinicians and youth can influence their satisfaction with treatment, understanding of their medical condition, collaboration, and subsequent appointment keeping [89–91]. Communication elements important to adolescents and emerging adults include the perception that their physician is trustworthy, frank, and open with them, patient-centered rather than condition-focused, (e.g.,

interested in the broader impact of their condition on their day to day life), and willing to discuss sensitive or personal issues (seeking permission first) [92, 93]. They also want someone who listens carefully and takes their concerns seriously, maintains confidentiality, provides understandable explanations, and involves them in decision making [92, 93]. Adolescents are less likely to be engaged if their clinic visit is brief or they feel rushed, if they are seeing a health professional whom they have not previously met or if there is a lack of privacy (i.e., medical students in the room). It may take at least five visits before young people feel they can trust a physician [94].

Health-care providers' support of the adolescent's autonomy and competence is important; adolescents react poorly to the use of coercion, such as scare tactics, or techniques that make them feel badly about themselves. For some adolescents, parental presence at appointments is supportive and confidence building; but at other times it may hinder communication, particularly around personal or sensitive topics [91, 92].

A recent study compared specialists' perceptions of the health-care preferences of chronically ill adolescents with the viewpoints of the adolescents themselves [93]. It showed that the physicians underestimated the importance of communicating as a friend, being trusted by the adolescent's parent or guardian, demonstrating a high level of proficiency in the medical or technical aspects of care (knowledge, experience, and careful clinical assessment) and providing a welcoming office [93].

The knowledge, attitudes, and skills that underpin effective communication with youth are increasingly recognized and taught at both undergraduate and postgraduate levels [15]. A stronger focus on developing the health-care team's proficiency in techniques that enhance communication with young people and their families may be one strategy to promote better transition to adult-focused care. Skills-based training workshops using role-play and simulated patients have led to more effective screening and counseling practices for adolescents by medical students [95] and primary care physicians [96].

Communication Issues Between the Pediatric and Adult Health-Care Teams

Effective and comprehensive communication between the adult and pediatric teams, both prior to and at the time of transfer, is essential for effective transition. Ideally, there should also be a mechanism to facilitate post transfer dialogue. Sharing of therapeutic protocols, to minimize treatment variation between centers, enhances the young person's confidence in the new treating team [5, 15]. A designated transition coordinator can help facilitate the transfer process and orientation of the young person to the adult site. A detailed medical, surgical, and psychosocial summary should be sent to the adult-focused team prior to the transfer event. At a minimum, it should include all significant medical, surgical, and nursing history, all noteworthy complications of therapy, relevant laboratory results, pathology reports, imaging results, operative reports and consultation letters, and pertinent psychosocial information. Areas in need of specific attention should be explicitly conveyed.

Health-Care Transition Programs and Tools

In preparation for transition, adolescents need to learn to convey disease-related information to new health-care professionals, understand the importance of taking their medications as prescribed, and know when and how to contact health-care professionals for both routine and emergency health issues. Acquisition of coping, problem-solving, and disease self-management skills, along with improved knowledge of their condition, may promote self-efficacy and facilitate improved health outcomes [97, 98].

Assessment of Patient Preparedness

A growing number of reports extol the benefits of developmentally appropriate transition processes, but there is a paucity of high level evidence

substantiating the effectiveness of transition programs in documenting a patient's progression along the continuum of transition preparation or validating a programs' accuracy in assessing a young adults' readiness for transfer to adult-focused care [31]. Data is also limited on the efficacy of transition programs in the short or long term [99]. Betz et al. described the Transition Health-Care Assessment tool to measure the adolescent's general and health self-management competencies [100, 101]. It contains 73 items addressing cognitive ability, medical stability, self-care skills, adherence, family functioning, social support system, self-advocacy, sexuality, educational/vocational training, health/lifestyle, and financial concerns. The second tool, developed by Buran et al. [102] assesses the medical, social, psychosocial, and economic needs of young adults with neural tube defects. Kennedy and colleagues have reported a tool that assesses the medical and non-medical needs of young adults' with spina bifida [103], and Capelli et al use 23 items to assess transfer readiness of young adults with cystic fibrosis [104]. The TRAQ transition readiness survey assesses patients' self-reported abilities in the area of disease understanding and self-management, independent interaction with the health-care system, and understanding of and access to adequate financing for health-care services [105].

Each of these assessment tools has drawbacks, such as being difficult to implement in a busy clinical practice, requiring a dedicated nurse, or addressing solely disease-specific or development-centered issues. There are also transition checklists published on the World Wide Web; they are fundamentally similar, varying in length, scope of interest, and mode of implementation, but none has been formally evaluated or validated.

There is a need for validated, rapidly administered generic tools to assess the acquisition of the essential skills and knowledge required to function as a self-regulated participant in an adult health-care setting. They should be standardized and generate both formative and summative data to monitor a patient's progression toward readiness for transfer.

The UNC "STARx" Transition Program and Instruments

Ferris and colleagues at the University of North Carolina (UNC) Kidney Center have developed the "STARx" transition program and instruments. The acronym stands for "Successful Transition to Adulthood with Rx" (Rx = treatment). It comprises tools to aid in the patient's acquisition of disease self-management skills and in the team's assessment and promotion of the transition process. These tools, currently being validated, include the Medical Passport, the Patient Self-Administered Transition Readiness Survey, and the health provider-administered TR$_x$ANSITION Score™.

The Medical Passport

This is a practical tool designed to encourage adolescents with CKD/ESKD to acquire basic disease self-management skills and improve their communication with health-care providers. The one created at UNC is a laminated, wallet-sized document containing the following patient-specific health information: name, their photograph (if they wish, or any other image of their choice), medical diagnosis, current medication list (type, dosage, frequency, and purpose), drug allergies, medical provider contact information, and a unique patient ID number (see Fig. 35.1). This UNC medical passport has been distributed to 142 adolescents and emerging adults (age 12–22 years) with chronic diseases such as CKD and inflammatory bowel disease. On preliminary analysis, 69% of these patients were able to present their passports 9 months after receipt. Age was independently associated with sustained passport-carrying (adjusted odds ratio 1.50 [95% CI: 1.18, 1.90]) [106]. The application in other health settings (e.g., emergency departments or in other health institutions) or as a patient education tool is being determined. An excellent interactive easily updated web-based transition passport is also available from the Hospital for Sick Children at the University of Toronto (http://www.sickkids.ca/myhealthpassport).

The Patient Self-administered "STAR$_x$" Transition Readiness Survey

This instrument was developed by Ferris' group at UNC based on published transition "check

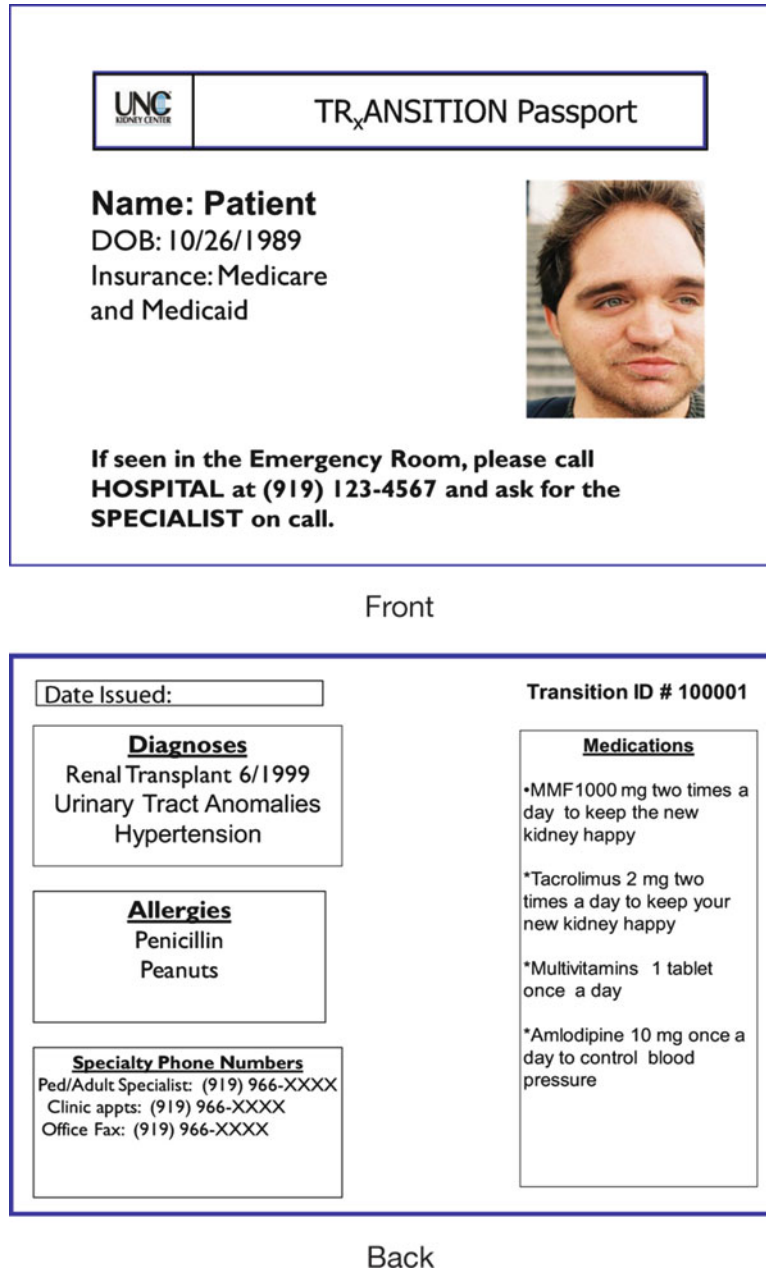

Fig. 35.1 The transition medical passport (view of both sides)

lists" of transition skills and using the Stages of Change Model. The triangulated methods and multiple phases of its development included: (1) exploratory interviews to define transition conceptually; (2) initial drafting of what would become a self-administered, closed-ended response instrument; (3) cognitive interviews (using the "concurrent think-aloud" technique where the responses are probed extensively) to pre-test the draft instrument and improve responder comprehension; and (4) pilot-testing. Participants in the process were current adolescent and young adult patients and adult graduates of the UNC Kidney Center's pediatric nephrology practice, who did not participate in the Transition Program. The "STAR$_x$" Transition

Readiness Survey includes self-reported knowledge of (1) disease diagnosis, (2) medications/treatment, (3) health insurance, (4) ability to make medical appointments, (5) ability to use health resources, and (6) disease self-management. Validation studies as a web-based tool are underway.

The UNC TR$_x$ANSITION Scale™

The UNC TR$_x$ANSITION Scale™ (trademark 2006, University of North Carolina) was initially developed for adolescents and emerging adults, 12–22 years of age, with CKD stages 1 through 5. It was designed with two purposes (1) to assess and monitor the HCT process longitudinally, and (2) to be brief, accessible (web based), and reproducible in clinical practice.

It comprises 10 domains of disease knowledge and or self-management which are desirable for the adolescent/young adult to achieve before transferring from pediatric to adult-focused care (based on published transition check lists) [107]. These 10 domains are: *T*ype of illness, *R*x (medications), *A*dherence, *N*utrition, *S*elf-management, *I*ssues of reproduction, *T*rade/school, *I*nsurance, *O*ngoing support, and *N*ew health providers. This tool is a structured interview administered by a health professional and it produces an overall score (with ten sub-scores). While it collects information by patient self-report, it also allows the health professional to confirm that the patient indeed has the knowledge claimed (i.e., the patient has to name his/her medication(s) to get credit for the answer). This tool guides health provider education activities and coaching on HCT, allowing the health provider to praise the adolescent on knowledge/skills they have already mastered, assist them in improving on tasks they perform adequately and help them focus upon those areas where they have the lowest competencies. Many areas of the UNC TRxANSITION Scale™ overlap with the self-administered "STARx" Transition Readiness Survey, but the Scale collects demonstrated skills whereas the self-report does not get confirmation by the health provider, it is simply a self-report scale.

Preliminary analysis of a baseline cross-sectional pilot study, to measure the association between the score of the UNC TR$_x$ANSITION Scale and the medical and socio-demographic characteristics in pediatric CKD patients, found that the overall TR$_x$ANSITION score increased with age and was not influenced by diagnosis, age at diagnosis, gender, race, having a single parent, insurance, CKD stage, or presumed adherence. Adolescents younger than 17 years had a significantly lower score than older teens and young adults, with those younger than 14 years having the lowest scores. This may reflect life experience and development over time as the adolescents grow, rather than duration of disease (as no significant difference was noted with age at diagnosis). Validation studies of this instrument are in progress.

Both, the UNC TRxANSITION Scale and the "STARx" Transition Readiness Survey account for patients' areas of expertise while guiding patient education activities in areas where the patients lack knowledge.

The Road Ahead

Transition programs that involve patients, families, pediatric and adult health-care providers, and interdisciplinary collaboration are believed to be key to ensuring a successful transition from pediatric to adult-focused health services. Evidence-based planning, effective coordination, and education of all transition participants are central to this endeavor. Research is needed to guide strategies and includes such areas as evidence-based tools to measure the health-care transition process, procedure implementation, validation of interventions, and identification of health-care transition outcomes. Suggested areas for study are listed in Table 35.5. There is still much to learn, but the challenges described on the preceding pages and the rewards of successful transition, such as optimizing health-related quality of life and survival, remain compelling.

Table 35.5 Areas for research in transition to adult care for adolescents with CKD

Patient factors
The impact of
Patient characteristics (normal skill attainment with maturation, age at diagnosis, cause of CKD, cognition, literacy, and self-activation)
Acquisition of disease self-management skills in the context of transition
Home situation (single parent, number of healthy or ill siblings)
The environment (access to insurance and social services)
Educational intervention programs (e.g., tutoring, teaching of coping skills, peer-mediated supports, and school reintegration programs)
Health team factors
The impact of
Well visits and preventative services on promoting the health, development, and acquisition of effective transition skills in children and adolescents with CKD/ESKD
Effective comanagement and Interdisciplinary collaboration, especially when patients reside far away from where they receive specialty care
Transition education programs for health-care team members, both pediatric and adult
Prospective multi-institutional studies
Track the process of transition for longitudinal information regarding
The effect of planned transition activities for patients at the pediatric site
Medium and long-term patient outcomes after transfer to adult care
HRQOL
Employment status
Morbidity (e.g., Cardiovascular and bone disease, dialysis access, malignancies, graft loss)
Pregnancy outcomes
Mortality
Systems issues
The value of transition clinics and adolescent/emerging adult joint clinics
Health-care system costs comparing proactive-planned transition interventions to ad hoc methods of dealing with problems as they arise

References

1. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. Lancet. 2007;369(9571):1481–9.
2. Kennedy A, Sawyer S. Transition from pediatric to adult services: are we getting it right? Curr Opin Pediatr. 2008;20(4):403–9.
3. 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(7):1020–6.
4. Reiss J, Gibson R. Health care transition: destinations unknown. Pediatrics. 2002;110(6 Pt 2):1307–14.
5. 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.
6. 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):1304–6.
7. Rosen DS, Blum RW, Britto M, Sawyer SM, Siegel DM. Society for adolescent medicine. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. J Adolesc Health. 2003; 33(4):309–11.
8. Australia and New Zealand Dialysis and Transplant Registry Report 2009. http://www.anzdata.org.au/v1/report_2009.html. Accessed 25 July 2011.
9. 2009 World Population Data Sheet. Population Reference Bureau. http://www.prb.org/Publications/Datasheets/2009/2009wpds.aspx. Accessed 25 July 2011.
10. Total Population Database Table_ European Union. Eurostat. http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home. Accessed 25 July 2011.
11. Bureau of Public Affairs: Background Notes. U.S. Department of State. http://www.state.gov/r/pa/ei/bgn/index.htm. Accessed 25 July 2011.
12. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD, U.S. Renal Data System, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. http://www.usrds.org/adr.htm. Accessed 25 July 2011.

13. Mitsnefes MM. Cardiovascular complications of pediatric chronic kidney disease. Pediatr Nephrol. 2008;23:27–39.
14. 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.
15. Bell LE, Sawyer SM. Transition of care to adult services for pediatric solid-organ transplant recipients. Pediatr Clin North Am. 2010;57(2):593–610.
16. Bell L. Adolescents with renal disease in an adult world: meeting the challenge of transition of care. Nephrol Dial Transplant. 2007;22(4):988–91.
17. Kieckhefer GM, Trahms CM. Supporting development of children with chronic conditions: from compliance toward shared management. Pediatr Nurs. 2000;26(4):354–63.
18. Knauth A, Verstappen A, Reiss J, Webb GD. Transition and transfer from pediatric to adult care of the young adult with complex congenital heart disease. Cardiol Clin. 2006;24(4):619–29.
19. Hersh A, Pang S, Curran M, Milojevic D, von Scheven E. The challenges of transferring chronic illness patients to adult care: reflections from pediatric and adult rheumatology at a US academic center. Pediatr Rheumatol. 2009;7:1–13.
20. Rosen DS. Transition of young people with respiratory diseases to adult health care. Paediatr Respir Rev. 2004;5(2):124–31.
21. Weissberg-Benchell J, Wolpert H, Anderson BJ. Transitioning from pediatric to adult care. Diabetes Care. 2007;30(10):2441–6.
22. Patton GC, Coffey C, Sawyer SM, Viner RM, Haller DM, Bose K, et al. Global patterns of mortality in young people: a systematic analysis of population health data. Lancet. 2009;374(9693):881–92.
23. Park MJ, Paul Mulye T, Adams SH, Brindis CD, Irwin J. The health status of young adults in the United States. J Adolesc Health. 2006;39(3):305–17.
24. Suris JC, Michaud PA, Akre C, Sawyer SM. Health risk behaviors in adolescents with chronic conditions. Pediatrics. 2008;122(5):e1113–8.
25. Annunziato RA, Emre S, Schneider B, Barton C, Dugan CA, Shemesh E. Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult services. Pediatr Transplant. 2007;11(6):608–14.
26. Watson AR. Problems and pitfalls of transition from paediatric to adult renal care. Pediatr Nephrol. 2005;20(2):113–7.
27. Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. J Adolesc Health. 1993;14(7):570–6.
28. NAPRTCS 2008 Annual Report. North American Pediatric Renal Trials and Collaborative Studies. https://web.emmes.com/study/ped/annlrept/Annual%20Report%20-2008.pdf. Accessed 25 July 2011.
29. Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. Pediatr Nephrol. 2006;21:917–30.
30. Bartosh SM, Leverson G, Robillard D, Sollinger HW. Long-term outcomes in pediatric renal transplant recipients who survive into adulthood. Transplantation. 2003;76(8):1195–200.
31. Broyer M, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, et al. Long-term social outcome of children after kidney transplantation. Transplantation. 2004;77(7):1033–7.
32. 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.
33. Davis I, Chang P, Nevins T. Successful renal transplantation accelerates development in young uremic children. Pediatrics. 1990;86:594–600.
34. Elzouki A, Carroll J, Butinar D, Moosa A. Improved neurological outcome in children with chronic renal disease from infancy. Pediatr Nephrol. 1994;8:205–10.
35. Lawry KW, Brouhard BH, Cunningham RJ. Cognitive functioning and school performance in children with renal failure. Pediatr Nephrol. 1994;8:326–9.
36. 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.
37. Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev. 2003;29:55–61.
38. 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.
39. Marsh JT, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int. 1991;39:155–63.
40. Levitsky DA, Strupp BJ. Malnutrition and the brain: changing concepts, changing concerns. J Nutr. 1995;125:2212S–20.
41. Lande MB, Kaczorowski JM, Auinger P, Schwartz GJ, Weitzman M. Elevated blood pressure and decreased cognitive function among school-age children and adolescents in the United States. J Pediatr. 2003;143:720–4.
42. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and ado-

lescents in the United States. Pediatrics. 2001;107:1381–6.
43. Grantham-McGregor S. A review of studies of the effect of severe malnutrition on mental development. J Nutr. 1995;125:2233S–8.
44. Gorman KS. Malnutrition and cognitive development: evidence from experimental/quasi-experimental studies among the mild-to-moderately malnourished. J Nutr. 1995;125:2239S–44.
45. Gipson DS, Wetherington CE, Duquette PJ, Hooper SR. The nervous system and chronic kidney disease in children. Pediatr Nephrol. 2004;19:832–9.
46. Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann NY Acad Sci. 2008;1124(1):111–26.
47. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469–80.
48. Luna B, Padmanabhan A, O'Hearn K. What has fMRI told us about the development of cognitive control through adolescence? Brain Cogn. 2010;72(1):101–13.
49. Steinberg L. A social neuroscience perspective on adolescent risk-taking. Dev Rev. 2008;28(1):78–106.
50. Fischer KW, Stein Z, Heikkinen K. Narrow assessments misrepresent development and misguide policy: comment on Steinberg, Cauffman, Woolard, Graham, and Banich (2009). Am Psychol. 2009;64(7):595–600.
51. The adolescent brain – why teenagers think and act differently. EDinformatics . http://www.edinformatics.com/news/teenage_brains.htm. Accessed 25 July 2011.
52. Giedd JN. The teen brain: insights from neuroimaging. J Adolesc Health. 2008;42(4):335–43.
53. Massey EK, Gebhardt WA, Garnefski N. Adolescent goal content and pursuit: a review of the literature from the past 16 years. Dev Rev. 2008;28(4):421–60.
54. Nurmi JE. How do adolescents see their future? A review of the development of future orientation and planning. Dev Rev. 1991;11(1):1–59.
55. Deci EL, Ryan RM. Facilitating optimal motivation and psychological well-being across life's domains. Can Psychol/Psychol Canadienne. 2008;49(1):14–23.
56. Joussemet M, Landry R, Koestner R. A self-determination theory perspective on parenting. Can Psychol/Psychol Canadienne. 2008;49(3):194–200.
57. Williams GC, Cox EM, Hedberg V, Deci EL. Extrinsic life goals and health risk behaviors in adolescents. J Appl Soc Psychol. 2000;30:1756–71.
58. Williams GC, Cox EM, Kouides R, Deci EL. Presenting the facts about smoking to adolescents: effects of an autonomy-supportive style. Arch Pediatr Adolesc Med. 1999;153(9):959–64.
59. Williams GC, McGregor H, Sharp D, Kouides RW, Levesque CS, Ryan RM, et al. A self-determination multiple risk intervention trial to improve smokers' health. J Gen Intern Med. 2006;21(12):1288–94.
60. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol. 2000;55:68–78.
61. Fredricks JA, Blumenfeld PC, Paris AH. School engagement: potential of the concept, state of the evidence. Rev Educ Res. 2004;74(1):59–109.
62. Rollnick S, Butler CC, McCambridge J, Kinnersley P, Elwyn G, Resnicow K. Consultations about changing behaviour. BMJ. 2005;331(7522):961–3.
63. Anderson BJ, Svoren B, Laffel L. Initiatives to promote effective self-care skills in children and adolescents with diabetes mellitus. Dis Manag & Health Outcomes. 2007;15(2):101–8.
64. Olsson CA, Boyce M, Toumbourou JW, Sawyer SM. The role of peer support in facilitating psychosocial adjustment to chronic illness in adolescence. Clin Child Psychol Psychiatry. 2005;10(1):78–87.
65. Bynner J. Childhood risks and protective factors in social exclusion. Child Soc. 2001;15(5):285–301.
66. 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(8):1561–8.
67. Groothoff JW, Grootenhuis MA, Offringa M, Stronks K, Hutten GJ, Heymans HSA. Social consequences in adult life of end-stage renal disease in childhood. J Pediatr. 2005;146(4):512–7.
68. Martinez YJ, Ercikan K. Chronic illnesses in Canadian children: what is the effect of illness on academic achievement, and anxiety and emotional disorders? Child Care Health Dev. 2009;35(3):391–401.
69. Janosz M, Archambault I, Morizot J, Pagani LS. School engagement trajectories and their differential predictive relations to dropout. J Soc Issues. 2008;64(1):21–40.
70. Goldstein S, Rosburg N, Warady B, 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.
71. 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(7):1899–905.
72. Morton MJS, Reynolds JM, Garralda ME, Postlethwaite RJ, Goh D. Psychiatric adjustment in end-stage renal disease: a follow up study of former paediatric patients. J Psychosom Res. 1994;38(4):293–303.
73. Pope C, Mays N. Qualitative methods in health research. In: Pope C, Mays N, editors. Qualitative research in health care. 3rd ed. Oxford: Wiley-Blackwell; 2006. p. 1–11.
74. Tong A, Morton R, Howard K, Craig JC. Adolescent experiences following organ transplantation: a systematic review of qualitative studies. J Pediatr. 2009;155(4):542–9.

75. Schaefer F. Cardiac disease in children with mild-to-moderate chronic kidney disease. Curr Opin Nephrol Hypertens. 2008;17:292–7.
76. Lilien MR, Groothoff JW. Cardiovascular disease in children with CKD or ESRD. Nat Rev Nephrol. 2009;5:229–35.
77. Pereira AA, Weiner DE, Scott T, Sarnak MJ. Cognitive function in dialysis patients. Am J Kidney Dis. 2005;45(3):448–62.
78. Furr LA. Psycho-social aspects of serious renal disease and dialysis: a review of the literature. Soc Work Health Care. 1998;27(3):97–118.
79. Melzer SM, Leadbeater B, Reisman L, Jaffe LR, Lieberman KV. Characteristics of social networks in adolescents with end-stage renal disease treated with renal transplantation. J Adolesc Health Care. 1989; 10(4):308–12.
80. Walker DA, Pearman D. Therapeutic recreation camps: an effective intervention for children and young people with chronic illness? Arch Dis Child. 2009;94(5):401–6.
81. Tew BJ, Payne H, Laurence KM. Must a family with a handicapped child be a handicapped family? Dev Med Child Neurol. 1974;16:95–8.
82. Lansky SB, Cairns NU, Hassanein R, Wehr J, Lowman JT. Childhood cancer: parental discord and divorce. Pediatrics. 1978;62:184–8.
83. 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.
84. Mehta M, Bagga A, Pande P, Bajaj G, Srivastava RN. Behavior problems in nephrotic syndrome. Indian Pediatr. 1995;32(12):1281–6.
85. Garralda ME, Jameson RA, Reynolds JM, Postlethwaite RJ. Psychiatric adjustment in children with chronic renal failure. J Child Psychol Psychiatry. 1988;29(1):79–90.
86. Soliday E, Kool E, Lande M. Family environment, child behavior, and medical indicators in children with kidney disease. Child Psychiatry Hum Dev. 2001;31(4):279–95.
87. Soliday E, Kool E, Lande MB. Psychosocial adjustment in children with kidney disease. J Pediatr Psychol. 2000;25(2):93–103.
88. Gutgesell ME, Payne N. Issues of adolescent psychological development in the 21st century. Pediatr Rev. 2004;25(3):79–85.
89. Litt IF, Cuskey WR. Satisfaction with health care: a predictor of adolescents' appointment keeping. J Adolesc Health Care. 1984;5(3):196–200.
90. Freed LH, Ellen JM, Irwin CE, Millstein SG. Determinants of adolescents' satisfaction with health care providers and intentions to keep follow-up appointments. J Adolesc Health. 1998;22(6): 475–9.
91. Beresford BA, Sloper P. Chronically ill adolescents' experiences of communicating with doctors: a qualitative study. J Adolesc Health. 2003;33(3):172–9.
92. Brown JD, Wissow LS. Discussion of sensitive health topics with youth during primary care visits: relationship to youth perceptions of care. J Adolesc Health. 2009;44(1):48–54.
93. Britto MT, Slap GB, DeVellis RF, Hornung RW, Atherton HD, Knopf JM, et al. Specialists understanding of the health care preferences of chronically ill adolescents. J Adolesc Health. 2007;40(4):334–41.
94. McDonagh JE, Kaufman M. The challenging adolescent. Rheumatology. 2009;48(8):872–5.
95. Feddock CA, Hoellein AR, Griffith CH, Wilson JF, Lineberry MJ, Haist SA. Enhancing knowledge and clinical skills through an adolescent medicine workshop. Arch Pediatr Adolesc Med. 2009;163(3):256–60.
96. Lustig JL, Ozer EM, Adams SH, Wibbelsman CJ, Fuster CD, Bonar RW, et al. Improving the delivery of adolescent clinical preventive services through skills-based training. Pediatrics. 2001;107(5):1100–7.
97. Creer TL, Holroyd KA. Self-management of chronic conditions: the legacy of Sir William Osler. Chronic Illn. 2006;2(1):7–14.
98. Meade MA, Creer TL, Mahan JD. A self-management program for adolescents and children with renal transplantation. J Clin Psychol Med Settings. 2003;10(3):165–71.
99. Betz CL. Transition of adolescents with special health care needs: review and analysis of the literature. Issues Compr Pediatr Nurs. 2004;27(3): 179–241.
100. Betz C, Redcay G, Tan S. Self-reported health care, self-care needs of transition-age youth: a pilot study. Issues Compr Pediatr Nurs. 2003;26(3):159–81.
101. Betz CL. California healthy and ready to wor k transition health care guide: developmental guidelines for teaching health care. Issues Compr Pediatr Nurs. 2000;23(4):203–44.
102. Buran CF, Sawin KJ, Brei TJ, Fastenau PS. Adolescents with myelomeningocele: activities, beliefs, expectations, and perceptions. Dev Med Child Neurol. 2004;46(4):244–52.
103. Kennedy S, Martis S, Kelley J, Walton B, Vlcek C, Hassanein R, et al. Identification of medical and nonmedical needs of adolescents and young adults with spina bifida and their families: a preliminary study. Child Health Care. 1998;27:47–61.
104. Cappelli M, MacDonald NE, McGrath PJ. Assessment of readiness to transfer to adult care for adolescents with cystic fibrosis. Child Health Care. 1989;18(4):218–24.
105. Sawicki GS, Lukens-Bull K, Yin X, Demars N, Huang IC, Livingood W et al. Measuring the transition readiness of youth with special healthcare needs: validation of the TRAQ – Transition Readiness Assessment Questionnaire. J Pediatr Psychol. 2011;36(2):160–171
106. Ferris ME, Kelly MM, Martin NB, Freeman KL, Kim S, Bickford K, et al. Sustained use of a practical tool to assist adolescents with disease self-management. J Adolesc Health. 2008;42(2, Suppl 1): 17. Abstract.
107. Ferris M, Gipson D, Ford C, Tolleson-Rinehart S, Bozik K, Chin H, et al. The UNC T.R.A.N.S.I.T.I.O.N. ScoreTM among adolescents with chronic kidney disease (CKD). J Am Soc Nephrol. 2007;18:F-PO1083. Abstract.

The Ethics of Withholding or Withdrawing Dialysis in the Pediatric ESRD Patient

36

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Keywords

Ethics • Treatment withholding • Treatment withdrawal • Quality of life • Quality of death • Decision making process • Maintenance dialysis • Renal replacement therapy

Medical ethics – based on autonomy, beneficence, non-maleficence, and justice – is present at many steps in the use of maintenance dialysis in the child with end-stage renal disease (ESRD) (Table 36.1) [2].

Is dialysis an ethical option in the management of ESRD in children?

Is there room for ethics in the choice of dialysis modalities?

On which bases can dialysis be withheld or withdrawn?

The situation is complicated by the traditional assumption that parents are entitled to make decisions on behalf of their child, as they have been generally regarded as the best-possible surrogate decision makers [1]. However, relying on parental judgment alone is no longer always sufficient. The ethical decision-making process can be made more difficult by family disagreement and even media intrusion. Indeed, the current practice of medicine must take into account the growing number of sources of information for patients, parents, and family doctors [3, 4].

Is Dialysis an Ethical Option in the Management of ESRD?

Transplantation Versus Dialysis

Kidney transplantation has been shown to be the best therapeutic option for children with ESRD, which suggests that dialysis should be reserved for those children who are not candidates for preemptive kidney transplantation. This reflects an ethical approach that benefits the individual, assuming better outcome and quality of life for the preemptively transplanted patient. However, the situation becomes more complicated when society as a whole is considered in the setting of a worldwide organ shortage, thus explaining the increasing number of patients who need to be treated by dialysis waiting for a transplant. Transplantation using

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Table 36.1 Ethical decisions: guidelines for practice [1]

• Always act in the child's best interests
• Never rush the decision. Continue treatment until it can be properly made
• Assemble all the available evidence
• Respect the opinion of everyone in the team
• Discuss the issues with the whole family
• Attempt a consensus wherever possible
• Make sure everyone appreciates the burden of care
• Try to avoid adding to the guilt of anyone involved
• Consider the child's palliative and terminal care
• Offer support for all those affected, parents, and staff alike
• Remember, we can only do the best we can. Sometimes there is no ideal solution

living donors allows a higher rate of preemptive transplantation, but this, too, may raise ethical problems if the choice of a living donation is only based on the option of a preemptive procedure.

In any case, dialysis may be regarded as a procedure that "prepares" the child for transplantation, although optimal dialysis must be provided to any child, independent of the estimated waiting time until the kidney transplant becomes available. Dialysis and transplantation requirements may be challenging for specific diseases such as oxalosis which require a combination of both (daily) hemodialysis (HD) and peritoneal dialysis (PD) prior to combined liver-kidney transplantation. Therefore, it appears that dialysis should always be a bridge to transplantation, and initiation of dialysis must be associated with a plan for transplantation, a condition which is not always found in developing countries.

Dialysis Technology

Today there is almost no technical limitation to dialysis in children, leaving ethical arguments as the principal remaining reasons for withholding dialysis therapy. Improvements in dialysis technology have allowed for advances in the treatment of ESRD in small children, infants, newborns, and even premature babies. In addition, PD with intensive nutritional support using enteral feeding has greatly improved infant dialysis outcomes worldwide.

Dialysis is a Demanding Treatment

Dialysis is a demanding treatment in children, especially in infants. Such a procedure must be acceptable for the patient, for the family (including sibs), and for caregivers. In addition to "normal" parental roles, being a parent of a child with chronic kidney disease (CKD) demands that the parent become a high-level health care provider, who has 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 of peer support within and outside the family structure. Parents of children with CKD need multidisciplinary support to obtain improved outcomes for their child (Table 36.2) [5, 6].

Today, for many infants with early onset ESRD, the parents have received preliminary information at the time of a prenatal diagnostic evaluation. However, it should not be assumed that the infant's postnatal kidney failure has been accepted by the parents because pregnancy termination was not performed or proposed following prenatal counseling. In addition, parents may not realize that their decision to consent to renal replacement therapy (RRT) during the first months/years of life for their child is a commitment to lifelong treatment, often leading to transition from dialysis to transplantation and back to dialysis, possibly more than once during the childhood years. Such a long-term project is linked to emotional, developmental, social, and economical issues for parents, who may find it difficult to grasp the full magnitude and extent of the care their child will require.

Is There Room for Ethics in the Choice of Dialysis Modalities?

Influence of Resources

The choice of dialysis modality should theoretically depend on a patient's requirements for individual optimal dialysis care. However, modality choice is often based on governmental economy, health insurance access, and local facilities, not

Table 36.2 Thematic schema representing parent perspectives on caring for a child with chronic kidney disease [5]

Absorbing the clinical environment	*Medicalizing parenting*	*Disrupting family norms*	*Coping strategies and support structures*
Confronting the diagnosis	A consuming routine	Spousal tension and dependency	Internal coping strategies (grieving, acceptance, asserting, reframing, focusing on the ill child, and comparing)
Invasive procedures	Pressure and isolation	Sibling neglect	External coping strategies (family, friends, community)
Conflict and trust	Struggle with feeding	Household and financial stress	Information need
Varying quality of care	Medical management	Decision to donate	
Losing ownership	Psychological trauma	Social restriction	
Jeopardizing relationship with staffs			

only for developing countries but also for developed countries that are experiencing more and more problems regarding healthcare organization.

Peritoneal dialysis is available in most countries, but in many developing countries is limited to the management of acute renal failure. The lack of access to transplantation as well as chronic PD leads to dialysis withdrawal when renal function does not return. In addition, many developing countries do not have adequately financed public or private healthcare systems, and patients must pay all of the cost of treatment. In contrast, most developed countries can now offer chronic PD for infants with the latest automated PD cyclers and full reimbursement by national or private healthcare systems.

A comparable situation exists for HD, since HD strategy ranges from one weekly session of conventional maintenance HD in developing countries to short daily high-flux online hemofiltration in developed countries.

Independent of these issues, in some countries the choice among RRT options may differ for uninsured, undocumented children compared to the children of citizens [7]. However, in most cases, hospitals with special pediatric expertise can absorb the expenditure associated with providing expensive life-saving care to such patients, with a risk of attracting an increasing number of these children from other hospitals. Again this is ethically advantageous at the individual level but questionable at the community level. Due to political and economical instability, this phenomenon may be increasing worldwide, and a search for local health policy alternatives should be encouraged.

Hospital Versus Home Environment

An argument for choosing HD or PD might be based on the possibility of having or avoiding home treatment. Peritoneal dialysis is mostly a home treatment, which means the presence of the cycler and associated devices in the child's bedroom, together with the child's usual games and books. Home care may enhance quality of life in some ways, but when dialysis is performed at home, the patient and his family are exposed daily to RRT omnipresence.

On the other hand, HD is performed in specialized hospital centers, which implies a specific time schedule, adaptation to dialysis unit requirements, and mostly car transportation. However, a home free from RRT devices may be a major advantage for some patients and their parents who prefer HD in the hospital center. In addition, hospital HD may also contribute to better treatment adherence and understanding through repeated individual education by HD staff. Home HD may be proposed for some patients in selected experienced centers.

Concomitant Treatments

Whatever the dialysis procedure, most children need to take several additional drugs (e.g., antihypertensive drugs, medications for prevention/treatment of bone disease, etc.) and require tube feeding and subcutaneous injections (e.g., erythropoiesis-stimulating agents, recombinant human growth

hormone) which may jeopardize overall therapeutic adherence. Because of the potential adverse consequences of multiple home medications and treatments on both health and quality of life, conservative measures must be limited to the smallest possible number of treatments, based on individual risk-to-benefit ratios.

On What Bases Can Dialysis Be Withheld or Withdrawn?

Ethical limitations for starting dialysis are based on its impact in terms of quality of life, morbidity, and mortality. This may be influenced by psychosocial variables, cultural background, and religious beliefs, all of which also can be regarded as coping mechanisms [8].

The risk of death among infants with ESRD has been estimated to be 4 times greater than that seen in older children, and 10 times that of transplant recipients. In addition, neurodevelopmental delay may affect 10–50% of infants on PD [9, 10]. Other disabilities seen in these infants may be linked to ESRD and RRT, such as complications of PD (e.g., leakage of dialysate, abdominal wall hernia, peritonitis, catheter dysfunction/revision/replacement, exit site infection, fluid leaks, and bowel perforation) and complications of HD (e.g., poor tolerance of HD sessions, catheter infections, technical and infections problems with arteriovenous fistula and rarely exacerbation of seizure disorders during dialysis). Other uncommon but potentially serious complications of dialysis seen in infants include blindness, motor deficit, cranial nerve palsy, and communication problems [9].

The important negative impact of coexistent non-renal comorbidity on the prognosis of the infant with ESRD (e.g., neurological injury, pulmonary hypoplasia, cardiac malformations, severe multiple malformation syndromes, and extreme prematurity) must be explained to parents as soon as possible [11, 12]. This may help parents understand and accept the gravity of their child's disability.

The primary disease causing ESRD may also be associated with specific life-threatening problems, such as oliguria and pulmonary hypoplasia in children with autosomal recessive polycystic kidney disease [9]. In children with an infantile form of primary hyperoxaluria type 1, therapeutic withdrawal may be an acceptable option in countries where combined liver and kidney transplantation is not available, because of the severity of life threatening systemic involvement [13]. While renal tubular dysgenesis usually presents with neonatal anuria, the renal ultrasound is usually normal, thus making understanding very challenging for parents and family [12].

The highest mortality risk associated with ESRD mainly affects very young children. The number of infants who die before starting dialysis is unknown since the decision to withhold dialysis is usually taken by neonatalogists, intensivists, and urologists, and not always including nephrologists. After starting dialysis in very young children, death may be due to pulmonary hypoplasia, major hemodynamic problems, or severe sepsis [1].

In most cases, parents expect their child to receive all available treatment, and recent developments are technically encouraging. However, the decision to withdraw or withhold RRT may still be considered by parents and medical team members in individual cases. Those contemplating such decisions should be aware that the law regarding treatment withdrawal is different from one country to the other. At times, an ethically defensible decision to withdraw or withhold RRT from a severely damaged child with ESRD who also has, for example, additional multiple irreparable malformations and profound brain injury may conflict with applicable law in one country but not in another. In such cases, the expertise of physicians, nurses, psychologists, developmental specialists, and other experienced members of the medical team should be combined with that of ethicists and legal experts to aid the family in reaching the best decision for their child that also does not place the medical team and treating facility in jeopardy of legal sanctions.

Dialysis Withdrawal/Withholding

Most papers on dialysis withdrawal/withholding deal with elderly populations and end-of-life discussions [14]. The acceptance of dialysis withdrawal is largely based on cultural and family background, for example, in elderly populations, it is less accepted by Blacks as compared with Whites and other race/ethnicity groups [14]. Interestingly, most patients withdrawing from RRT are those who anticipated (verbally or in writing) making their own medical decisions; such advance directives have been regarded as a "good death" [2, 15].

In infants with ESRD, the main factors which have been reported to influence the decision-making process regarding initiation of RRT are coexistent serious medical abnormalities, anticipated morbidity for the child, and the family's right to decide [16]. In a survey performed in 1998, the parental right to refuse RRT was "usually acceptable" for 50% of primarily North American pediatric nephrologists in the case of ESRD in a newborn and for only 25% of them when ESRD occurred in an older infant [16]. In a similar survey of primarily European pediatric nephrologists performed in 2002 [17], the infant's expected resultant quality of life, based on long-term living conditions, was the main criterion used by physicians to make decisions regarding withdrawal or withholding of RRT; relational aspects of life (i.e., the child's likely ability to communicate with family members) and the child's long-term prognosis were also considered. From the same study, the level of parent involvement in the decision-making process differed among centers. The same group carried out semi-directed interviews with 46 French speaking pediatric nephrologists [18]; it was concluded that treatment decisions were not based on scientific criteria, but on the individual family's capacity to accept the child's handicap, the family's past experiences, and the physician's own projections. Physicians also reported that their task was particularly difficult when their decision could potentially contribute directly to death of the child (e.g., treatment withdrawal or acceleration of the process). They felt that their duty was more to help families in the acceptance of medical team decisions than to encourage family participation in the decision-making process. Indeed, since babies cannot speak for themselves, life and death decisions must be made for them by proxy; it is unlikely that such decisions can be made completely free from personal feelings that can unavoidably influence opinions about the "best interests" of the infant [1].

The American Academy of Pediatrics Committee on Bioethics reasonably recommended that individual decisions on withdrawal/withholding treatment should be made jointly by clinicians and parents in a partnership based on communication of facts and feelings [19].

During the last decade, experience in the management of RRT in very young children has dramatically improved, not only in terms of device and techniques, but also in terms of mortality, morbidity, and quality of life [8, ESPN-ERA Registry 2010]. A very young age at initiation of RRT still has a negative prognostic value, but this alone cannot remain a contraindication to any form of RRT. This may change the rationale for dialysis withdrawal/withholding, which is currently already very limited. Indeed, aggressive early treatment can be offered to all infants, but it must be discussed in cases of severe associated comorbidity (mainly neurological) and in countries with limited resources. Most children survive the first 6–12 months of life on dialysis, and can then be treated successfully with kidney transplantation.

Depending on the country and its laws, the issue of RRT withdrawal may be more challenging with adolescents who are deemed to be competent to give informed consent, and who have the moral right to choose to die rather than to continue treatment [20]. Such decisions should be made cooperatively by the adolescents, physicians, and parents in a supportive environment. Some teams include a child psychiatrist or clinical psychologist in order to offer staff support and an outlet for parents to use without fear of upsetting those on whose physical help their child

depends [1]. Occasionally, the adolescent patient may disagree with the parents, physicians or both; in such circumstances, ethical practice should be based on the foundation of an accurate medical assessment of prognosis and treatment options and the prospect of the clinical course with and without treatment [21]. Sincere attempts to provide this information must be made even if it requires repeated clinical visits and personal interviews. The physician should therefore assess the adolescent's ability to understand and reflect on the choice, to balance values, and to accept the implications of treatment decisions. Following such an approach, most adolescents are capable of making competent healthcare decisions, and the physician should do his or her best to accept and respect this decision and allow the competent adolescent to exercise autonomy [21]. However, such a strategy is exposed to a strong influence by the physician's culture, own experience, and religious beliefs [22].

In most conditions, despite facing profound and persuasive challenges, parents strive to fulfill their dual parental and health care provider responsibilities. However, they need better support structures to help them cope with the difficulties encountered during all stages of their child's illness, independent of age [5].

Conclusion

Ethics can play a major role in the management of the child requiring RRT. While there is no universally accepted "ethical" approach for dialysis indications and practices, recently there seems to be a growing international consensus based on evidence-based information, expert practice, technical availability, and ethical tools. However, the criteria used to decide whether to withhold or to withdraw life-sustaining RRT are not yet standardized. Research in this field is essential, leading hopefully to future guidelines to assist with these difficult decisions.

Medical indications for dialysis withdrawal/withholding have dramatically decreased on the basis of both scientific advances and worldwide cultural changes regarding death. Such decisions are therefore more and more challenging and must be supported by a multidisciplinary approach and expertise. These arguments reinforce the need for full-scale ethical committees in every hospital (Table 36.3) [23].

Table 36.3 Issues considered by clinical ethics committees [23]

• Withholding or withdrawing treatment
• Do not resuscitate orders
• Advance directives
• Consent
• Capacity
• Refusal of treatment
• Confidentiality
• Genetic testing
• Assisted reproduction
• Issues around intensive care
• Issues in emerging medicine

References

1. Shooter M, Watson A. The ethics of withholding and withdrawing dialysis therapy in children. Pediatr Nephrol. 2000;14:347–51.
2. Swartz RD, Perry E. Advance directives are associated with"good deaths" in chronic dialysis patients. J Am Soc Nephrol. 1993;3:1623–30.
3. Cargill A, Watson AR. Sources of information on renal conditions used by families. Pediatr Nephrol. 2002;17:648–51.
4. Tuffrey C, Finlay F. Use of the internet by parents of paediatric outpatients. Arch Dis Child. 2002;87:534–6.
5. 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;36:549–57.
6. Tong A, Lowe A, Sainsbury P, Craig JC. Experience of parents who have children with chronic kidney disease: a systematic review of qualitative studies. Pediatrics. 2008;121:349–60.
7. Young J, Flores G, Berman S. Providing life-saving health care to undocumented children: controversies and ethical issues. Pediatrics. 2004;114:1316–20.
8. Patel SS, Shah VS, Peterson RA, Kimmel PL. Psychosocial variables, quality of life, and religious beliefs in ESRD patients treated with hemodialysis. Am J Kidney Dis. 2002;40:1013–22.
9. 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;155:111–7.

10. 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.
11. Bunchman TE. Infant dialysis: the future is now. J Pediatr. 2000;136:1–2.
12. Waisman D, Kessel I, Ish-Shalom N, Maroun L, Riskin-Mashiah S, Falik-Zaccai T, Weintraub Z, Albersheim S, Rotschild A. The anuric preterm newborn infant with a normal renal ultrasound: a diagnostic and ethical challenge. Prenat Diagn. 2006;26:350–3.
13. Cochat P, Koch-Nogueira PC, Mahmoud MA, Jamieson NV, Scheinman JI, Rolland MO. Primary hyperoxaluria in infants: medical, ethical and economic issues. J Pediatr. 1999;135:746–50.
14. Tamura MK, Goldstein MK, Pérez-Stable EJ. Preferences for dialysis withdrawal and engagement in advance care planning within a diverse sample of dialysis patients. Nephrol Dial Transplant. 2010;25:237–42.
15. Andresen EM, Nanda U, Toce S. Research on the quality of death in children. QoL Newsletter. 2002;28:17–8.
16. Geary DF. Attitudes of pediatric nephrologists to management of end-stage renal disease in infants. J Pediatr. 1998;133:154–6.
17. Fauriel I, Moutel G, Moutard ML, Montuclard L, Duchange N, Callies I, François I, Cochat P, Hervé C. Decisions concerning potentially life-sustaining treatments in paediatric nephrology: a multicentre study in French-speaking countries. Nephrol Dial Transplant. 2004;19:1252–7.
18. Fauriel I, Moutel G, Duchange N, Montuuclard L, Moutard ML, Cochat P, Hervé C. Decision making concerning life-sustaining treatment in paediatric nephrology: professional's experiences and values. Nephrol Dial Transplant. 2005;20:2746–50.
19. American Academics of Pediatrics Committee on Bioethics. Ethics and the care of critically ill infants and children. Pediatrics. 1996;98:149–52.
20. Doyal L, Henning P. Stopping treatment for end-stage renal failure: the rights of children and adolescents. Pediatr Nephrol. 1994;8:768–71.
21. Doig C, Burguess E. Withholding life-sustaining treatments: are adolescents competent to make these decisions? Can Med Assoc J. 2000;162:1585–8.
22. Jagsi R, Soleymani Lehmann L. The ethics of medical education. Br Med J. 2004;329:332–4.
23. Slowther A, Johnston C, Goodall J, Hope T. Development of clinical ethics committees. Br Med J. 2004;328:950–2.

Acute Kidney Injury: Diagnosis and Treatment with Peritoneal Dialysis, Hemodialysis, and CRRT

37

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Keywords
Acute kidney injury • Peritoneal dialysis • Hemodialysis • CRRT • AKI

In response to growing evidence that even small declines in kidney function can adversely affect outcome in severely ill patients, the term acute kidney injury (AKI) was introduced in 2005 to better represent the dynamic clinical entity traditionally known as acute renal failure (ARF). Acute kidney injury affects an increasing proportion of critically ill pediatric and adult patients who now survive medical conditions and surgical complications that once were often fatal. Identifying the pathophysiologic principles underlying the development, progression, and resolution of AKI is the focus of much ongoing investigation. Improvements in classification systems along with consistency of applied defining criteria will enhance our understanding of the etiology and progressive nature of AKI in children and help define the role of early intervention. Advances in diagnosis, most notably the introduction of newer biomarkers, and the widespread availability of an increasing number of effective renal replacement treatment modalities have raised hopes of improved outcomes. This chapter focuses on the diagnosis and medical and dialytic management of pediatric AKI.

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Definition of Acute Kidney Injury (AKI)

Acute kidney injury has been classically defined as an abrupt, prolonged yet often reversible loss of the ability of the kidneys to maintain homeostasis of the body fluids. Retention of nitrogenous wastes is a consistent feature of AKI; significant reduction in urine output is not [1, 2]. Objective diagnostic criteria have ranged from a change in a biomarker (e.g., increase in serum creatinine), to a clinical sign (reduction in urine output), to a therapeutic maneuver (need for dialysis support) [3–5]. In fact, by the year 2002, more than 30 different definitions of AKI had been published [6].

This lack of consensus on AKI diagnostic criteria has confounded efforts to study the condition, establish incidence and prevalence rates,

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Table 37.1 The RIFLE AKI classification systema

AKI stage	Serum creatinine criteria	Urine output criteria
1 (***Risk***)	Absolute increase ≥ 0.3 mg/dL or Value is 1.5× baseline value or GFR decrease by >25%	<0.5 mL/kg/h for >6 h
2 (***Injury***)	Value is 2× baseline value or GFR decrease by >50%	<0.5 mL/kg/h for >12 h
3 (***Failure***)	Value is ≥3× baseline value or GFR decrease by >75% or Value ≥4 mg/dL with absolute increase ≥0.5 mg/dL or Patient is receiving renal Replacement therapy	<0.3 mL/kg/h for 24 h or Anuria for 12 h
Loss	Persistent AKI = complete loss of renal function for >4 weeks	
ESRD	End-stage renal disease	

[a]With AKIN modifications; see text

define risk factors, and monitor outcomes. Following a series of consensus conferences beginning in 2000 known as the "Acute Dialysis Quality Initiative" (ADQI), a sensitive definition of AKI was developed based on five degrees of increasing severity and worsening outcome (the "RIFLE" criteria): Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease. (Table 37.1) The RIFLE criteria are based on absolute values and changes in serum creatinine levels, estimated glomerular filtration rates and/or urine output, reflecting the dynamic process of AKI, which can progress from mild to severe forms [6].

Initial application and validation of the RIFLE criteria in the adult critical care population demonstrated reasonable predictive correlation between the different degrees of AKI according to the RIFLE criteria and mortality [7, 8]. Modifications of the original criteria were proposed in 2005 by the Acute Kidney Injury Network (AKIN) both to broaden consensus and reflect new evidence that discrete changes in serum creatinine levels in adults as small as 0.3 mg/dL were associated with worsening outcomes [9]. Table 37.1 incorporates both the original RIFLE category definitions (in italics) with the AKIN modifications which replace RIFLE levels R, I, and F with AKIN stages 1, 2, and 3.

In a landmark study of 150 critically ill children, Akcan-Arikan and Goldstein and their colleagues in Houston developed a pediatric-specific AKI classification system that is shown in Table 37.2 [10].

In all three AKI staging systems (RIFLE, AKIN, and pRIFLE) patients are classified according to either urine output or serum creatinine/estimated creatinine clearance (cCcl) criteria, whichever is worse.

The relative simplicity of the pRIFLE is attractive, but to be successful a clinical condition definition and severity classification system must also prove to be a sensitive and valid predictor of outcomes. Subsequent reports from Europe and North America have confirmed the pRIFLE's ability to identify children at greater risk for AKI and poorer outcomes in a variety of clinical settings, including burn injury and following cardiac surgery [11–13]. The potential utility of the pRIFLE is shown in another study of 103 consecutive patients admitted to a pediatric intensive care unit in Amsterdam [14]. Plotz and colleagues identified 60 patients with AKI by pRIFLE at a

Table 37.2 Pediatric-modified (pRIFLE) criteria

AKI category	Estimated creatinine clearance (eCcl)	Urine output
Risk	eCcl decrease by 25%	<0.5 mL/kg/h for
Injury	eCcl decrease by 50%	<0.5 mL/kg/h for 16 h
Failure	eCcl decrease by 75% or eCcl < 35 mL/min/1.73 m2	<0.3 mL/kg/h for 24 h or Anuric for 12 h
Loss	Persistent loss >4 weeks	
ESRD	End-stage renal disease defined As persistent failure >3 months	

eCcl estimated creatinine clearance

mean of 1.9 ± 1.6 days after admission. These patients had a five times greater risk of dying (25% vs. 5%) compared to patients without AKI. A recent report has demonstrated successful extension of the use of the pRIFLE to non-critically ill children at risk for AKI due to aminoglycoside exposure [15].

Based on these encouraging reports, widespread use of the pRIFLE should promote early recognition of AKI in pediatric patients and may prove useful in preventing progression of renal failure by identifying those patients who could benefit from earlier treatment. In addition, the widespread acceptance of pRIFLE will facilitate progress in research on this complex clinical condition.

The Epidemiology of AKI in Children

The incidence and prevalence of AKI varies according to the pediatric population studied, the definition of AKI employed, and the country of origin of the report, making comparative analysis difficult. For example, a retrospective study from Italy reported an incidence of AKI (defined as need for dialysis) of 2.7% in children undergoing cardiopulmonary bypass surgery [16], while another similarly designed study from the United Kingdom found an overall AKI incidence of 3.2 per 100,000 children [17]. A prospective study validating the Pediatric Logistic Organ Dysfunction (PELOD) score in pediatric intensive care units (PICU), demonstrated an incidence of AKI (defined as serum creatinine levels above 55–140 μmol/L depending on age of the child) of 129 per 1,000 admissions [18]. The absence of a common definition for pediatric AKI makes these and many other studies difficult to interpret or compare.

Pathophysiology of AKI

Several key pathophysiological processes thought to be important in the development of AKI are briefly described in the next section of this chapter. For a more detailed discussion the reader is encouraged to see the excellent reviews by Lamiere, van Biesen and van Holder [1], Boneventure and Weinberg [19] and Sutton et al. [20] upon which the following discussion is largely based.

Renal Blood Flow (RBF) Autoregulation

Autoregulatory mechanisms in the kidney act to preserve renal blood flow (RBF) and glomerular capillary perfusion pressure during periods of hypotension or hypoperfusion by adjusting afferent and efferent glomerular arteriolar vascular resistances to produce a pressure gradient at the level of the glomerular capillary bed. In states of hypoperfusion, the afferent arteriole dilates and the efferent arteriole vasoconstricts to maintain the transglomerular pressure gradient, thereby maintaining glomerular filtration.

Mediators that serve as regulators of renal blood flow by acting as vasoconstrictors include angiotensin II, thromboxane A2, and endothelin. Catecholamines may also exert a vasoconstrictive

effect indirectly by altering production of both vasoconstrictors and vasodilators. Unopposed vasoconstriction of both afferent and efferent renal arterioles eliminates the transglomerular pressure gradient necessary for glomerular filtration which is consequently dependent on afferent arteriolar vasodilatation. Prostaglandins appear to play a substantial role as renal vasodilators, along with nitric oxide (NO) produced locally by vascular endothelium. Diffuse endothelial damage, as is seen in states of inflammation such as sepsis, alter organ autoregulatory function through diminished NO production. Additionally, the macula densa has a direct reflex vasodilation effect on the afferent arteriole, the "myogenic reflex," which causes relaxation in response to the same stimuli as renin release. Finally, atrial naturetic peptide (ANP) released from myocytes in response to atrial stretch in states of volume overload acts to dilate the afferent arterioles and increase glomerular filtration.

The Classical Theory of Ischemic AKI

Ischemic acute renal injury ranges from mild prerenal azotemia to acute tubular necrosis and is caused by an absolute or relative reduction in renal perfusion resulting in reduction in glomerular filtration rate (GFR) and increases in serum creatinine and blood urea nitrogen levels. Oliguria occurs frequently, but not always. At first, compensatory mechanisms affecting RBF autoregulation attempt to restore renal perfusion and GFR to normal by vasodilation of the afferent arteriole and maintenance of fluid delivery to the distal nephron. In the setting of generalized hypotension, multiple potent systemic compensatory mechanisms are activated that establish a generalized milieu of vasoconstriction in an effort to restore blood pressure to normal. If renal hypoperfusion persists, vasoconstriction of the efferent arteriole occurs in an effort to maintain a constant glomerular capillary hydrostatic pressure. The intricate balance of autoregulatory vasoconstriction and vasodilation at the level of the glomerulus needed to sustain a reversible state of prerenal azotemia requires a symphony of physiologic forces acting in harmony to sustain renal function until normal perfusion and blood pressure can be restored.

When hypoperfusion is not corrected in time, RBF autoregulation fails, resulting in conversion of reversible prerenal azotemia to acute tubular necrosis. Persistent afferent and efferent arteriolar vasoconstriction is relatively unopposed as vascular relaxation mechanisms become less effective, leading to congestion in the outer medulla and causing tubular injury. Tubular cells swell, lose their brush border membranes and begin to exfoliate, resulting in tubular obstruction. Activation of endothelial cells by ischemic injury upregulates adhesion molecules, trapping leukocytes and platelets while launching a cytokine-driven inflammatory cascade that causes further endothelial injury and worsening ischemia.

Vascular Response to Ischemia and Cell Energetics

In normal function, the kidneys receive approximately 20–30% of cardiac output, and consume 7% of delivered oxygen. In times of physiologic stress, oxygen consumption by the kidney may increase dramatically with little means of increasing total renal blood flow, unlike myocardial blood flow, which under similar conditions may increase as much as tenfold to meet metabolic demands. These factors place the metabolically active nephron units at great risk for oxygen debt in the presence of global hypoperfusion and/or hypoxemia. Cortical nephrons are at the greatest risk for oxygen debt, perhaps because their blood supply is the most distal from the renal artery and they are the most metabolically active. During these periods of hypoxic/ischemic stress, kidney adenosine triphosphate (ATP) stores are consumed rapidly, and energy availability becomes dependent on local mitochondrial regeneration of ATP from adenosine diphosphate, along with neosynthesis and/or regeneration of ATP from purine precursors and adenosine monophosphate (AMP).

Cellular recovery from an ischemic event is dependent upon the length of the insult and the prior metabolic status of the patient. For example, an unstressed patient with normal cardiac output will recover renal function quickly following aortic or renal artery cross clamping with rapid local regeneration of ATP, while a patient in a low cardiac output state with a high metabolic demand, as is seen in sepsis, will not recover as rapidly from an acute ischemic event, in part because the ability to regenerate ATP from local precursors is diminished. During these periods, AMP is shunted away metabolically to form adenosine and inosine, from which regeneration of ATP requires extensive metabolic remodeling. Hence, energetic recovery is hampered, extending the injury period beyond the period of acute ischemia.

Free Radical Injury

During periods of recovery from oxidative stress, toxic by-products are created, such as oxygen free radicals. Highly reactive species, such as hydroxyl radical (OH) and superoxide anion (O_2–) cause direct injury to proteins by oxidizing amino acid residues and changing the structure or function of important enzymes. Additionally, the lipoprotein bilayer and ultrastructure of the cell is affected, causing cell rupture and an increase in cell membrane permeability, thereby reducing the cell's ability to isolate the cytosol from the surrounding milieu. Direct DNA damage can occur which limits the ability of a cell to perform important reparative functions. Hence, through a variety of mechanisms, further cell injury and death is incurred during the reperfusion phase after an acute ischemic event.

Tubular Cell Alterations

Renal tubular epithelial cells are highly metabolically active in order to provide the energy required to fuel active solute transport. The straight proximal segment of the renal tubule (S3 segment) is highly susceptible to injury, as it contains many Na+/K + ATPase-dependent transport channels. These channels are found predominantly on the basolateral surface of the cell, and are anchored in place by cytoskeletal elements. Injury to the cell, either through primary ischemia/hypoxia, or due to reactive oxygen species, causes the Na+/K/+ ATPase to mislocate through the fluid lipoprotein bilayer and come to reside on the apical surface. Additionally, energy needs for this ATPase are not met, and function is reduced. Particularly, damaging is the loss of active calcium transport that normally sequesters calcium predominantly in the extracellular fluid. This calcium gradient is also maintained via metabolically active transport channels, including a Ca++ ATPase. Protein migration from the basolateral to apical surface and reduced activity of Ca++ ion channels disrupt the polarity of the electrochemical gradient established by the tubular epithelium which is vital to normal function. This loss in polarity may explain the increased solute delivery to the distal nephron seen in AKI. Changes in cytoskeleton structure are also seen in arteries, arterioles, and in the vasa recta. These changes may play a role in the loss of autoregulation of renal blood flow.

Renal Tubule Obstruction/Backflow

Insults to the renal tubular epithelium cause cell death and diminished or absent regeneration. The resultant cellular debris sloughs off and enters the tubular lumen. In some cases, this debris is felt to obstruct the tubular lumen, especially in the inferior segment of the Loop of Henle thereby raising tubule intra-lumenal pressure and further reducing the gradient from the glomerular capillary to Bowman's space necessary for effective glomerular filtration. Due to the loss of the integrity of tubular epithelium, tubular obstruction may also cause back flow of ultrafiltrate into the surrounding interstitium. Extruded tubular fluid may alter the interstitial milieu substantially, affecting corticomedullary osmolarity and local electrochemical gradients, as well as causing direct cell injury and further propagating renal dysfunction.

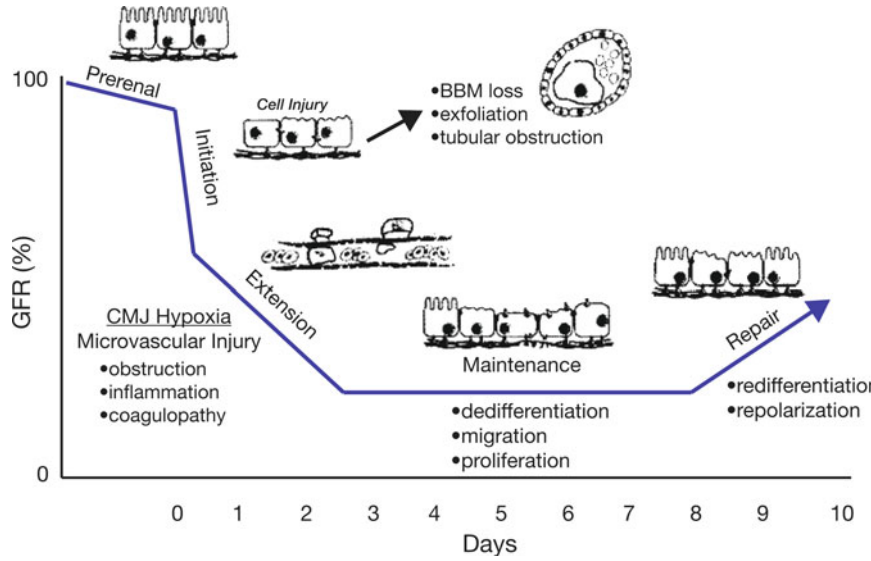

Fig. 37.1 Stages of ischemic acute kidney injury (Adapted with permission from Ref. [20]) depicting the relationship between the clinical phases and the cellular phases of ischemic acute renal failure (ARF), and the temporal impact on organ function as represented by the glomerular filtration rate (GFR). See text for details. *BBM* brush border membrane; *CMJ* corticomedullary junction

Summary of the Classical Theory

Taken together, there are classically four phases to the progression of parenchymal injury during ischemic AKI [20] (Fig. 37.1). The first phase ("initiation") follows the decrease in perfusion and ATP depletion caused by the acute ischemic insult. The second phase ("extension") is marked by ischemia reperfusion injuries that may cause further damage. During this phase, inflammation leads to prolongation of ischemia and aggravation of injury. Proximal tubules regenerate during the extension phase, but cells from the S3 segment of the same proximal tubule and from the medullary thick ascending limb can undergo necrosis and apoptosis. The differential effects of therapy if applied during the extension phase in experimental models supports the notion that severity of injury during this phase is closely correlated with prognosis of renal recovery. During the third phase ("maintenance"), necrosis and apoptosis persist via inflammation and cell injury. Finally, during the last phase ("recovery"), several mechanisms occur concomitantly resulting in repair, regeneration, and proliferation of injured cells. The degree and extent of injury likely determine whether or not the kidneys will recover fully, progress to end-stage renal disease, or leave the patient with chronic kidney disease.

The Clinical Syndrome of Acute Kidney Injury

The clinical syndrome of acute kidney injury may be divided into prerenal, intrinsic renal, and postrenal categories (see Table 37.3), and further subdivided into oliguric and nonoliguric forms. AKI may also be categorized as primary or secondary. AKI is primary when kidney dysfunction is due, for example, to acute glomerulonephritis or to hemolytic-uremic syndrome (HUS). AKI is secondary when it is caused by a systemic disorder such as sepsis or shock. In developed nations, primary AKI [23, 24] was once the most common form seen in children. In recent years, with advances in the treatment of other childhood pathologies, secondary AKI due to sepsis,

Table 37.3 Causes of acute kidney injury (Adapted from Refs. [21, 22])

Prerenal
Intravascular volume depletion
Bleeding, trauma
GI losses: diarrhea, vomiting
Renal losses: diabetes insipidus
Skin/mucous membrane losses: burns, fever (prolonged)
Third space losses: pancreatitis, hypoalbuminemia, crush injuries
Decreased cardiac output
Congestive heart failure
Cardiomyopathy
Sepsis
Drugs (overdose), anesthetics
Anaphylaxis
Renal vasoconstriction
Liver disease, sepsis, hypercalcemia
Drugs
Angiotensin-converting enzyme inhibitors
Nonsteroidal anti-inflammatory drugs
Renal (intrinsic)
Acute tubular necrosis (ATN)
Hemolytic-uremic syndrome (HUS)
Glomerulonephritis/rapidly progressive glomerulonephritis
Post-infectious glomerulonephritis
Systemic lupus erythematosis
Membranoproliferative glomerulonephritis
IgA nephropathy
Henoch-Schonlein purpura
Pulmonary-renal syndromes
Wegner's granulomatosis
Goodpasture's syndrome
Acute interstitial nephritis
Nephrotoxins
Drugs: aminoglycosides, cyclosporine A, amphotericin B, cisplatinum
Toxins: ethylene glycol, heavy metals, herbal remedies
Pigments: hemolysis, rhabdomyolysis
Postrenal (obstructive)
Ureter
Nephrolithiasis, sloughed renal papillae
Post-operative ureteric surgery
Hemorrhage, tumor
Bladder
Calculi, blood clots, bladder catheter obstruction
Neurogenic bladder
Tumor
Urethral
Valves, phimosis, strictures

nephrotoxic drugs, and renal ischemia in children undergoing hematopoetic stem cell transplantation, solid organ transplantation, or cardiac surgery represent the majority of cases of AKI [25, 26].

Demographics of AKI in Children

Geographical location and cultural traditions influence the causes of AKI in children (Table 37.3). In developing countries, infectious diseases are the main causes of AKI. Two studies from Nigeria observed that 71% of cases of AKI were secondary [27, 28] with malaria the most common cause. Other common causes were gastroenteritis and human immunodeficiency virus (HIV) nephropathy [28]. In India, HUS and glomerulonephritis still represent the predominant cases of AKI [23]. Some long standing local customs [29] such as use of herbal medicines in developing countries are associated with AKI. In recent years, herbal medicine-induced AKI is seen with increasing frequency in developed countries [30, 31].

Risk Factors and Associated Causes of AKI

Risk factors for AKI are varied and dependent on the patient population studied. In most circumstances, more than one risk factor is present prior to the development of AKI [32, 33].

Primary risk factors for AKI seen in adults are septic shock (40–50%) [32, 34, 35], other types of shock (e.g., cardiogenic, hypovolemic) [34], and nephrotoxic drugs [34]. An international multicenter prospective observational study of 29,269 critically ill adults identified increased risk for AKI in patients with septic shock (47.5%), cardiogenic shock (27%), hypovolemia (26%), and nephrotoxic drugs such as aminoglycosides, antifungal agents, calcineurin inhibitors, and angiotensin-converting enzyme inhibitors in cases of associated hypovolemia (19%) [4].

Information on risk factors for AKI in children is sparse and largely limited to single center reports. Sepsis, hypovolemia, cardiac dysfunction, cardiac bypass surgery, and nephrotoxic medications have been implicated [36, 37]. Sepsis, septic shock, and nephrotoxic drug-induced AKI stand apart from other causes due to the increasing frequency with which these entities are seen in the pediatric critical care setting. Drug-induced AKI accounts for up to 16% of

pediatric AKI [26], becoming more prevalent in sicker populations [38].

AKI induced by drugs occurs by two predominant mechanisms: direct toxicity to renal tubular epithelium, as is seen with aminoglycosides and amphotericin, and interference with autoregulatory mechanisms leading to unrestricted vasoconstriction and reduced renal blood flow, as is seen with nonsteroidal anti-inflammatory drug (NSAID) toxicity. Prevention of drug-induced AKI is more effective than any available therapy; recognition of high risk patients is therefore necessary. A detailed discussion of specific drugs known to cause AKI is beyond the scope of this chapter and may be found in several excellent reviews [38, 39].

Contrast Nephropathy

A syndrome of acute kidney injury associated with exposure to radiocontrast materials is known as contrast nephropathy. Contrast nephropathy results in AKI requiring hospitalization in 12 % of adult patients who have undergone imaging with contrast agents [40], and is associated with an increased risk of mortality in the year following the episode of AKI [41]. The incidence in children is unknown. Patients with chronic kidney disease or diabetes are at increased risk [41]. Volume and osmolality of contrast administered is directly associated with risk of AKI [42, 43], and non ionic agents are thought to be safer, especially in patients with chronic renal disease [44].

The pathophysiology of contrast nephropathy is still largely unknown. Severe vasoconstriction following contrast administration has been implicated [45, 46], as has direct cytotoxicity via oxygen free radical generation [47]. The rise in serum creatinine occurs 1–2 days after the imaging procedure and is usually unaccompanied by a decrease in urine output [48]. Dialysis is required in a minority of patients. No treatment exists other than support if AKI occurs. However, in recent years, attention has focused on prevention [38, 49]. A recent meta-analysis of prevention strategies recommends pre- and post-contrast intravenous hydration with bicarbonate-containing fluids and use of low or iso-osmolar contrast agents in the smallest volume possible in patients with pre-existing kidney disease who are at increased risk. N-acetylcysteine and ascorbic acid have also been suggested for use as free radical scavengers in the higher risk populations [44].

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is seen in patients undergoing the first cycle of chemotherapy where rapid tumor destruction occurs. It is more frequent in certain tumors such as lymphoma and acute lymphoblastic leukemia, with an incidence in these high risk patients approaching 10% [50]. Patients usually present with a metabolic disorder linked to the rapid cell turnover, such as hyperuricemia, hyperkalemia, hyperphosphatemia, and resulting hypocalcemia. Prevention and early recognition of patients at risk for TLS is critical. Avoidance of nephrotoxic drugs and volume depletion is also important [51], as is prevention of hyperuricemia with drugs such as allopurinol and more recently recombinant urate oxidase (Rasburicase®) [52, 53]. Early and aggressive use of Rasburicase® has all but eliminated TLS in some pediatric oncology centers. Urinary alkalinization to diminish uric acid precipitation in the tubule has been recommended, but should be used with caution as it may increase precipitation of calcium phosphate crystals. Targeting the urinary pH to around 7 is usually sufficient to aid uric acid elimination; alkalinization of the urine should be stopped once a normal serum uric acid level is reached [54]. When severe AKI occurs and RRT is required, intermittent hemodialysis will effectively reduce uric acid and phosphate levels; however, rebound often occurs. As a result, continuous renal replacement therapy (CRRT) is often recommended in this situation [54]. The need for RRT of any type usually can be avoided by prompt recognition of TLS risk and early Rasburicase® treatment.

AKI Due to Urinary Tract Obstruction

Obstruction to flow of tubular ultrafiltrate can cause significant renal dysfunction. Glomerular

filtration is a product of the balance between hydrostatic and oncotic pressure gradients at Bowman's space. Intratubular pressure is normally very low compared to the driving hydrostatic pressure across the glomerular capillary bed. However, with obstruction to tubular ultrafiltrate flow, the pressure in Bowman's space rises and becomes a significant inhibitor of glomerular filtration. Obstruction to ultrafiltrate flow may occur at the tubular level, as is seen with ATN or intratubular crystal precipitation, or may occur in the renal collecting system, ureter, bladder, or urethra. Unilateral obstruction may not be clinically evident due to compensatory alterations in function of the unaffected kidney [55]. However, in cases of bilateral obstruction or obstruction occurring in a solitary kidney, clinically significant changes in renal function will occur, leading to AKI.

Diagnosis of Pre-renal Versus Intrinsic Versus Postrenal AKI

Prompt determination of pre-renal or postrenal AKI should be the goal of initial evaluation in patients with acutely diminished renal function in the critical care setting, as these conditions are most amenable to therapy. The history and physical exam will be helpful in some cases, but in many critically ill patients history and physical findings can be difficult to interpret.

The ready availability of bedside ultrasonography has made determination of postrenal failure due to urinary tract obstruction the simplest of these diagnoses to make. All patients with AKI should have a renal sonogram performed within 12 h of onset of AKI, and in patients where the index of suspicion for obstruction is high, the sonogram should be obtained immediately. Delay in relief of urinary tract obstruction risks permanent renal injury. Similarly, prompt determination of renal tubular function indices such as the fractional excretion of sodium (FE_{Na}) or urea (FE_{UN}) can also be helpful in differentiating pre-renal from intrinsic AKI (see below). When history, physical examination, renal sonography, and renal tubular function indices suggest pre-renal AKI, attention can be turned to measures designed to increase renal perfusion. In general, the child with pre-renal AKI is not likely to benefit from the use of diuretics which may result in further renal damage. When signs and indices point to intrinsic AKI, attention should be turned to conservative management strategies (e.g., dietary and fluid restriction, adjustment of drug doses, etc.) in which judicious use of diuretics can be helpful while plans are made for possible renal replacement therapy (RRT).

Fractional Excretion of Sodium (FE_{Na})

FE_{Na} is easily calculated from a random urine sample. In cases of pre-renal AKI due to hypovolemia, most sodium should be reabsorbed in the proximal tubule and thus the FE_{Na} should be less than 1%. If the tubules are damaged as seen in acute tubular necrosis, the FE_{Na} is often in the range of 2–3% [56, 57]. The FE_{Na} can be calculated as follows [58]:

$$\mathrm{Fe_{Na}}(\%) = \frac{\text{Quantity of } \mathrm{Na^+} \text{excreted}}{\text{Quantity of } \mathrm{Na^+} \text{filtered}} \times 100$$

$$\mathrm{FE_{Na}}(\%) = \frac{\mathrm{U_{Na}} \times \mathrm{V}}{\mathrm{P_{Na}} \times \left(\mathrm{Ucr} \times \frac{\mathrm{V}}{\mathrm{Pcr}} \right)} \times 100$$

$$= \frac{\mathrm{U_{Na}} \times \mathrm{Pcr}}{\mathrm{P_{Na}} \times \mathrm{Ucr}} \times 100$$

where, the amount of Na excreted is equal to the product of urine concentration of Na (U_{Na}) and urine volume (V); the amount of Na filtered is equal to the product of the plasma concentration of Na (P_{Na}) and the glomerular filtration rate(Ucr × V/Pcr).

FE_{Na} can be less than 1% in conditions other than hypovolemia such as congestive heart failure, nephrotic syndrome or cirrhosis [56]. It can also be less than 1% in contrast nephropathy or heme pigment nephropathy [56].

Urine sodium and FE_{Na} are unreliable if diuretics are given. If measured, urine should be collected based on the half-life of the diuretics administered. For example, in the case of furosemide, the urine sample should be taken at least 6 h after the most recent dose. Caution should

also be exercised in the neonatal population when using this ratio. FE_{Na} is appropriately elevated in newborns making the transition from intra- to extra-uterine life. This ratio is even less reliable in those infants born preterm.

Fractional Excretion of Urea (FE_{UN})

Due to the limited value of the FE_{Na} in circumstances where diuretics have been administered, the concept of measuring fractional excretion of urea (FE_{UN}) has been proposed. In states of clinical dehydration, the urinary excretion of urea should also decrease [59]. The FE_{UN} should be less than 35% in hypovolemic states of prerenal AKI while in the case of ATN it should be above 50%. A hospital based prospective study conducted comparative analysis of FE_{Na} and FE_{UN} in their respective abilities to differentiate between prerenal AKI and acute tubular necrosis in the presence of diuretics [60]. In this study, FE_{UN} (<35%) had a better sensitivity and specificity (85% and 92%, respectively) in differentiating AKI due to pre-renal causes vs. ATN particularly where diuretics were employed. More importantly, a high positive predictive value of 98% was noted for the FE_{UN}. Studies evaluating FE_{UN} in children with AKI are limited.

Newer Biomarkers of AKI

Serum creatinine concentration, while an easily measured biomarker of AKI, is relatively insensitive, since a rise in creatinine signifies that damage has already occurred. Recent identification of a series of novel, increasingly specific and sensitive biomarkers has sparked renewed interest in the early diagnosis and management of AKI. The principal utility of these markers is to detect early signs of injury that could lead the clinician to alter management in order to prevent further damage to the kidneys. Early markers may also serve to predict severity of injury and help in monitoring the effect of an intervention. An excellent review of biomarkers in AKI has been recently published [61].

Biomarkers should ideally be noninvasive, reproducible, accurate, reliable, and have a high predictive ability (specific and sensitive). They should also be easy to perform, relatively inexpensive, and the results rapidly available. Several AKI biomarkers currently being evaluated will be discussed briefly.

Cystatin C

Cystatin C is a cysteine protease inhibitor that unlike serum creatinine is freely filtered, completely reabsorbed and catabolyzed by the tubular epithelial cells, and not secreted. It is stable and not influenced by body mass, gender, or age. More interestingly, its measurement is simple, automated, and easily available [62]. One prospective study in an adult population at risk for AKI showed that an increase of 50% in serum cystatin C level predicted AKI 1–2 days prior to a rise in serum creatinine [63]. Another study demonstrated that cystatin C had a better correlation with GFR than serum creatinine in critically ill adults [64]. Cystatin C levels were also able to predict the need for renal replacement therapy but could not differentiate among various causes of AKI. Cystatin C measurement has also been useful in kidney transplantation [65]. Cystatin C has also been demonstrated to correlate with AKI in children suffering from malaria [66]. So far, no prospective study of the value of cystatin C in predicting AKI in children has been published.

Kidney Injury Molecule (KIM-1)

KIM-1 is a transmembrane receptor that undergoes cleavage and is found in urine following ischemic injury [67]. In a small study, KIM-1 was able to differentiate ischemic renal injury from prerenal causes and chronic kidney disease [67]. To date, no large study has validated the predictive value of KIM-1 in AKI in adults. KIM-1 is also undergoing analysis and evaluation for its usefulness as a predictive tool for AKI in children.

Neutrophil Gelatinase–Associated Lipocalin (NGAL)

NGAL is a protein bound to gelatinase first described in neutrophils [68]. Circulating NGAL is normally reabsorbed at the level of the proximal tubule. Following ischemia, NGAL is secreted in the thick ascending limb and is found in the urine. A study in 71 children undergoing cardiopulmonary bypass surgery measured urinary NGAL 2 h post surgery [69]. Twenty children had an increase in urinary NGAL that preceded a rise in serum creatinine by 2–4 days. The specificity and sensitivity were excellent at 98 % and 100%, respectively. NGAL has been shown to be useful as a predictor of AKI in patients with HUS [70]. However, NGAL may be increased in patients with infections, limiting its value in diagnosing early AKI in septic patients. Urinary NGAL measurement has recently become commercially available.

Interleukin-18 (IL-18)

IL-18 is a pro-inflammatory cytokine cleaved to the mature form by caspase-1 and found in the urine following ischemia [71]. Many studies have observed an increase in urinary IL-18 that predicts an increase in serum creatinine in diverse patient populations [72–74]. It has also been used to differentiate among the diverse causes of AKI [72]. When combined with NGAL, IL-18 predicted the duration of AKI in children following cardiac surgery [69]. A commercial assay is available.

Other Biomarkers

Other markers such as sodium/hydrogen exchanger isoform 3 (NHE3), N-acetyl-β-glucosaminidase (NAG), and matrix metalloproteinase 9 (MMP-9) may be useful in early detection of AKI, but to date assays are not easily performed nor is there enough preliminary data to support their clinical use [67, 75].

Utility of Biomarkers of AKI

The value of these biomarkers in predicting AKI is under intense study. While urinary IL-18 and NGAL are good predictors of AKI in many clinical settings, in situations of complex pediatric patients their value may be diminished. Serum cystatin C measurement is promising, but large prospective studies in patient populations with complex diseases need to be performed before its utility can be fully established. Before these markers make a significant impact on clinical management in pediatric patients developing AKI, there is a need for simple, accurate, inexpensive, and rapid methods of measuring them. Additionally, prospective studies in diverse pediatric patient groups developing AKI are required.

Imaging the Kidneys in AKI

Renal Ultrasonography

Renal ultrasonography remains the renal imaging modality of choice for pediatric patients with newly diagnosed or worsening AKI. Resolution of anatomic detail by ultrasound (US) is generally excellent and avoids exposure to contrast agents or radiation. However, the US assessment of renal function is limited. In AKI, its primary role is to initially identify postrenal causes of AKI by demonstrating hydronephrosis [76–78]. Ultrasound abnormalities may not be appreciated in cases of prerenal AKI, but intrinsic AKI can be appreciated by a variety of anatomic changes. Measurement of renal size may give an indication of the chronicity of renal failure. Enlarged kidneys (standardized to patient's age and size) are suggestive of AKI due to medical renal diseases, such as acute interstitial nephritis, renal vein thrombosis, or infectious processes. Chronic kidney disease is suggested by the presence of small (for age/size) kidneys. An increase in echogenicity/echotexture may indicate chronic kidney disease in older children [79] but can be misleading in neonates [80].

Since blood flow to the kidneys is reduced but not eliminated in most cases of AKI, Doppler flow scanning may allow detection of abnormal or low renal blood flow states that can be indicative of renal artery stenosis or thrombosis [81, 82].

Nuclear Medicine Imaging in AKI

Radionuclide imaging can be employed to assess tubular function and blood flow [83] in AKI. However, significant delays in nuclide excretion by tubules can occur in both prerenal and intrinsic renal AKI, limiting its usefulness, unless blood flow is completely absent [84].

Computed Tomography (CT) in AKI

Computed tomography offers advantages when US is limited by technical issues. It is also valuable in trauma assessment when kidneys are involved [85, 86]. Non-contrast CT scans are valuable in demonstrating the renal pelvis and proximal ureter using sequential transverse sections to identify sites of ureteral obstruction. CT can also help identify primary causes of obstruction such as stones, tumors, or congenital abnormalities. Residual renal function may be identified using contrast-enhanced CT scans. In this setting, the pattern of a delayed and prolonged nephrogram may be demonstrated [87]. While technically useful, the risk of contrast nephropathy limits its usefulness as does the need for anesthesia in children for adequate studies.

Magnetic Resonance Imaging (MRI) in AKI

In recent years, magnetic resonance urography (MRU) has provided a significant advance in assessment of pediatric renal disease and AKI [87, 88]. MRU can identify collecting system morphology regardless of excretory function. It has also been utilized to effectively identify causes of postrenal AKI in terms of obstruction with a high sensitivity and specificity [89]. While both static and dynamic (gadolinium-enhanced) techniques are utilized in MRU evaluation [90], the use of gadolinium is contraindicated in patients with diminished renal function (eGFR < 30 mL/min/1.73 m^2) due to the risk of nephrogenic systemic fibrosis [91].

Renal Biopsy in AKI

Renal biopsy is considered the "gold standard" for diagnosing the underlying cause of AKI. This is especially true in pediatric patients where both prerenal and post renal causes of AKI have been excluded. Practically speaking, the benefits and risks of renal biopsy need to be carefully considered [92]. Risks include: infection, bleeding/transfusion, loss of kidney, inadequate sampling, and any anesthetic risks, depending on whether conscious sedation or general anesthesia is used. This is especially true in critical care situations where patients are already at increased risk for bleeding complications. Renal biopsy should be considered in situations where the underlying pattern of disease, in terms of history, biochemical, and imaging studies, is unclear, and the biopsy may shed light on the potential therapeutic options available. This is especially critical in the case of pediatric patients with the clinical presentation of rapidly progressive glomerulonephritis. Early diagnosis and appropriate intervention in this renal medical emergency may prevent progression from AKI to chronic kidney disease. Another important group to consider is pediatric renal transplant patients with AKI. Early biopsy diagnosis of acute rejection may direct therapeutic intervention and therefore prevent further decline in renal function [93–99].

Despite increased efforts to recognize and prevent AKI, progression to acute renal failure and loss (pRIFLE levels F and L) continues to occur with alarming frequency. The treatment of critically ill and injured children requires ready availability of renal replacement therapy (RRT) adaptable for use in children of all ages and sizes. In the following segments of this chapter, we review the three RRT modalities commonly used in pediatric patients with AKI: acute peritoneal dialysis, acute hemodialysis, and continuous renal replacement therapy.

Acute Peritoneal Dialysis

Acute peritoneal dialysis is still the modality of choice in many countries, especially in the developing world [100–102] as it is a relatively cheap form of dialysis which does not require sophisticated technical expertise or equipment. There is no necessity for highly trained dialysis or intensive care nurses to perform the procedure. Another of its major advantages over the filter-dependent procedures is that it avoids the need for vascular access, which can be a problem in infants and small children with multiple intravenous access for fluids and inotropes. It also avoids the need for blood priming in a child who is hemodynamically unstable, and large volumes of fluid can be removed slowly over a prolonged period, maintaining hemodynamic stability. Together with gradual correction of acid–base and electrolyte abnormalities, it is not associated with dialysis disequilibrium due to the relatively slower solute clearance, including nitrogenous waste products. Another advantage of acute peritoneal dialysis is the provision of calories with the use of hypertonic glucose solutions. This is important in the critically ill child where intravenous access for nutrition and maintenance of glycemia is also a problem. Moreover, in the coagulopathic child, anticoagulation can be avoided.

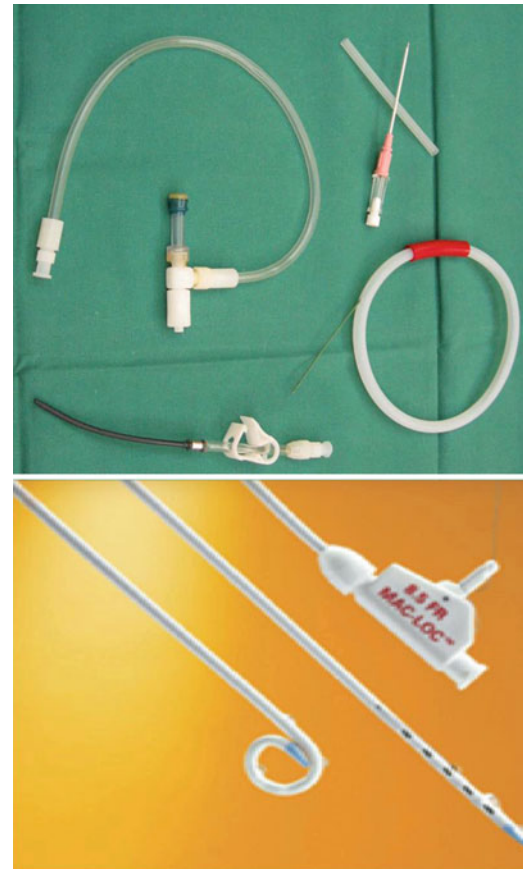

Fig. 37.2 (**a**) Peritoneal dialysis catheter using Seldinger technique for insertion. (**b**) Cook Mac-Loc Multipurpose Drainage catheter (CMMDC)

Acute Peritoneal Dialysis Catheters

Traditionally, acute peritoneal dialysis has been performed using semi-rigid stylet catheters requiring a trochar and canula method of insertion, the main advantage of which is the ease of insertion by the pediatric nephrologist without surgical intervention and general anesthesia [103]. However, this carries a high risk of perforation of viscus, especially in neonates, both at the time of insertion and with increasing dialysis duration. In order to minimize the risk of bowel perforation, infusing 10–20 mL/kg normal saline to create ascites prior to catheter insertion is useful. The incidence of peritonitis is highest with the semi-rigid catheter, particularly if it has been kept in place for longer than 72 h [103].

The newer techniques are performed with soft catheters where a Seldinger technique is utilized to insert the catheter over a guide-wire (Fig. 37.2a). This is a very useful technique, especially in infancy as it carries a minimal risk of dialysate leakage since no incision is required for the catheter insertion. Consequently, the risk of peritonitis is less and these catheters can be kept for up to 5 days without any complications [104]. Recently, another catheter, the Cook Mac-Loc Multipurpose Drainage catheter (CMMDC) (Fig. 37.2b) has been shown to be useful in infants and children, with a longer complication-free period, similar to surgically placed Tenckhoff catheter [105]. In low birth weight infants less than 1.5 kg where the length of these catheters may be excessive, a 14-gauge intravenous plastic cannula can be used as a dialysis catheter.

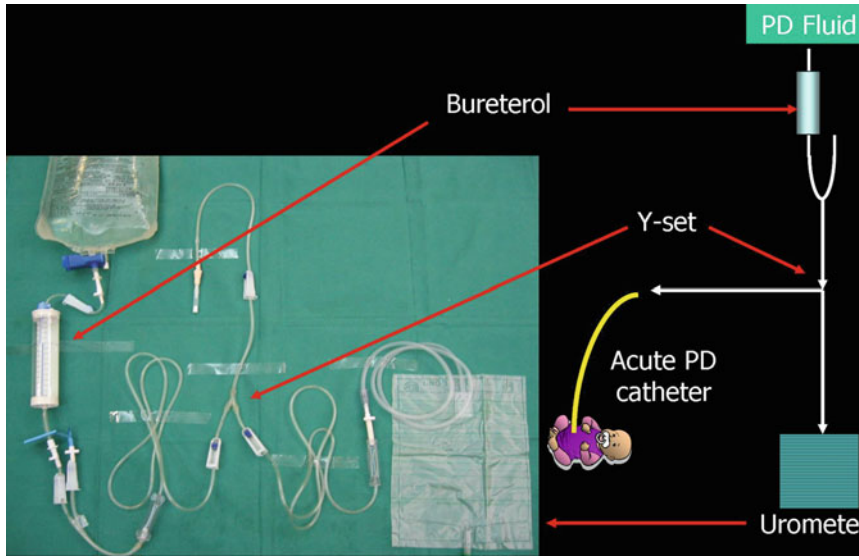

Fig. 37.3 Manual peritoneal dialysis setup for infants and young children

In high risk patients, especially those with bowel dilatation, direct surgical insertion using a single cuffed catheter to avoid perforation is safer. In fact, many cardiovascular surgeons prophylactically place a Tenckhoff catheter during cardiac surgery in infants. Some units use tunneled double cuffed permanent Tenckhoff catheters, since a good immediately functioning catheter with adequate drainage is almost assured. The main disadvantage of tunneled cuffed permanent catheters is the limitation of dialysate fill volumes in the initial week post-catheter insertion in order to avoid leakage [104]. These soft catheters pose a minimal risk to perforation of bowel or other intraperitoneal structures, and have a lower risk of peritonitis. In addition, if automated cyclers are used for the dialysis procedure, these catheters are preferable as they are associated with less technical malfunction resulting in machine alarms.

Technique of Acute Peritoneal Dialysis

Peritoneal dialysis is usually carried out manually in premature babies and small infants. Because of the small dialysate volumes involved, use of automated volumetric cyclers is often not possible due to the excessive "dead space" in the cycler tubings, resulting in poor drainage. The manual dialysis setup involves a Buretrol device, which is basically a sterile graduated cylinder, to which the dialysate bag is attached to one end, while the other end is connected to the patient's peritoneal catheter via a Y-set (Fig. 37.3). The other limb of the Y-set is connected to the drainage line, which drains into a graduated drain such as a urometer, so that the effluent volume can be accurately measured. This is very important in young infants in order to monitor the ultrafiltration closely so as to prevent fluid overload. Preassembled manual exchange systems for infants are available worldwide, but may be expensive in developing countries.

The availability of automated cyclers (Fig. 37.4) that can deliver small exchange volumes of less than 100 mL has largely supplanted the manual acute procedures in young children and infants, limiting nursing effort and repeated opening of the catheter. These cyclers automatically deliver the fill volume, which is the amount of fluid delivered to the peritoneal cavity during each dialysis cycle. After an appropriate dwell time that has been programmed into the cycler, the drain phase occurs, and the ultrafiltrate volume is computed from the difference between the

Fig. 37.4 Automated cyclers for peritoneal dialysis

drain and fill volumes at each cycle. The movement of fluid in and out of the patient is mediated either by gravity or a pump-driven system, or a combination of the two, with accurate delivery of the fill volume and measurement of drainage and ultrafiltrate volume. Another advantage of automated cyclers is the heater platform for warming the peritoneal dialysis solution before inflow into the abdomen, to prevent discomfort and promote solute transport.

Acute Peritoneal Dialysis Prescription

The dialysis prescription for acute peritoneal dialysis comprises four major components, the exchange volume, dialysate composition, individual cycle time consisting of fill, dwell, and drain, and total length of the dialysis session. For acute peritoneal dialysis, the target exchange fill volume for adequate dialysis in terms of fluid and solute clearance, without the risk of leakage, is 30 mL/kg. However, smaller initial volumes of 10 mL/kg should be used for at least 24–48 h, if there is a risk of leakage, for example if the incision is too wide or a tunneled cuffed catheter is used.

In manual dialysis, the inflow time, which is the time taken for the dialysate fill volume to flow into the peritoneal cavity by gravity, is about 10–15 min. This may be influenced by the height of the dialysate bag above the abdomen, the inflow volume and inflow resistance, such as kinking of the catheter. In automated peritoneal dialysis, dialysate is pumped into the abdomen with an inflow time of about 5 min. The dwell time is the time from the end of inflow to the beginning of the drain and should be at least 30 min, where the gradient for solute and fluid removal is optimal [106, 107]. This is followed by the drain period, which usually takes about 20–30 min. In manual dialysis, the drain occurs entirely by gravity, and therefore the drain time and volume is dependent on the vertical distance of the urometer below the abdomen. If the intraperitoneal fluid reservoir is too low, drainage may also be poor, hence increasing the fill volume may be indicated. It is important to ensure complete drainage, that is, the drain volume should exceed the fill volume, so as not to aggravate the fluid overload state and respiratory compromise, especially in infants with acute kidney injury.

Table 37.4 Peritoneal dialysis fluid composition

Content	Lactate-based (mmol/L)	Bicarbonate-based (mmol/L)
Dextrose	1.5% 2.5% 4.25%	0.0% 1.5% 2.5% 4.25%
Sodium	132	140
Chloride	96	110
Bicarbonate	0	35
Calcium	1.8	1.8
Lactate	40	0
Potassium	0	0
Magnesium	0.75	0.75

To stabilize the patient, hourly exchanges for 48–72 h are usually required, to remove the accumulated solutes and excess fluids. Subsequently, if the patient requires maintenance dialysis, the dwell times can be extended, similar to chronic peritoneal dialysis, with increasing volumes up to 40–45 mL/kg if cuffed catheters have been used. The peritoneal dialysis should be continued until the urine output improves, indicating recovering renal function.

Commercially available peritoneal dialysis solutions are usually dextrose-based, in concentrations of 1.5%, 2.5%, and 4.25% (Table 37.4). The initial dialysate composition to ensure adequate ultrafiltration is with 2.5% dextrose. In neonates where there may be a problem with hyperglycemia, it may be more appropriate to use an intermediate composition of 2.0% by mixing equal volumes of 1.5% with 2.5% dextrose infused through two Buretrols connected via the Y-set. Higher dextrose concentrations can be substituted depending on the amount of ultrafiltration needed, and the patient's hemodynamic parameters. As the standard peritoneal dialysis solutions are lactate-based, this may be a problem in patients with hepatic dysfunction and hemodynamic instability with lactic acidosis. Hence bicarbonate-based solutions which are available commercially can be used in place of the lactate-based solutions (Table 37.4), with addition of the appropriate amount of dextrose, if necessary, to obtain the desired concentration.

Following insertion of the acute peritoneal catheter, heparin should be added to the dialysate solution to prevent catheter blockage by fibrin clot. The initial dose of heparin should be 250 U/L dialysate. If the drain outflow is heavily blood-stained, this can be increased to a maximum of 1,000 U/L dialysate. The heparin is not absorbed systemically, and will therefore not be a problem in coagulopathic patients. If the patient is not on systemic antibiotics, intraperitoneal antibiotics such as cefazolin should be added prophylactically to cover for gram positive skin commensals. As patients on continuous peritoneal dialysis are at risk of developing hypokalemia, potassium should preferably be added to the intravenous fluid regimen if they are not feeding, rather than to the dialysate to avoid frequent bag changes due to changing orders. Potassium can be added to the dialysate, if the hypokalemia is severe enough such that the maximum safe concentration of potassium infusion will be exceeded.

Problems of Acute Peritoneal Dialysis

Although acute peritoneal dialysis has certain advantages over filter-dependent procedures, there are several problems that make this technique difficult especially in the small infant. Firstly, catheter problems are common such as catheter leakage into the subcutaneous tissue and hernia sites especially inguinal. Often the presence of a congenital diaphragmatic "hole" results in problematic pleural effusion. In fact, patients after cardiothoracic surgery may have a diaphragmatic pleuroperitoneal communication which results in a large pleural effusion once peritoneal dialysis is initiated. Drainage is often poor because of catheter malposition, kinking, omental wrapping, and fibrin clot. This is especially true for the relatively small bore non-cuffed peritoneal catheters in infants. Inadequate drainage may also be due to constipation. Patients may require bowel cathartics to try to improve drainage, and sometimes, even manipulation of the catheter position may be required. If a fibrin clot is suspected, flushing with heparin and in recalcitrant cases,

fibrinolytic agents such as urokinase, may be useful. Bowel perforation is a serious problem particularly with use of semi-rigid catheters, and is suspected when the peritoneal effluent is contaminated with feces or is blood-stained. Severe abdominal pain and shock may occur, and the catheter has to be removed, with bowel repair and treatment of sepsis.

Poor ultrafiltration is another concern, especially in critically ill infants due to the low fill volume with inadequate fluid reservoir intraperitoneally. Often it is not possible to increase the dwell to the desired volume, as many of these critically ill infants have acute respiratory distress syndrome, and the peritoneal fluid volume results in splinting of the diaphragm. In fact, during the inflow phase, these infants often desaturate, and require increase in the ventilatory pressures. As a result, there is poor ultrafiltration, which aggravates the fluid retention, worsening the respiratory distress. These ill patients are often hypotensive requiring multiple inotropic support. The resultant decrease in bowel perfusion due to vasoconstriction of the mesenteric vessels also contributes to the poor ultrafiltration. Additionally, there is a decrease in the osmotic gradient, because of increased absorption of glucose from the dialysate in this age group, resulting in poor ultrafiltration. There is an increased risk of peritonitis with the use of non-cuffed catheters, especially if there is leakage around the exit site. With the use of higher dialysate dextrose concentrations, hyperglycemia can be a problem, and may require insulin administration. In the severely ill child, lactic acidosis may be difficult to control due to the slower solute clearance, and may be aggravated by the lactate in the dialysate.

The slow and not very efficient removal of all types of molecules in acute peritoneal dialysis, as well as the unreliable ultrafiltration represents a considerable drawback compared to other modalities of acute dialysis especially the continuous venovenous hemodiafiltration. In fact, these problems are magnified in the young infants, especially neonates due to the small dialysate volumes involved. Hence acute peritoneal dialysis may not provide adequate clearances in the hypercatabolic patient with severe hyperkalemia, hyperphosphatemia, or inborn errors of metabolism such as hyperammonemia or organic acidemias. Therefore acute peritoneal dialysis is currently best for "uncomplicated" or medical causes of acute renal failure such as glomerular diseases, drug-induced acute tubular necrosis, ischemic acute tubular necrosis if hemodynamically stable, hemolytic-uremic syndrome, infections such as leptospirosis, and snake bites. On the other hand, absolute contraindications to peritoneal dialysis include recent abdominal surgery and necrotizing enterocolitis, common causes of acute kidney injury in neonates and infants, as well as the presence of a ventriculo-peritoneal shunt, because of the high risk of peritonitis.

Optimal Dosing in Acute Peritoneal Dialysis

The clearance of small solutes is lower with acute peritoneal dialysis over 24 h, than with a 4-hour hemodialysis session [108]. Thus the question often arises as to whether dialysis adequacy can be improved in prescribing acute peritoneal dialysis. It is increasingly recognized that the delivered dose of dialysis influences patient outcomes in acute renal failure [109–111]. In uremia, the goal therefore is to aim for maximum possible clearance to compensate for catabolic stress, utilizing continuous peritoneal exchange. As fluid overload is often the critical problem in premature infants and neonates, achieving adequate ultrafiltration reliably is also important. The obstacles to achieving this target using the conventional method of acute intermittent peritoneal dialysis include relatively poor solute clearance due to limitations in dwell volume and intermittent nature of the dwell, and the unpredictable ultrafiltration rate due to technical problems with drainage, associated hypotension requiring multiple inotropic support and increased intra-abdominal pressure. Therefore methods to increase dialysis adequacy include chronic equilibrated peritoneal dialysis, high-volume peritoneal dialysis, tidal peritoneal dialysis, and continuous flow peritoneal dialysis (Fig. 37.5) [112].

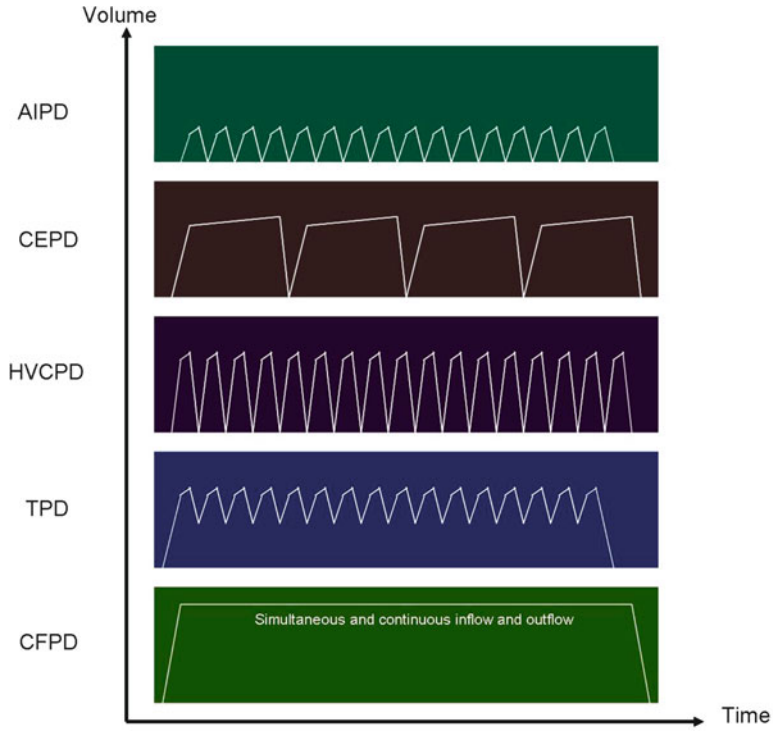

Fig. 37.5 Techniques of acute peritoneal dialysis. *AIPD* acute intermittent peritoneal dialysis. *CEPD* chronic equilibrated peritoneal dialysis. *TPD* tidal peritoneal dialysis. *HVPD* high-volume peritoneal dialysis. *CFPD* continuous flow peritoneal dialysis

Continuous Equilibrated Peritoneal Dialysis

Continuous equilibrated peritoneal dialysis is similar to continuous ambulatory peritoneal dialysis, in that it requires a larger fill volume than normally used for acute intermittent peritoneal dialysis, approximately 40–45 mL/kg or 1,200 mL/m^2, with long dwells of 2–6 h. The clearance of small molecules will probably be similar to acute intermittent peritoneal dialysis, however middle molecule clearance is possibly higher due to the long dwells.

High-Volume Continuous Peritoneal Dialysis

High-volume continuous peritoneal dialysis has been shown to provide a dialysis dose approaching that of high dose continuous renal replacement therapies or daily hemodialysis in adults. This modality of dialysis is designed to achieve high small solute clearances, and in adults involve a fill volume of 2 L, with very frequent exchanges between 18 and 24 exchanges over a 24-hour period. It is carried out through a Tenckhoff catheter, using an automated peritoneal dialysis cycler, with a prescribed Kt/Vurea of at least 0.65 per session. Studies on high-volume continuous peritoneal dialysis have demonstrated a delivered Kt/Vurea per session of approximately 0.55, and a weekly Kt/Vurea of greater than 3.0 [113]. Additionally, there was an increase in the solute reduction index over conventional acute peritoneal dialysis. Unfortunately, there is no satisfactory measure of dialysis adequacy in acute kidney injury [114]. The role of Kt/Vurea as an index of adequacy is controversial in the hypercatabolic patient with acute kidney injury, as the urea volume of distribution is variable, and exceeds total body water [115].

Tidal Peritoneal Dialysis

One method of increasing dialysis adequacy in mild-moderate hypercatabolic patients with acute kidney injury is to perform tidal peritoneal dialysis. Tidal peritoneal dialysis involves leaving a

Table 37.5 Comparison of peritoneal urea and creatinine clearances and ultrafiltration rates in continuous flow peritoneal dialysis

	Dialysate flow rate (mL/min)	Peritoneal urea clearance (mL/min)	Peritoneal creatinine clearance (mL/min)	Ultrafiltration rate (mL/min)
Raj et al. [20]: single lumen catheter with single needle device	141	26.5	24.1	3
Mineshima et al. [23]: double lumen catheter	100	14.1	No data	2.5
Cruz et al. [24]: 2 separate catheters	200	40	28	13.4
Freida et al. [25]: 2 separate catheters	100–150	21–36	13–33	2–8
Amerling et al. [26]: 2 separate catheters	200–300	25–75	No data	12–17

large volume of dialysis solution, at least 30% of the fill volume (15 mL/kg), in the peritoneal cavity throughout the dialysis session in order to optimize solute clearance. The tidal drain volume is replaced with fresh dialysate, which is the tidal fill volume. By increasing the number of tidal volumes, small solute clearance can be increased, and because of the longer duration of contact between dialysate and peritoneum, dialysis efficiency is improved further in terms of middle molecule clearance.

In a prospective cross-over study in adult patients with acute kidney injury, tidal peritoneal dialysis was able to produce higher solute clearances as shown by the clearance of creatinine, urea, potassium, and phosphate, at the expense of greater protein loss, compared to continuous low-dose equilibrating peritoneal dialysis [116]. Ultrafiltration was better in the patients receiving tidal dialysis, probably related in part to the lower dextrose absorption. With the smaller volumes required in children, tidal peritoneal dialysis is an attractive dialysis option in acute kidney injury, especially in patients who are unstable with filling and draining [117].

Continuous Flow Peritoneal Dialysis

Another novel method to improve peritoneal clearances is continuous flow peritoneal dialysis where the dialysate flow rate is increased tremendously, up to a range of 100–300 mL/min corrected for body surface area in a single pass, by synchronized inflow and outflow of sterile dialysate, or by recirculating a single large exchange through an external regenerating apparatus. Two catheters are required, one in the pelvis and one directed toward the diaphragm to achieve maximal port separation. Alternatively, an efficient dual lumen catheter with minimal intraperitoneal recirculation could be used. Kinetic studies have shown that increasing the dialysate flow rate in continuous flow peritoneal dialysis will increase peritoneal solute clearances. Higher urea clearances 2–5 times more than standard peritoneal dialysis, with peritoneal urea clearances approaching 25–60 mL/min as compared to 17 mL/min, as well as higher ultrafiltration rates of more than 10 mL/min have been achieved (Table 37.5) [118–123]. Unfortunately, it is also associated with massive protein losses.

Continuous flow peritoneal dialysis has been used to treat patients with hypercatabolic acute kidney injury, using the hemofiltration machines to deliver and even to regenerate the dialysate.

Acute Intermittent Hemodialysis

In many countries, intermittent hemodialysis is the mainstay of dialysis for acute kidney injury in older children, where it is performed in adult centers. Its main advantage is the rapid ultrafiltration and solute removal. It is therefore indicated in the emergency treatment of toxic poisonings such as lithium intoxication, severe electrolyte imbalance such as hyperkalemia, metabolic abnormalities such as hyperammonemia, tumor lysis syndrome, and acute fluid overload. In infants with severe hyperammonemia or children with lithium intoxication, hemodialysis results in rapid reduction of

the solute below toxic levels [124, 125]. Unfortunately, once hemodialysis is terminated, there is usually a rebound of the toxic solute in the serum, which can be detrimental. The patient is often continued on continuous venovenous hemodiafiltration to prevent this rebound, once the initial hemodialysis procedure is completed [125, 126].

Acute intermittent hemodialysis is suitable for hemodynamically stable patients who can tolerate rapid fluid shifts. This is a versatile modality as it allows for ultrafiltration without solute removal, as well as adjustment of the dialysate bath to treat electrolyte abnormalities such as hypernatremia. Moreover, because of the intermittent nature of the dialysis, even patients in the intensive care unit can be mobilized for other procedures. Systematic reviews in adult patients have shown that in hemodynamically stable patients, the continuous forms of renal replacement therapies do not appear to have a survival advantage over acute hemodialysis [127–129].

Vascular Access

The delivery of an adequate dialysis dose is crucial to the survival of patients with acute kidney injury, thus a good functional vascular access is an essential component for adequate renal replacement therapy. However in infants and children, vascular access may be a problem. For acute dialysis, vascular access is generally obtained through a double lumen hemodialysis catheter. This can be inserted either in the femoral, internal jugular, or subclavian veins. The former two access sites are preferred, as subclavian catheters have been associated with venous stenosis at the subclavian-internal jugular junction. In infants, the minimum catheter size for adequate blood flow is a 7-French double lumen, or 5-French single lumen where two catheters will be necessary (Table 37.6). It is preferable to use the jugular veins, as femoral access is often complicated by high intra-abdominal pressure. Alternatively, umbilical veins can be used for catheter access. Patient characteristics (coagulopathy, previous surgeries, altered local anatomy, cardiopulmonary reserve capacity), availability of insertion site in a "heavily catheterized" critically ill child, operator's skills and experience, and risk of complications may influence the choice of catheter placement. For example, a femoral vein placement is favorable for a patient on high-frequency oscillatory ventilation as this will be technically easier and has no risk of pneumothorax associated with internal jugular venous access. In patients with limited vascular access, a triple-lumen catheter is preferred if the size is appropriate. The hemodialysis catheters can be inserted at the bedside using the Seldinger technique, or by the interventional radiologists or surgeons in the case of tunneled permanent catheters.

Table 37.6 Appropriate size of hemodialysis catheters based on body weight. F: French size

Body weight (kg)	Single lumen	Double lumen (F)
Neonate	5 F	5.0–7.0
3–6		7.0
6–15		8.0
>15		9.0
15–30		10.0
>30		11.5

Dialyzers

The membrane properties of the dialyzer such as membrane thickness, pore size, and density affect dialysis efficiency, with varying clearances for small and middle molecular weight solutes. The total area of the dialyzer is important when choosing the appropriate size for the patient. Dialyzer surface area should approximate the size of the patient [130].

Another important property of the dialysis membrane is biocompatibility. Currently, two types of membranes are in use, cellulose-based and synthetic. Cellulose membranes can be broadly classified into unsubstituted such as cuprophan membranes and substituted such as cellulose acetate and cellulose diacetate. Cuprophan membranes have been reported to activate complement, accompanied by upregulation of neutrophil adhesion molecules and neutrophilic infiltration, resulting in dialysis-induced

renal injury [131–134]. However there is some controversy as to whether synthetic membranes such as the polysulfone membranes, are better than cellulose-based membranes. In earlier randomized controlled studies, adult patients with nonoliguric acute kidney injury who were using dialyzers with biocompatible membranes appeared to have better survival rates and renal recovery [135]. On the other hand, in three separate meta-analyses in adult patients with acute kidney injury, there is conflicting data as to whether synthetic membranes confer a survival benefit [136–139]. Current opinion is that the use of biocompatible synthetic membranes does not appear to confer any significant clinical advantage either in terms of mortality or recovery of renal function, except for the subgroup comparison with cuprophan membranes [138, 139].

Another consideration in the choice of dialyzers is the use of low or high flux membranes. High flux membranes have larger pores resulting in greater clearances of higher molecular weight solutes, and at the same time, carry the risk of back transport from the dialysate, of water-borne solute contaminants. In a systematic review comparing the use of high flux and low flux membranes in acute kidney injury in adults, there was no difference in the risk of mortality or dialysis dependence in survivors [139]. However, in another meta-analysis, there appeared to be a significant advantage in terms of recovery of renal function, with the use of high flux membranes [138].

High-cut-off-point membranes with a nominal cut-off point of 60 kD, have greater cytokine clearance and enhanced adsorption properties than conventional high flux dialyzers [140], and have been developed for use in septic patients with acute kidney injury [141, 142]. These membranes are made from polyamide/polyarylethersulfone, polysulfone, or cellulose triacetate. Treatment using high-cut-off-point membranes has been shown in animal models of sepsis to have beneficial effects on immune cell function and survival [143]. Preliminary clinical studies show that use of these membranes in adult patients with acute kidney injury was associated with decreased need for vasopressor therapy, with no reports of serious adverse effects [142].

Another important consideration is the use of the synthetic polyacrylonitrile (AN69) membranes which can lead to the bradykinin release syndrome [144]. Here the patient develops acute anaphylaxis associated with acute hypotension, tachycardia, and a drop in the central venous pressure. This is immediately reversible by removing the system, and can be avoided by avoiding priming with blood banked blood. Alternatively, the blood prime can be dialyzed against the bicarbonate dialysate for at least an hour prior to connection to the patient [145, 146].

Hemodialysis Prescription

All children should be dialysed using volume controlled machines and bicarbonate dialysate. Factors affecting the individual hemodialysis prescription include the extracorporeal circuit volume, the dialyzer size, blood flow rate, dialysate flow rate, ultrafiltration required, dialysate composition, anticoagulation, and length of sessions.

The total volume of the extracorporeal circuit includes the volume of the tubing, comprising both the arterial and venous lines, and the volume of the dialyzer, and should be less than 8% of the patient's blood volume calculated as 70 mL/kg for children, and 80 mL/kg for infants. If the extracorporeal blood volume exceeds 10–15% of the patient's total blood volume, a blood prime is recommended [147]. Depending on the hemodynamic status of the patient, the lines may still need to be primed with 0.9% saline or 5% albumin, even if this volume is not exceeded.

Blood flow rate depends on the size of the vascular access and is in the range of 5–7 mL/kg/min, up to a maximum of 300–400 mL/min [130]. Dialysate flow rate should be at least 1.5 times greater than the blood flow rate, in order to maximize diffusion gradients of solutes. Aim for urea clearances of 2–3 mL/kg/min; however, in order to avoid dialysis disequilibrium, urea clearances should be gradually increased over three sessions, starting at 30% of target. Ultrafiltration targets should not exceed 0.2 mL/kg/min. Other factors that must be considered are patient's ability to tolerate rapid fluid shifts, the need for vasoactive

Table 37.7 Heparinization protocol

Type of heparinization	Loading dose (U/kg)	Maintenance dose (U/kg/h)
Regular	50 (Adults: 1,500 U)	30–50 (Adults: 750 U/h)
Low-dose	>15 kg: 10–20, ≤15 kg: 5–10 (Adults: 1,000 U)	5–10 (Adults: 500 U/h)

substances to maintain blood pressure and total fluid removal goals.

Dialysate composition should be tailored based on the patient's current electrolyte status. Current hemodialysis machines use a sophisticated proportioning system to mix dialysate online from commercially available concentrates. The final concentrations of sodium, calcium, potassium, and bicarbonate can be changed according to the clinical situation.

Heparin is the most commonly used anticoagulant for intermittent hemodialysis. A loading dose of heparin may be given at the start of dialysis followed by a maintenance dose (Table 37.7). To monitor therapy, the activated partial thromboplastin time (aPTT) or activated clotting time (ACT) is used. The aPTT should be kept at 1.2–1.5 times the baseline, and the ACT between 120 and 180 s.

In coagulopathic patients, heparin-free dialysis can be performed by intermittently flushing the circuit with 0.9% saline. The filter pressure should be monitored, and dialyzer inspected for early clot formation. Unfortunately, this method not only adds to the ultrafiltration target, but also results in a decrease in the dialysis efficiency within the stipulated time period.

For patients with heparin-induced thrombocytopenia, low-molecular-weight heparins have been recommended [148]. Alternative anticoagulation protocols for patients with coagulopathies include regional anticoagulation of the circuit with a heparin-protamine protocol, regional citrate, thrombin antagonists such as hirudin and argatroban, and platelet inhibiting agents such as prostacyclin and nafamostat [149].

Problems of Acute Intermittent Hemodialysis

Hemodialysis in young children is notoriously difficult in view of the smaller blood volumes present. This problem is accentuated in the critically ill child, where inotropic support is usually required to support the systemic blood pressure. Moreover, these children often have acute respiratory distress syndrome and are hypoxemic, or they have other associated clinical problems such as congestive heart failure and cerebral edema. Therefore maintenance of an adequate blood pressure in these children is critical to alleviate tissue hypoxia.

Technical advances in the delivery of hemodialysis have dramatically reduced the propensity to cause intradialytic hypotension. The use of volume-controlled dialysis machines, biocompatible synthetic dialysis membranes, and bicarbonate-based dialysate have helped decrease the incidence of intradialytic hypotension. In adult studies, it has been demonstrated that priming the circuit with isotonic saline, discontinuing vasodilator therapy, keeping the dialysate sodium greater than 145 mmol/L and setting the dialysate temperature to below 37°C result in lesser hemodynamic instability and better outcomes [150]. Additionally, use of in-line hematocrit monitoring to minimize abrupt changes in extracellular volume is useful in young children with hemodynamic instability where large acute changes in extracellular volume are not well tolerated [151]. This method of performing intradialytic noninvasive blood volume monitoring provides an estimate of the postdialysis refilling rate (Fig. 37.6), which in turn reflects the status of the intravascular volume.

Rapid hemodialysis using dialyzers with larger surface areas, in patients with very high plasma urea concentrations may also result in the dialysis disequilibrium syndrome, characterized by neurological symptoms such as fatigue, headache, nausea, vomiting, altered consciousness, convulsions, and coma [152]. Measures to prevent the disequilibrium syndrome include decreasing the initial dialysis dose, increasing dialysate sodium concentration (143–146 mmol/L), and administration of osmotically active substances such as intravenous mannitol (0.5–1 g/kg) to prevent rapid osmolar shifts that can cause cerebral edema.

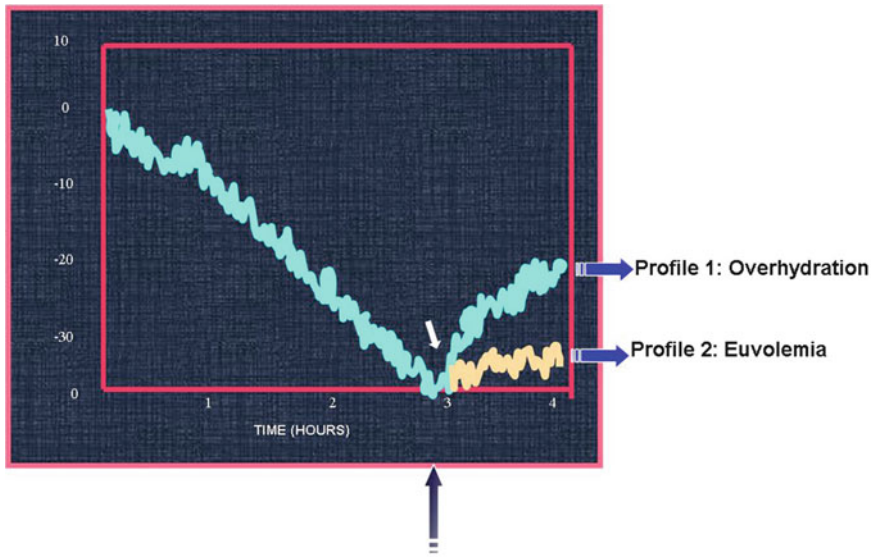

Fig. 37.6 Intradialytic noninvasive blood volume monitoring: pattern of post-dialysis refilling rate. Profile 1: overhydration. Profile 2: euvolemia

The smaller blood volumes in infants and young children place them at risk for blood loss due to clotting of the dialyzer. However, when compared to continuous renal replacement therapies, anticoagulation in intermittent hemodialysis is needed only for a limited period, or may be dispensed with altogether, whereas with continuous renal replacement therapy, there is a continuous struggle between filter coagulation and bleeding.

Infection of the catheter exit site is another potential complication in patients on hemodialysis. In the event of signs of infection such as fever, the appropriate cultures should be taken, and empiric antibiotics started.

Optimal Dosing in Acute Intermittent Hemodialysis

The prescription for acute intermittent hemodialysis comprises the dose delivered per session and the frequency of the sessions. Studies in adults have shown that in acute kidney injury, a Kt/Vurea greater than 1.2 was associated with improved survival in patients with intermediate severity of illness, but did not influence outcomes in the severely ill patients [153]. In an earlier study, daily hemodialysis was associated with a significant reduction in mortality, fewer hypotensive episodes during hemodialysis, and more rapid resolution of acute renal failure [154]. However, the delivered dialysis dose was low (Kt/Vurea of 0.94) in the patients who received intermittent dialysis, and could account for the worse outcome in this group. In contrast, the VA/NIH Acute Renal Failure Trial Network (ATN) Study did not demonstrate any difference in mortality when a more intensive dosing strategy was employed [155]. Based on these results, intermittent hemodialysis with a delivered Kt/Vurea of at least 1.2 per treatment, on alternate days, is probably sufficient for patients with acute kidney injury, unless there are indications for more intensive daily therapy, such as control of fluid volume or severe electrolyte abnormalities such as hyperkalemia or acidosis, in the smaller children.

Hybrid Therapies

A critically ill patient with severe hemodynamic instability cannot tolerate intermittent treatments carried out for 3–4 h a day and would require gentler dialysis for an extended period to improve efficiency. Since 1988, hybrid therapies which utilize the standard intermittent hemodialysis

machine technology, while providing the slower solute and fluid removal associated with continuous renal replacement therapies, have been developed for use in less stable adult patients with acute kidney injury [156, 157]. The terms for these modalities include sustained low-efficiency daily dialysis (SLEDD) or extended daily dialysis (EDD) or slow continuous dialysis (SCD) [158]. SLED is a slower dialytic modality that runs for prolonged periods using conventional dialysis machines with low blood pump speeds (200 mL/min or less) and dialysis flow rates (100–300 mL/min) for 6–12 h daily [159].

Variants such as sustained low-efficiency daily diafiltration (SLEDD-f), aimed at improving clearance of putative middle molecular inflammatory mediators of the systemic inflammatory response associated with sepsis have been developed for clinical use [160, 161]. Advantages of SLEDD-f over continuous venovenous hemodiafiltration include faster clearance of small solutes and fluid removal, whilst maintaining hemodynamic stability [162]. It allows flexible treatment schedules so that patients are accessible and can be mobilized for other medical treatments. The ability to use online production of fluid for filtrate replacement similar to the commercial hemofiltration solutions and depyrogenated saline in terms of microbial counts, endotoxin concentration, and cytokine-inducing activity, avoids the need for pre-packaged hemofiltration solutions [163, 164].

Hybrid therapies also have lesser heparin requirement and less frequent clotting. The reported incidence of clotting is 17–26% with heparin, while the reported incidence of circuit clotting without anticoagulation is 24–26% using single pass machines, and lower using batch systems [165]. This may be due to the difference in blood pump technology between the systems, with much greater leukocyte and platelet activation using the standard occlusive roller pump. Regional citrate anticoagulation in continuous venovenous hemodiafiltration is often associated with electrolyte abnormalities such as hypernatremia and metabolic alkalosis. Hybrid therapies, with the high diffusive capacity for solutes, are able to correct any alkalosis or hypernatremia, while at the same time remove the calcium chelated citrate complexes, an advantage in patients with liver failure [166].

With hybrid therapies, phosphate removal can be very extensive. Hypophosphatemia and metabolic alkalosis is easily induced in a critically ill patient, especially those on prolonged parenteral nutrition. In these instances, it may be prudent to incorporate phosphate in the dialysate solution at 0.1–0.2 mmol/kg, and reduce the dialysate bicarbonate concentration [167].

Current recommendations for hybrid therapies in adult patients state that treatment be provided at least three times per week with monitoring of the delivered dose to achieve a Kt/Vurea of at least 1.2 per treatment [167]. There is no evidence that more frequent treatment is associated with improved outcomes, unless necessitated by specific indications such as fluid overload, hyperkalemia, and hypercatabolism. In a study on adult patients comparing continuous venovenous hemofiltration with EDD, the urea reduction ratio was similar between the two groups [168]. This suggests that the effect of a 12-hour SLED is equivalent to 23 h of continuous renal replacement therapy. Many adult centers now perform nocturnal SLED so that patients may be available during the day for other diagnostic procedures, avoiding interruptions of therapy.

Continuous Renal Replacement Therapies

The most recent addition to available renal replacement therapies for the management of AKI in children is a family of continuous extracorporeal therapies now called CRRT (for continuous renal replacement therapy). This advance in the treatment of AKI offers several advantages over traditional dialysis methods when used in critically ill, unstable patients. Because CRRT is continuous, removal of solutes and modification of the volume and composition of the extracellular fluid occur gradually and evenly over time. Unstable patients who are often intolerant of the abrupt fluid volume and solute concentration changes that accompany standard hemodialysis treatments can usually be safely treated with

CRRT. The precision and stability with which fluid and electrolyte balance can be maintained using CRRT is unmatched by any currently available dialysis therapies, except perhaps one of the newer hybrid therapies discussed in the previous section. Even continuous peritoneal dialysis does not allow the control of fluid removal as can be done with CRRT, and only with CRRT can electrolytes or any formed elements of the circulation such as plasma proteins, platelets, or red blood cells be removed or added independently of changes in the volume status of the patient.

The inherent logic of the basic CRRT system is striking: a small "hemofilter" that is highly permeable to water and small solutes but impermeable to plasma proteins and the formed elements of the blood is placed in an extracorporeal circuit. As the blood perfuses the hemofilter an ultrafiltrate of plasma is removed in a manner analogous to glomerular filtration. The ultrafiltrate is concurrently replaced using a fluid with an electrolyte composition that is either similar to that of normal plasma or specifically designed to correct abnormal electrolyte concentrations in the individual patient. A portion of the ultrafiltrate can be replaced with total parenteral nutrition and other fluid therapies, and in patients with fluid overload, a portion simply is not replaced, resulting in predictable and controllable negative fluid balance.

The basic principles of CRRT are similar for adults and children. However, the application of these modalities in children requires attention to several important details unique to therapy in pediatric patients. For example, extracorporeal blood volume considerations and the need for blood circuit priming, the critical importance of nutritional support, and the use of CRRT to manage conditions unique to pediatric patients such as inborn errors of metabolism all demand a perspective different from that used to treat adult patients with CRRT. But by far the most demanding and often vexing considerations arising in pediatric CRRT are related to the need to adapt and downsize equipment and prescriptions designed for adult-size patients in order to meet the special needs of pediatric patients ranging in size and maturity from 2 kg premature neonates to 100+ kg adolescents.

Treatment with CRRT is now widely available in pediatric centers throughout the world, and in some has become the preferred method of renal replacement therapy (RRT). In this segment of Chap. 37, we review current approaches to CRRT in children, with attention to several unique aspects of pediatric CRRT that must be considered when managing the pediatric patient.

Historical Notes

The development of CRRT can be traced to the early days of maintenance hemodialysis. In the mid-1960s, Lee Henderson described a renal replacement therapy that relied solely on ultrafiltration, using membranes that were much more permeable to water and small solutes than the typical hemodialysis membranes [169]. The technique was first called "diafiltration," and later, more appropriately, "hemofiltration." Henderson showed that by pumping blood at high flow rates through an extracorporeal circuit containing a highly permeable filter, large volumes of an ultrafiltrate of plasma could be generated. This uremic fluid could be replaced concurrently with fluid that had an electrolyte composition similar to normal plasma, without the urea and other accumulated waste products. Thus, hemofiltration had many similarities with hemodialysis: both required vascular access, an extracorporeal circuit, a semipermeable membrane, and a blood pump. The difference lay in the manner in which solutes were primarily removed from the blood [170].

During any RRT in which a semipermeable membrane is used, there are two mechanisms that can be involved in the transfer of solutes: diffusion and convection. Diffusive transport is driven by solute concentration gradients that exist between blood and dialysate. Solute molecules are transferred across the membrane in the direction of lower solute concentration at a rate that is inversely proportional to molecular size and mildly influenced by molecular charge. Convective transport occurs when a solute molecule is swept through the membrane by a moving stream of ultrafiltrate, a process called "solvent drag." Convective transport is independent of

any solute concentration gradient that might be present; only the direction and force of transmembrane fluid flux are important determinants of convective transport (see also Chap. 2 (Biology of Dialysis).

During hemodialysis, solute movement across the dialysis membrane from blood to dialysate is primarily the result of diffusion, although a small amount of convective transport occurs as a result of ultrafiltration. During hemofiltration, since no dialysate is used, diffusive transport cannot occur, and solute transfer is entirely dependent on convective transport. The relative inefficiency with which small solutes are removed from the blood by convective transport when compared to diffusive transport is one of the most distinctive features of hemofiltration. For intermittent hemofiltration to serve as an alternative to the much more efficient intermittent hemodialysis, a very large volume of ultrafiltrate had to be generated and continuously and accurately replaced with a sterile, pyrogen-free and thus costly replacement fluid. As a result, intermittent hemofiltration never seriously challenged intermittent hemodialysis for preeminence as a chronic RRT [171].

The conceptualization of *continuous* hemofiltration as a treatment for acute renal failure was the contribution of a team of nephrologists in Gottingen, Germany led by Peter Kramer. In a brief German language report published in 1977, Kramer, who was familiar with the use of intermittent pumped hemofiltration in patients with acute or chronic renal failure, described a novel RRT used to treat fluid overload which he termed continuous arteriovenous hemofiltration (CAVH) [172]. In CAVH, catheters were placed in an artery and vein and were connected by relatively short, large-bore tubing to a hemofilter placed between them. An ultrafiltrate line leading from the hemofilter to a collection vessel completed the assembly. Relying solely on the cardiac function of the patient to pump blood though the hemofilter, the CAVH system was able to produce relatively large volumes of ultrafiltrate over time. An in-depth description of the circumstances that led pioneering nephrologists in Vincenza, Italy to first apply CAVH to a pediatric patient can be found in Chap. 38.

The simplicity of the CAVH system when used in children was appealing, but there were difficulties. Yet, despite the often low mean arterial pressures seen in critically ill infants and children, CAVH quickly found a place in pediatric intensive care units in North America and Europe [173–177]. Early problems with controlling ultrafiltration rates (UFR) from the surprisingly efficient adult-size hemofilters then available were addressed by using volumetric IV pumps attached to the ultrafiltrate line to regulate UFR. When it was recognized that the IV pumps were unreliable, adding downstream, weight-based urometers allowed individual titration of UFR to reflect pump performance. A better solution for infants was the development of small hemofilters (see Chap. 38).

In order to achieve predictable and more controllable ultrafiltration, and avoid the risks of long-term arterial cannulation, blood pump–driven CRRT systems were introduced in the early 1990s. Double-lumen central venous catheters could now be used as CRRT vascular access, thereby changing the name of the therapy to CVVH (continuous venovenous hemofiltration). The ongoing evolution of these technologies has resulted in more sensitive pumping systems that have increased the safety of CVVH in small patients. These and other developments have made CRRT a more attractive and viable option for critically ill children with AKI and metabolic disorders, such that CRRT is becoming the preferred method of acute therapy in many pediatric intensive care units [178].

Indications and Modality Options

In general, the indications for initiating CRRT in children and adults are similar and most often involve the treatment of AKI and fluid overload in a critically ill patient [179, 180]. CRRT can also be used to treat infants who have inborn errors of metabolism and can be readily combined with extracorporeal membrane oxygenation [181, 182]. Advantages and disadvantages of CRRT when compared with acute hemodialysis and peritoneal dialysis are summarized in Table 37.8.

Table 37.8 Comparative advantages and disadvantages of acute RRT therapies

Therapy	Advantages	Disadvantages
CRRT	Hemodynamic stability No disequilibrium syndrome Slow, gentle fluid and solute removal Increased solute removal ICU nurses can manage machines	Requires blood prime in small pts Requires vascular access Requires anticoagulation Requires patient immobilization Risks nutrient depletion Can worsen oligo-anuria Requires expensive machinery Unavailable in many emerging countries Difficult to use in tiny infants Relatively high cost
Acute HD	Rapid clearance of small solutes and toxins Rapid removal of large fluid volumes Immobilization limited to few hrs/day Widely available in developed countries	Requires blood prime in small pts Requires vascular access Requires anticoagulation Requires specialized nursing Requires expensive machinery Relatively high cost Difficult to use in tiny infants
Acute PD	Readily available throughout world No vascular access No anticoagulation required No disequilibrium syndrome Managed by ICU nurses Relatively low cost No complex machinery Can be used in tiny infants	Inefficient removal solutes, fluid Acute peritoneal access prone to leaks, obstruction Can cause respiratory compromise from abdominal distension

Because CRRT is continuous and can be conducted over days to weeks, overall solute clearance and fluid removal is easily superior to other modalities. However, this feature also has negative aspects, primarily the need to remain relatively immobilized while connected to the CRRT circuit for prolonged periods. As a result, small children typically require long-term sedation and occasionally even paralysis to prevent the small movements that can readily disrupt flow in the hypersensitive CRRT circuit.

CRRT is composed of and refers to a variety of modalities that primarily take advantage of one or both solute clearance mechanisms. In continuous venovenous hemofiltration (CVVH), blood flows through the hemofilter generating large volumes of ultrafiltrate which are replaced by introduction into the blood path of a physiologic "replacement fluid" either before (pre-dilution) or after (post-dilution) the hemofilter (see Fig. 37.7a). Clearance is thus exclusively convective. If instead of replacement fluid infused into the blood path a dialysate is infused into the hemofilter, clearance becomes primarily diffusive as in hemodialysis. Hence the name for this CRRT modality: continuous venovenous hemodialysis (CVVHD, Fig. 37.7b). When both replacement fluid and dialysate are used to combine both convective and diffusive clearances, the therapy is known as continuous venovenous hemodiafiltration (CVVHDF, Fig. 37.7c). The relative advantages of one CRRT modality over another have been debated inconclusively for a more than a decade, fueled in part in the US by the initial lack of an FDA-approved replacement fluid , leading some centers to avoid the convective therapies (CVVH and CVVHDF) altogether. Now that FDA-approved replacement fluids are readily available, proper comparative modality studies can be designed in centers offering all three modalities.

CRRT Machines

The choice of CRRT machinery for pediatric patients is based entirely on local practice and is often most influenced by cost and local experience, as well as the preferences of the adult CRRT

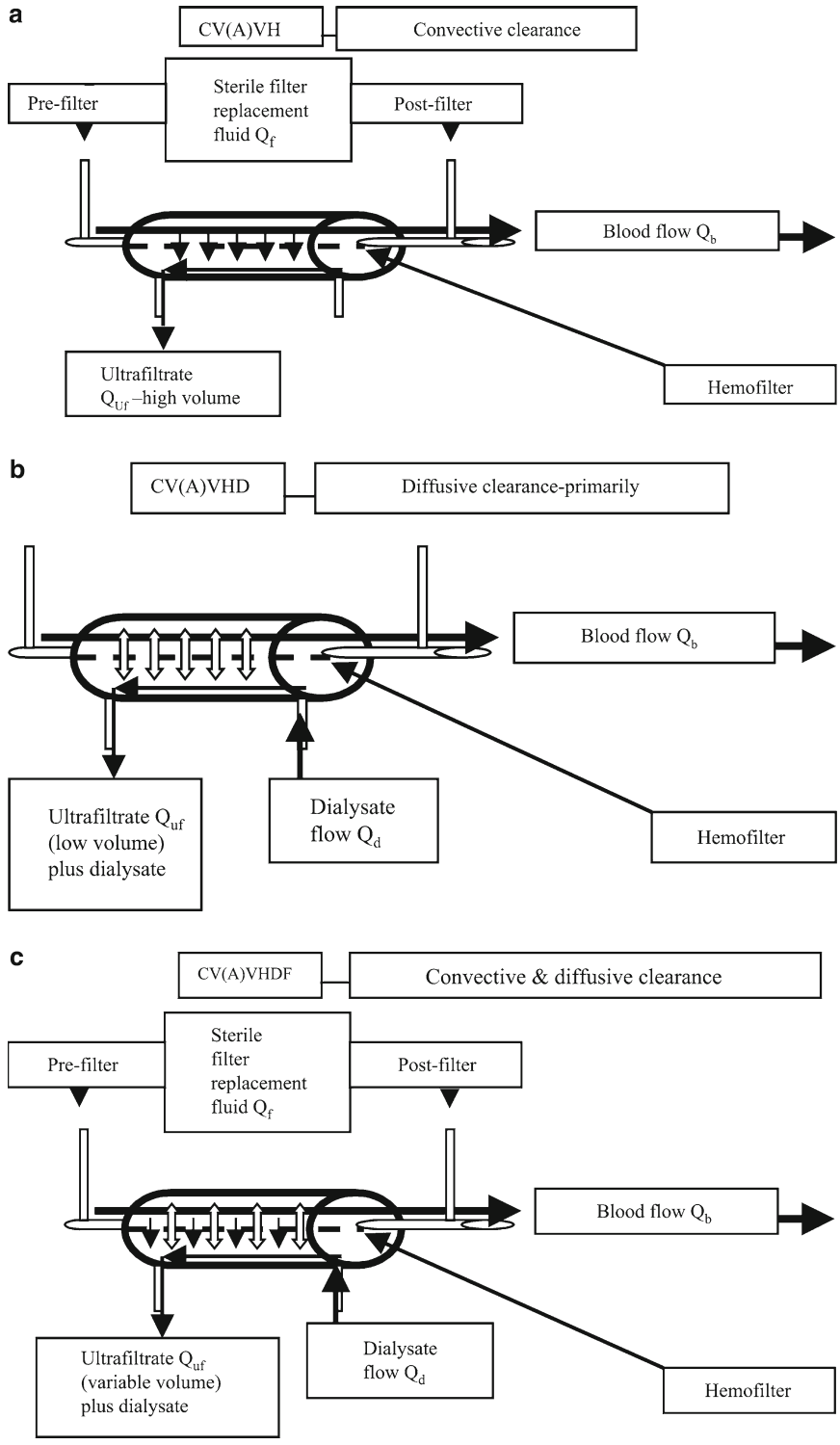

Fig. 37.7 (**a**) Diagram of a convective based (CVVH) continuous renal replacement therapy (Note use of either pre- or post-filter replacement fluid rather than dialysate). (**b**) Diagram of diffusion based (CVVHD) continuous renal replacement therapy (Note use of dialysate rather than replacement fluid. Dialysate flow is countercurrent to blood flow). (**c**) Diagram of combined convective and diffusive based (CVVHDF) continuous renal replacement therapies (Note use of both dialysate and replacement fluids)

program in settings where pediatric and adult facilities and services are combined. To date, no machine has been found superior for pediatric CRRT. In fact, no machines have been found to be particularly well suited for use in children. Fortunately, all have improved ultrafiltration controls and pumps that have reduced error rates to only a fraction of those seen in the early days of CAVH when IV pumps were used [183]. All offer blood path warming devices to minimize the risk of hypothermia and most can be run at the lower blood flow rates suitable for use in infants and small children. A detailed discussion of the various components and features of the available machines is beyond the scope of this chapter. Suffice it to say that there is no currently available optimal pediatric CRRT machine (see also Chap. 38).

Vascular Access

As with all extracorporeal therapies, the success of CRRT treatment is dependent on the quality of the vascular access. Adequate blood flow (Qb) is essential to providing optimal therapy with minimal interruption, reducing the likelihood of circuit loss due to clotting. In pediatric patients, the choice of vascular access catheter size and insertion site is critical. Table 37.6 contains a listing of available catheters suitable for use in children who are receiving either acute hemodialysis or CRRT.

In general, the right internal jugular insertion site with the tip of the double lumen catheter residing within the right atrium provides the best all around performance, especially in infants and small children. When the catheter tip resides within a central vein (e.g., the subclavian or superior or inferior vena cava) the catheter diameter can approach the diameter of the surrounding vessel. The collapse of the vessel wall against the catheter will occlude the side ports of the catheter's arterial limb causing rapid rise in access negative pressure and stoppage of flow. Femoral access can perform well and may be safer due to its relative ease of insertion. However, prolonged use often requires heavy sedation or even paralysis, as minimal flexing of the hip in an awake and moving patient will too easily crimp the catheter and result in a stoppage of flow. Many nephrologists prefer to avoid using the subclavian vein as some patients may not regain renal function and ultimately require an upper extremity arteriovenous fistula which functions poorly when there is stenosis of the subclavian vein due to its prior use for RRT (see Chap. 3(Demographics of Dialysis in Children) [Brandt chapter]).

Blood flow rates for CRRT are determined by the size of the child, the machine being used and the vascular access. Short, large bore catheters provide improved performance due to lower resistance to flow [184]. As with HD, longer, smaller bore catheters (e.g,. Broviac catheters, umbilical vessel catheters) are unsuitable for use in CRRT due to their high flow resistance.

Blood Flow Rates

With a well-functioning vascular access it is possible to adjust blood flow rate (Qb) to fit the size of the child and the clinical setting. As with pediatric HD, Qb can be prescribed initially based on body weight, but recommendations vary widely from 10 to 12 mL/kg-min in neonates to 2–4 mL/kg-min in adolescents. Higher Qb will support longer filter life by reducing the likelihood of filter fiber clotting. Higher Qb also facilitates increased patient fluid removal by providing greater filter plasma flow rates and reduces the loss of clearance efficiency from predilution mode CVVH or CVVHDF. However, not all patients will tolerate a higher Qb, especially at initiation of CRRT. In general, it is best to begin with caution and advance Qb to the targeted rate over the first 30 min as tolerated.

Solutions

As was seen in HD, the tolerability of CRRT has been greatly improved with the introduction of bicarbonate-based CRRT solutions. When solutions used lactate as the buffer, worsening lactic acidosis was common leading to hypotension and depression of cardiac function [185]. A series of comparative clinical trials of lactate- and bicarbonate-based CRRT fluids in adults [186, 187]

and children [188] have so clearly demonstrated the superiority of bicarbonate as a buffer in this setting that bicarbonate-based replacement fluid and dialysate is now the standard of care for CRRT.

Along with bicarbonate (and small amounts of lactate for stability), CRRT solutions also contain various amounts of sodium, potassium, chloride, glucose, calcium, phosphate, and magnesium. Bicarbonate-based, FDA-approved CRRT solutions are now available from several manufacturers in a dizzying array of electrolyte formulations. Most hospital pharmacies will stock only a single brand and in only a few formulations. There are clinical settings, however that call for different solutions. A key feature of CRRT, especially in small patients, is the tendency over time for the composition of the CRRT fluids to eventually determine the electrolyte composition of the patient. A fluid low in potassium, phosphorous, and magnesium may be appropriate at initiation of CRRT when concentrations of these electrolytes in AKI patients are often elevated. However, depending on the CRRT prescription, within a surprisingly short time the patient will become frankly deficient in these electrolytes which can complicate management. Thus while a "starter" fluid with reduced potassium, phosphorous, and magnesium is needed, a more physiologic fluid that adds back these electrolytes in physiologic concentrations should follow. Rather than stocking multiple formulations, some pharmacies may prefer to add potassium, phosphorous, magnesium, and even additional bicarbonate to the "starter" solutions as needed, a practice that may add risks associated with potential pharmacy errors and increase costs.

Calcium is always left out of solutions when phosphate is present ; in addition, calcium has usually but not always been left out of CRRT solutions used with citrate anticoagulation, as will be discussed below.

Hemofilter Membranes

A wide variety of hemofilter membranes have been developed for use with CRRT, none of which have been shown to be superior. However, the use of one highly biocompatible membrane, the AN-69 polyacrilonitrile membrane, has been associated in pediatric patients with the "bradykinen release phenomenon," characterized by a precipitous decline in blood pressure 5–10 min after initiating CRRT, especially when a blood prime has been used [144, 189]. Exposure of the blood to the highly negatively charged AN69 membrane co-activates pre-kallikrein and Hageman factor resulting in the release of bradykinen, a potent vasodilator. The reaction is potentiated by exposure to blood with an acid pH, which is typical of banked blood used for blood priming the circuit in infants for whom the circuit volume exceeds 10–15% of the estimated blood volume. Thus in small infants the use of a blood prime with an AN69 membrane can result in profound hypotension. Buffering the blood to physiologic pH prior to priming the circuit or infusing the blood post filter at the same rate as a saline prime have been shown to be effective in minimizing the bradykinen release syndrome, as has avoidance of the AN69 membrane [145, 190].

Anticoagulation

Activation of the clotting cascade occurs in CRRT circuits due to contact of the circulating blood with artificial surfaces. Low blood flow rates, turbulent flow, small catheters, and high hematocrits hasten this effect. Anticoagulation regimens using mixed molecular weight heparin or sodium citrate are the most commonly used in pediatric CRRT, and either can be effective. Early comparison of observed outcomes in pediatric centers showed equal filter life span with heparin and citrate, but more hemorrhagic events in the heparin group [191]. However, controlled studies are lacking, and centers tend to adopt one method or the other based on local experience and practice.

It is also possible in certain situations to use no anticoagulation, relying on periodic saline flushes of the circuit. This approach is typically considered in patients with evidence of a sustained coagulopathy due to disseminated intravascular coagulopathy or hepatic failure. However, many of these patients are receiving periodic fresh frozen plasma and platelet infusions to correct the

underlying coagulopathy that will clot a CRRT system when no anticoagulation is used. Moreover, patients with hepatic failure may have a paradoxical hypercoagulable state. An uncontrolled study has shown the no coagulation/saline flushes approach to be associated with an inferior circuit life span compared to heparin and citrate anticoagulation [191].

Heparin has been the mainstay of HD anticoagulation for decades. It is not surprising then that many pediatric CRRT programs began with and continue to rely on heparin to maintain circuit patency. Heparin is infused in the CRRT circuit pre-filter and titrated to achieve a targeted post-filter partial thromboplastin time (PTT) 1.5–2 times normal, or an activated clotting time (ACT) between 180 and 220 s. This is usually accomplished by giving an initial heparin bolus of 20–30 units/kg, followed by a continuous infusion of 10–20 units/kg h. Alternatively, the circuit may be rinsed and primed with 1–2 L of normal saline to which has been added 2,500–5,000 units/L of heparin, followed by the pre-filter heparin infusion.

As first proposed by Mehta and colleagues in San Diego in 1990, sodium citrate anticoagulation has gained wide acceptance in pediatric CRRT programs due to its ease of administration and low side effects profile compared to heparin [192]. By infusing citrate into the arterial limb of the CRRT tubing as it leaves the catheter, calcium ions are bound to the citrate, reducing available calcium and thereby greatly inhibiting coagulation within the circuit, since normal coagulation is calcium-dependent. Systemic hypocalcemia is prevented by infusing calcium chloride back into the patient at a central site away from the CRRT circuit. Thus, citrate anticoagulation achieves truly regional anticoagulation by affecting only the circuit, thereby eliminating the increased risk of bleeding seen with heparin.

The original citrate protocol proposed by Mehta and colleagues used 4% trisodium citrate, which is high in sodium (440 mEq/L) and requires pharmacy-made solutions that are hyponatremic and risk pharmacy error. Alternatively, the commercially available ACD-A (Baxter Healthcare Deerfield, IL) is now widely used in conjunction with calcium-free dialysis and replacement solutions [192]. A commonly employed approach in pediatric CRRT using ACD-A was first described by Bunchman and colleagues in 2002 [193]. A circuit ionized calcium concentration goal of 0.25–0.4 mmols/L is achieved by titrating the citrate infusion rate according to the measured post-filter ionized calcium concentration. Because available calcium in the circuit is a function of blood flow rate (Qb), the initial ACD-A rate is set to equal in mL/h 1.5–2 times the blood flow rate in mL/min. Thus for a Qb of 100 mL/min, the initial ACD-A rate is set at 150–200 mL/h. A 0.8% calcium chloride in normal saline solution is then infused to maintain the desired systemic ionized calcium concentration, usually 1.1–1.3 mmols/L. The initial CaCl2 infusion rate is usually 50–75% of the citrate infusion rate. Thus for a Qb of 100 mL/min and a citrate rate of 200 mL/h, the initial CaCl2 rate is 100–150 mL/h. Separate sliding scales are used to adjust citrate infusion rates according to the periodically measured circuit ionized calcium level and CaCl2 infusion rates according to systemic ionized calcium levels. The system often stabilizes rapidly allowing reduced frequency of monitoring after the first 4–6 h.

Adverse effects of citrate anticoagulation include metabolic alkalosis, citrate toxicity, and hyperglycemia in infants when ACD-A is used. Because citrate is metabolized by the liver to bicarbonate in a ~3:1 manner (~3 mol of bicarbonate for every mol of citrate), patients receiving citrate anticoagulation are prone to develop metabolic alkalosis. Fortunately, citrate is readily cleared by dialysis [194]. Thus, metabolic alkalosis can be forestalled by increasing the dialysate flow rate to increase citrate clearance in patients receiving CVVHD or CVVHDF. Reducing the citrate infusion rate and temporarily using normal saline (pH = 5.4) as a replacement solution can also be effective.

Citrate toxicity may be diagnosed by monitoring the ratio of the total calcium to the ionized calcium levels [195]. Citrate toxicity occurs when citrate clearance falls behind citrate delivery. Total calcium levels rise and the ratio of total calcium to systemic ionized calcium levels rises precipitously. As citrate accumulation progresses, it becomes more difficult to maintain the declining systemic ionized calcium levels within normal

ranges. Since citrate is cleared metabolically by the liver, patients with diminished liver function are at increased risk for citrate toxicity. A falling serum ionized calcium level in the face of a rising total calcium in a patient with liver dysfunction is a sure sign of citrate toxicity. Treatment often requires reducing the citrate rate after a brief period off citrate entirely. An initial citrate infusion rate of 50–70% of the usual rate is also recommended in patients with hepatic insufficiency who are at increased risk for citrate toxicity.

Nutrition

One of the most attractive features of CRRT is the ability to provide complete nutrition without risk of fluid overload. Optimization of energy and protein intake in these highly catabolic patients is potentially important to ultimate survival. However, CRRT also contributes to negative nitrogen balance through the loss of free amino acids and peptides . Studies by Maxvold and colleagues in pediatric CRRT patients have shown that nutritional prescriptions delivering the RDI for protein result in negative nitrogen balance [196]. Similar studies in adults have confirmed these observations [197]. Current nutritional recommendations for adults and children receiving CRRT include a daily intake of amino acids of 2.5–3 g/kg. Under most circumstances, a BUN of 40–60 mg/dL is a reliable indicator of adequate amino acid/protein intake.

Inborn Errors of Metabolism

The acute treatment of several inborn errors of metabolism requires the rapid removal of toxic substances, primarily ammonia, which is elevated in urea cycle defects and some organic acidemias [198, 199]. While hemodialysis is usually recommended to lower very high ammonia levels most effectively, rebound is rapid after cessation of dialysis. Many centers now begin treatment with HD and segue directly to CRRT to prevent rebound. High Qb and dialysate flow rates are recommended to maximize clearance of ammonia. Unlike too aggressive small solute clearance with HD in the setting of AKI, there is no disequilibrium syndrome associated with rapid reductions in serum ammonia levels. Highly efficient CRRT carries the increased risk of electrolyte depletion requiring the immediate use of phosphate-containing CRRT solutions.

Extracorporeal Membrane Oxygenation

The widespread use of extracorporeal membrane oxygenation (ECMO) in neonatal and pediatric critical care units along with the common occurrence of AKI in these patients with multiple organ dysfunction has led to the need to incorporate CRRT into the ECMO therapy circuit. Fortunately, this is readily accomplished. The ECMO circuit is fully heparinized obviating the need to anticoagulate the CRRT circuit. Blood flow in the ECMO circuit is often 20–30 times that required for optimal CRRT. Placement of the CRRT circuit is traditionally post- to pre-oxygenator. However, this may effectively shunt oxygenated blood away from the patient. Newer ECMO circuits with multiple access nipples allow the insertion of the CRRT circuit in an entirely pre-oxygenator location. Close collaboration between CRRT and ECMO teams is required to find the best location for the CRRT circuit and to coordinate concomitant therapy goals [182].

Plasmapheresis

CRRT can be readily combined concurrently with plasma exchange procedures without interrupting CRRT. As first described by Yorgin and associates in 2000, the placement of a three-way stopcock at both arterial and venous limbs of the CRRT circuit at the connection to the double lumen catheter allows diversion of blood through the centrifugation plasmapheresis machine [200]. At initiation of plasmapheresis, Qb on the CRRT machine must be reduced by the blood flow rate of the pheresis machine, which in turn may require reduction in CRRT replacement fluid rate.

Thermic Control

Infants and small children have large body surface area to weight ratios. In addition, a relatively large fraction of total circulating blood volume is in the extracorporeal circuit at any given time, placing these children at substantial risk for hypothermia during CRRT. In-line fluid warmers can be used, but will increase priming volume. Line warmers that can be applied to the return line offer the best results. Thermic control devices may also mask a fever in a small child.

Circuit-to-Circuit Exchange

Infants receiving prolonged CRRT may require repeated blood primes, with multiple exposures to blood-borne diseases, HLA antigen sensitization and bradykinen syndrome. After the initial blood prime, subsequent routine circuit changes can be accomplished by priming a new machine with the blood that resides in the old machine. The circuit is discontinued, the catheter flushed and locked with heparinized saline or tPA, and a saline-primed circuit on a new machine is connected to the venous line of the old circuit. Blood from the old circuit is then used to fill the new circuit, the new circuit then attached to the patient [201].

Prescription

The optimal "dose" of renal replacement therapy is not known. Studies by Ronco and colleagues of adults with AKI treated with CVVH established a total convective clearance (replacement fluid plus patient fluid removal) target of 35 mL/kg h as a threshold below which survival was significantly worse [202]. In a subset of these patients with sepsis there was a trend in favor of improved survival with total convective clearances >/= 45 mL/kg h. Recent studies by the VA/NIH Acute Renal Failure Network have shown that there was no difference in survival associated with more intensive RRT (35 mL/kg h) compared to less intensive (20 mL/kg h) therapy [155]. These studies are confounded by the use of different modalities involving different amounts of convective and diffusive solute removal. However, the thought that by attempting to push clearances ever higher outcomes would be improved seems unlikely. This is a particularly important observation in pediatric CRRT where the use of large filters in small patients allows achievement of very high clearances that can be nutritionally harmful. Despite theoretical considerations that seemed to favor high clearance targets in cytokine-driven illnesses like sepsis [203] and preliminary results in septic adults treated with very high flow CRRT [204], available evidence does not support the use of clearance targets above 20–35 mL/kg h. For pediatric patients, this translates to 2–3 L/1.73 m^2 h, rates that are reasonably easy to achieve.

A representative prescription for pediatric CRRT would include a blood flow rate of 4–6 mL/kg/min and a dialysate or replacement fluid rate (or the sum of both in the case of CVVHDF) of at least 2,000–3,000 mL/1.73 m^2 h.

Outcome

Survival of pediatric patients treated with CRRT has been reported in single center studies to vary widely by disease and modality [205–207]. Recent evidence points to the degree of fluid overload as an independent determinant of outcome in pediatric patients treated with CRRT. Goldstein and colleagues first showed this effect in a single center study [205] that has been confirmed by a large multicenter study from the prospective pediatric CRRT (ppCRRT) registry [208]. Patient survival was inversely correlated with percent fluid overload at initiation of CRRT; survivors had a mean fluid overload of 14.2% while in non-survivors mean fluid overload was 25.4%, a difference that was highly significant and independent of diagnosis or severity of illness [205]. Further analysis of the ppCRRT Registry data has established 20% fluid overload as the threshold above which mortality of pediatric patients receiving CRRT is four times that of patients with less than 10% fluid overload at

initiation of CRRT [208]. These data suggest that earlier initiation of measures to control fluid accumulation, including CRRT, may improve survival.

Conclusion

AKI is frequently seen in the pediatric population, often associated with high risk of mortality or long-term morbidity. Recent advances in the understanding of the pathophysiology of AKI have pointed to newer diagnostic and therapeutic strategies that focus on early recognition and treatment. Exciting developments in technology have made renal replacement therapies more accessible and more easily applied in the pediatric setting. Yet despite these advances mortality rates among children who suffer AKI remain disturbingly high. Hopefully, future developments will bring about improved outcomes for the majority of children afflicted with AKI.

References

1. Lameire N, Van Biesen W, Vanholder R. Acute kidney injury. Lancet. 2005;365(9457):417–30.
2. Bellomo R, Kellum J, Ronco C. Acute kidney injury: time for consensus. Intensive Care Med. 2001;27(11): 1685–8.
3. Singri N, Ahya SN, Levin ML. Acute kidney injury. JAMA. 2003;289(6):747–51.
4. Uchino S, et al. Acute kidney injury in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
5. Flynn JT, et al. Peritoneal dialysis for management of pediatric acute kidney injury. Perit Dial Int. 2001;21(4):390–4.
6. Bellomo R, et al. Acute kidney injury – 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.
7. Bell M, et al. Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. Nephrol Dial Transplant. 2005;20(2):354–60.
8. Abosaif NY, et al. The outcome of acute kidney injury in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. Am J Kidney Dis. 2005;46(6):1038–48.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
10. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71:1028–35.
11. Zappitelli M, Bernier PL, Saczkowski RS, Tchervenkov CI, Gottesman R, Dancea A, Hyder A, Alkandari O. A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. Kidney Int. 2009;76:885–92.
12. Palmieri T, Lavrentieva A, Greenhaigh D. An assessment of acute kidney injury with modified RIFLE criteria in pediatric patients with severe burns. Intensive Care Med. 2009;35:2125–9.
13. Bakkaloglu A, Kalyoncu M, Poyrazoglu H, Delibas A, Ozkaya O, Peru H, Alpay H, Soylemezoglu O, Gur-Given A, Bak M, Bircan Z, Akil I, Ozcakar B, Uncu N, Karabay-Bayazit A, Sonmez F, Turkish Society for Pediatric Nephrology Acute Kidney Injury Study Group. Etiology and outcome of acute kidney injury in children. Pediatr Nephrol. 2010;25:1453–61.
14. Plotz FB, Bouma AB, van Wijk JA, Kneyber MC, Bokenkamp A. Pediatric acute kidney injury in the ICU: an independent evaluation of pRIFLE criteria. Intensive Care Med. 2008;34:1713–7.
15. Zappitelli M, Moffet BS, Hyder A, Goldstein SL. Acute kidney injury in non-critically ill children treated with aminoglycoside antibiotics in a tertiary healthcare center: a retrospective cohort study. Nephrol Dial Transplant. 2011;26:144–50.
16. Picca S, et al. Risks of acute kidney injury after cardiopulmonary bypass surgery in children: a retrospective 10-year case-control study. Nephrol Dial Transplant. 1995;10(5):630–6.
17. Moghal NE, Brocklebank JT, Meadow SR. A review of acute kidney injury in children: incidence, etiology and outcome. Clin Nephrol. 1998;49(2):91–5.
18. Leteurtre S, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet. 2003; 362(9379):192–7.
19. Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute kidney injury. J Am Soc Nephrol. 2003;14(8):2199–210.
20. Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. Kidney Int. 2002;62:1532–9.
21. Brady HR, Clarkson MR, Lieberthal W. Acute kidney injury. In: Brenner BM, editor. Brenner & Rector's The Kidney. 7th ed. Philadelphia: Saunders; 2004. p. 1215–70.
22. Andreoli SP. Clinical evaluation and management. In: Avner ED, Harmon WE, Niaudet P, editors. Pediatric nephrology. 5th ed. Baltimore: Lippincott Williams and Wilkins; 2004. p. 1233–34.

23. Arora P, et al. Prognosis of acute kidney injury in children: a multivariate analysis. Pediatr Nephrol. 1997;11(2):153–5.
24. Flynn JT. Causes, management approaches, and outcome of acute kidney injury in children. Curr Opin Pediatr. 1998;10(2):184–9.
25. Bunchman TE, et al. Pediatric acute kidney injury: outcome by modality and disease. Pediatr Nephrol. 2001;16(12):1067–71.
26. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric AKI epidemiology at a tertiary care center from 1999 to 2001. Am J Kidney Dis. 2005;45(1): 96–101.
27. Olowu WA, Adelusola KA. Pediatric acute kidney injury in southwestern Nigeria. Kidney Int. 2004;66(4):1541–8.
28. Anochie IC, Eke FU. Acute kidney injury in Nigerian children: Port Harcourt experience. Pediatr Nephrol. 2005;20(11):1610–4.
29. Mabina MH, Moodley J, Pitsoe SB. The use of traditional herbal medication during pregnancy. Trop Doct. 1997;27(2):84–6.
30. Kadiri S, et al. The causes and course of acute tubular necrosis in Nigerians. Afr J Med Med Sci. 1992;21(1):91–6.
31. Jha V, Chugh KS. Nephropathy associated with animal, plant, and chemical toxins in the tropics. Semin Nephrol. 2003;23(1):49–65.
32. Liano F, et al. The spectrum of acute kidney injury in the intensive care unit compared with that seen in other settings. The Madrid Acute kidney injury Study Group. Kidney Int Suppl. 1998;66:S16–24.
33. Uchino S, et al. Diuretics and mortality in acute kidney injury. Crit Care Med. 2004;32(8):1669–77.
34. Brivet FG, et al. Acute kidney injury in intensive care units – causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on acute kidney injury. Crit Care Med. 1996;24(2):192–8.
35. Cosentino F, Chaff C, Piedmonte M. Risk factors influencing survival in ICU acute kidney injury. Nephrol Dial Transplant. 1994;9(Suppl 4):179–82.
36. Medina Villanueva A, et al. Acute kidney injury in critically-ill children. A preliminary study. An Pediatr (Barc). 2004;61(6):509–14.
37. Skippen PW, Krahn GE. Acute kidney injury in children undergoing cardiopulmonary bypass. Crit Care Resusc. 2005;7(4):286–91.
38. Taber SS. Drug-associated renal dysfunction. Crit Care Clin. 2006;22(2):357–74.
39. Tune BM, Reznik VM, Mendoza SA. Renal complications of drug therapy. In: Holliday MA, Barratt TM, Avner ED, editors. Pediatric nephrology. 3rd ed. Baltimore, MD: Williams and Wilkins; 1994. p. 1212–26.
40. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39(5):930–6.
41. Rihal CS, et al. Incidence and prognostic importance of acute kidney injury after percutaneous coronary intervention. Circulation. 2002;105(19):2259–64.
42. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology. 1993;188(1): 171–8.
43. Solomon R. The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high risk patients. Kidney Int. 2005;68(5):2256–63.
44. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA. 2006; 295(23):2765–79.
45. Cantley LG, et al. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. Kidney Int. 1993;44(6):1217–23.
46. Pflueger A, et al. Role of adenosine in contrast media-induced acute kidney injury in diabetes mellitus. Mayo Clin Proc. 2000;75(12):1275–83.
47. Persson PG. The cancer foundation: donations greater than ever. Lakartidningen. 2006;103(6): 391.
48. Rudnick MR, et al. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism – a critical review. Am J Kidney Dis. 1994;24(4):713–27.
49. Peixoto AJ. Critical issues in nephrology. Clin Chest Med. 2003;24(4):561–581.
50. Mato AR, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. Leuk Lymphoma. 2006;47(5):877–83.
51. Sallan S. Management of acute tumor lysis syndrome. Semin Oncol. 2001;28(2 Suppl 5):9–12.
52. Wang LY, et al. Recombinant urate oxidase (rasburicase) for the prevention and treatment of tumor lysis syndrome in patients with hematologic malignancies. Acta Haematol. 2006;115(1–2):35–8.
53. Goldman SC, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001;97(10):2998–3003.
54. Davidson MB, et al. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. Am J Med. 2004;116(8):546–54.
55. Palevsky PM. Acute kidney injury. J Am Soc Nephrol. 2003;2(2):41–76.
56. Rose BD. Meaning and application of urine chemistries. Clinical physiology of acid-base and electrolyte disorders. 5th edition. 2001. p. 405–14.
57. Zarich S, Fang LS, Diamond JR. Diamond, fractional excretion of sodium. Exceptions to its diagnostic value. Arch Intern Med. 1985;145(1):108–12.
58. Miller TR, et al. Urinary diagnostic indices in acute kidney injury: a prospective study. Ann Intern Med. 1978;89(1):47–50.
59. Goldstein MH, Lenz PR, Levitt MF. Effect of urine flow rate on urea reabsorption in man: urea as a "tubular marker". J Appl Physiol. 1969;26(5): 594–9.
60. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute kidney injury. Kidney Int. 2002;62(6):2223–9.

61. Zhou H, et al. Acute kidney injury biomarkers-need, present status, and future promise. J Am Soc Nephrol (NephSAP). 2006;5(2):63–71.
62. Herget-Rosenthal S, et al. Prognostic value of tubular proteinuria and enzymuria in nonoliguric acute tubular necrosis. Clin Chem. 2004;50(3):552–8.
63. Herget-Rosenthal S, et al. Early detection of acute kidney injury by serum cystatin C. Kidney Int. 2004;66(3):1115–22.
64. Villa P, et al. Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. Crit Care. 2005;9(2):R139–43.
65. White C, et al. Estimating glomerular filtration rate in kidney transplantation: a comparison between serum creatinine and cystatin C-based methods. J Am Soc Nephrol. 2005;16(12):3763–70.
66. Burchard GD, et al. Renal dysfunction in children with uncomplicated, *Plasmodium falciparum* malaria in Tamale, Ghana. Ann Trop Med Parasitol. 2003;97(4):345–50.
67. Han WK, et al. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002;62(1):237–44.
68. Kjeldsen L, Cowland JB, Borregaard N. Human neutrophil gelatinase-associated lipocalin and homologous proteins in rat and mouse. Biochim Biophys Acta. 2000;1482(1–2):272–83.
69. Mishra J, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365(9466): 1231–8.
70. Trachtman H, et al. Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. Pediatr Nephrol. 2006;21(7):989–94.
71. Melnikov VY, et al. Impaired IL-18 processing protects caspase-1-deficient mice from ischemic acute kidney injury. J Clin Invest. 2001;107(9):1145–52.
72. Parikh CR, et al. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis. 2004;43(3):405–14.
73. Parikh CR, et al. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol. 2005;16(10):3046–52.
74. Parikh CR, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2006;70(1):199–203.
75. du Cheyron D, et al. Urinary measurement of Na+/H+exchanger isoform 3 (NHE3) protein as new marker of tubule injury in critically ill patients with AKI. Am J Kidney Dis. 2003;42(3):497–506.
76. Kiely EA, Hartnell GG, Gibson RN, et al. Measurement of bladder volume by real-time ultrasound. Br J Urol. 1987;60:33–35.
77. Ireton RC, Krieger JN, Cardenas DD, et al. Bladder volume determination using a dedicated, portable ultrasound scanner. J Urol. 1990;143:909–11.
78. Mainprize TC, Drutz HP. Accuracy of total bladder volume and residual urine measurements: comparison between real-time ultrasound and catheterization. Am J Obstet Gynecol. 1989;160:1013–16.
79. Coleman BG. Ultrasonography of the upper genitourinary tract. Urol Clin North Am. 1985;12:633–44.
80. Mercado-Deane MG, Beeson JE, John SD. US of renal insufficiency in neonates. Radiographics. 2002; 22(6):1429–38.
81. Krumme B, Blum U, Schwertfeger E, et al. Diagnosis of renovascular disease by intra- and extra-renal Doppler scanning. Kidney Int. 1996;50:1288–92.
82. Platt JF, Rubin JM, Ellis JH. Lupus nephritis: predictive value of conventional and Doppler US and comparison with serologic and biopsy parameters. Radiology. 1997;203:82–8.
83. Goldfarb CR, Srivastava NC, Grotas AB, Ongseng F, Nagler HM. Radionuclide imaging in urology. Urol Clin North Am. 2006;33(3):319–28.
84. Sherman RA, Byun KJ. Nuclear medicine in acute and chronic renal failure. Semin Nucl Med. 1982; 12:265–79.
85. Buckley JC, McAninch JW. The diagnosis, management, and outcomes of pediatric renal injuries. Urol Clin North Am. 2006;33:33–40.
86. Alsikafi NF, Rosenstein DI. Staging, evaluation, and nonoperative management of renal injuries. Urol Clin North Am. 2006;33:13–9.
87. Kawashima A, Glockner JF, King Jr BF. CT urography and MR urography. Radiol Clin North Am. 2003;41(5):945–61.
88. Huang AJ, Lee VS, Rusinek H. MR imaging of renal function. Radiol Clin North Am. 2003;41(5): 1001–1017.
89. Nolte-Ernsting CCA, Adam GB, Gunther RW. MR urography: examination techniques and clinical applications. Eur Radiol. 2001;11:355–72.
90. Borthne AS, Pierre-Jerome C, Gjesdal KI, Storaas T, Courivaud F, Eriksen M. Pediatric excretory MR urography: comparative study of enhanced and non-enhanced techniques. Eur Radiol. 2003;13(6): 1423–27.
91. Prince MR, Zhang HL, Peowda JC, Grossman ME, Silvers DN. Nephrogenic systemic fibrosis and its impact on abdominal imaging. Radiographics. 2009;29:1565–74.
92. Al Makdama A, Al-Akash S. Safety of percutaneous renal biopsy as an outpatient procedure in pediatric patients. Ann Saudi Med. 2006;26(4):303–5.
93. Vande Walle J, Mauel R, Raes A, Vandekerckhove K, Donckerwolcke R. AKI in children with minimal change nephrotic syndrome may be related to functional changes of the glomerular basal membrane. Am J Kidney Dis. 2004;43(3):399–404.
94. Subtirelu MM, Flynn JT, Schechner RS, Pullman JM, Feuerstein D, Del Rio M. Acute kidney injury in a pediatric kidney allograft recipient treated with intravenous immunoglobulin for parvovirus B19 induced pure red cell aplasia. Pediatr Transplant. 2005;9(6):801–4.
95. Demirkaya E, Atay AA, Musabak U, Sengul A, Gok F. Ceftriaxone-related hemolysis and acute kidney injury. Pediatr Nephrol. 2006;5:733–6.
96. Korbet SM. Percutaneous renal biopsy. Semin Nephrol. 2002;22:254–67.

97. Solez K, Racusen LC. Role of the renal biopsy in acute kidney injury. Contrib Nephrol. 2001;132: 68–75.
98. Preston RA, Stemmer CL, Materson BJ, et al. Renal biopsy in patients 65 years of age or older: an analysis of the results of 334 biopsies. J Am Geriatr Soc. 1990;38:669–74.
99. Jennette JC, Falk RJ. Diagnosis and management of glomerular diseases. Med Clin North Am. 1997;81:653–77.
100. Gong WK, Tan TH, Murugasu B, et al. 18 years experience in pediatric acute dialysis: analysis of predictors of outcome. Pediatr Nephrol. 2001;16: 212–15.
101. Anochie IC, Eke FU. Pediatric acute peritoneal dialysis in southern Nigeria. Postgrad Med J. 2006;82: 228–30.
102. Phadke KD, Dinaker C. The challenges of treating children with renal failure in a developing country. Perit Dial Int. 2001;21:S326–S29.
103. Wong SN, Geary DF. Comparison of temporary and permanent catheters for acute peritoneal dialysis. Arch Dis Child. 1988;63:827–31.
104. Chadha V, Warady BA, Blowey DL, et al. Tenckhoff catheters prove superior to cook catheters in pediatric acute peritoneal dialysis. Am J Kidney Dis. 2000;35:1111–6.
105. Auron A, Warady BA, Simon S, et al. Use of the multipurpose drainage catheter for the provision of acute peritoneal dialysis in infants and children. Am J Kidney Dis. 2007;49:650–5.
106. Lamiere N. Principles of peritoneal dialysis and its application in acute renal failure, vol. 1357. In: Ronco C, Bellomo R, editors. Critical care nephrology. Dordrecht: Kluwer Academic Publishers; 1998.
107. Rubin J, Adair C, Barnes T, et al. Dialysate flow rate and peritoneal clearance. Am J Kidney Dis. 1984; 4:260–67.
108. Mehta RL, Letteri JM, National Kidney Foundation Council on Dialysis. Current status of renal replacement therapy for acute renal failure. Am J Nephrol. 1999;19:377–82.
109. Leblanc M, Tapoyai M, Paganini EP. What dialysis dose should be provided in acute renal failure? Adv Ren Replace Ther. 1995;2:255–64.
110. Schiff HMD, Lang MS. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med. 2002;348:305–10.
111. Ronco C, Bellomo R, Honel P. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomized trial. Lancet. 2002;356:26–30.
112. Chionh CY, Soni S, Cruz DN, et al. Peritoneal dialysis for acute kidney injury: techniques and dose. Contrib Nephrol. 2009;163:278–84.
113. Gabriel DP, do Nascimento GVR, Caramori JT, et al. High volume peritoneal dialysis for acute renal failure. Perit Dial Int. 2007;27:277–82.
114. Evanson JA, Ikizler TA, Wingard R, et al. Measurement of the delivery of dialysis in acute renal failure. Kidney Int. 1999;55:1501–8.
115. Himmelfarb J, Evanson J, Hakim RM, et al. Urea volume of distribution exceeds total body water in patients with acute renal failure. Kidney Int. 2002;61: 317–23.
116. Chitalia VC, Almeida AF, Rai H, et al. Is peritoneal dialysis adequate for hypercatabolic acute renal failure in developing countries? Kidney Int. 2002;61: 747–57.
117. Flynn JT, Kershaw DB, Smoyer WE, et al. Peritoneal dialysis for management of pediatric acute renal failure. Perit Dial Int. 2001;21:390–94.
118. Ronco C, Amerling R. Continuous flow peritoneal dialysis: current state-of-the-art and obstacles to further development. Contrib Nephrol. 2006;150: 310–20.
119. Raj DS, Self M, Work J. Hybrid dialysis: recirculation peritoneal dialysis revisited. Am J Kidney Dis. 2000;36:56–67.
120. Mineshima M, Suzuki S, Sato Y, et al. Solute removal characteristics of continuous recirculation peritoneal dialysis in experimental and clinical studies. ASAIO J. 2000;46:95–8.
121. Cruz C, Melendez A, Gotch FA, et al. Single-pass continuous flow peritoneal dialysis using two catheters. Semin Dial. 2001;14:391–4.
122. Frieda P, Issad B. Continuous flow peritoneal dialysis: assessment of fluid and solute removal in a high-flow model of "fresh dialysate single pass". Perit Dial Int. 2003;23:348–55.
123. Amerling R, Glezerman I, Savransky E, et al. Continuous flow peritoneal dialysis: current perspectives. Contrib Nephrol. 2003;140:294–304.
124. Rajpoot DK, Gargus JJ. Acute hemodialysis for hyperammonemia in small neonates. Pediatr Nephrol. 2004;19:390–5.
125. Meyer RJ, Flynn JT, Brophy PD, et al. Hemodialysis followed by continuous hemofiltration for treatment of lithium intoxication in children. Am J Kidney Dis. 2001;37:1044–7.
126. McBryde KD, Kershaw DB, Bunchman TE, et al. Renal replacement therapy in the treatment of confirmed or suspected inborn errors of metabolism. J Pediatr. 2006;148:770–8.
127. Rabindranath K, Adams J, Macleod AM, et al. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007;(3):CD003773.
128. Bagshaw SM, Berthiaume LR, Delaney A, et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med. 2008;36: 610–7.
129. Antoun TA, Palevsky PM. Selection of modality of renal replacement therapy. Semin Dial. 2009;22: 108–13.
130. Strazdins V, Watson AR, Harvey B. Renal replacement therapy for acute renal failure in children. Pediatr Nephrol. 2004;19:199–207.
131. Schulman G, Fogo A, Gung A, et al. Complement activation retards resolution of acute ischemic renal failure in the rat. Kidney Int. 1991;40:1069–74.

132. Himmelfarb J, Zaoui P, Hakim RM. Modulation of granulocyte LAM-1 and MAC-1 during dialysis – a prospective, randomized controlled trial. Kidney Int. 1992;41:388–95.
133. Lamba NM, Gaylor JD, Courtney JM, et al. Complement activation by cellulose: investigation of the effects of time, area, flow rate, shear rate and temperature on C3a generation in vitro, using a parallel plate flow cell. J Mater Sci Mater Med. 1998;9:409–14.
134. Varela MP, Kimmel PL, Phillips TM, et al. Biocompatibility of hemodialysis membranes: interrelations between plasma complement and cytokine levels. Blood Purif. 2001;19:370–9.
135. Himmelfarb J, Rubin NT, Chandran P, et al. A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. J Am Soc Nephrol. 1998;9:257–66.
136. Jaber BL, Lau J, Schmid CH, et al. Effect of biocompatibility of hemodialysis membranes on mortality in acute renal failure: a meta-analysis. Clin Nephrol. 2002;57:274–82.
137. Subramainian S, Venkataraman R, Kellum J. Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. Kidney Int. 2002;62:1819–23.
138. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure (Review). Cochrane Database Syst Rev. 2008;(1):CD005283.
139. Pannu N, Klarenbach S, Wiebe N, et al. Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299:793–805.
140. Uchino S, Bellomo R, Morimatsu H, et al. Cytokine dialysis: an ex-vivo study. ASAIO J. 2002;48:650–3.
141. Haase M, Bellomo R, Baldwin I, et al. Hemodialysis membrane with a high molecular-weight cutoff and cytokine levels in sepsis complicated by acute renal failure: a phase 1 randomized trial. Am J Kidney Dis. 2007;50:296–304.
142. Haase M, Bellomo R, Baldwin I, et al. High cut-off point membranes in septic acute renal failure: a systematic review. Int J Artif Organs. 2007;30:1031–1041.
143. Rimmelé T, Assadi A, Cattenoz M, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. Nephrol Dial Transplant. 2009;24:421–27.
144. Brophy PD, Mottes TA, Kudelka TL, et al. AN-69 membrane reactions are pH-dependent and preventable. Am J Kidney Dis. 2001;38:173–8.
145. Pasko DA, Mottes TA, Mueller BA. Pre-dialysis of blood prime continuous hemodialysis normalizes pH and electrolytes. Pediatr Nephrol. 2003;18:1177–83.
146. Hackbarth RM, Eding D, Gianoli Smith C, et al. Zero balance ultrafiltration (Z-BUF) in blood-primed CRRT circuits achieves electrolyte and acid-base homeostasis prior to patient connection. Pediatr Nephrol. 2005;20:1328–33.
147. Goldstein SL. Overview of pediatric renal replacement therapy in acute renal failure. Artif Organs. 2003;27:781–5.
148. Lai KN, Wang AY, Ho K, et al. Use of low-dose low molecular weight heparin in hemodialysis. Am J Kidney Dis. 1996;28:721–6.
149. Tolwani AJ, Wille KM. Anticoagulation for continuous renal replacement therapy. Semin Dial. 2009;22:141–5.
150. Schortgen F, Soubrier N, Delclaux C, et al. Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: usefulnessof practice guidelines. Am J Respir Crit Care Med. 2000;162:197–202.
151. Dheu C, Terzic J, Menouer S, et al. Importance of the curve shape for interpretation of blood volume monitor changes during haemodiafiltration. Pediatr Nephrol. 2009;24:1419–23.
152. Patel N, Dalal P, Panesar M. Dialysis disequilibrium syndrome: a narrative review. Semin Dial. 2008;21:493–98.
153. Ramos P, Marshall MR, Golper TA. Acute hemodialysis prescription. In: Berns SJ, Palevsky PM, Post TW, editors. UpToDate® v17.3. www.uptodate.com. Accessed 30 Sep 2009.
154. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med. 2002;346:305–10.
155. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359:7–20.
156. Kudoh Y, Imura O. Slow continuous hemodialysis – new therapy for acute renal failure in critically ill patients – part 1. Theoretical consideration and new technique. Jpn Circ J. 1988;52:1171–82.
157. Kudoh Y, Shiiki M, Sasa Y, et al. Slow continuous hemodialysis – new therapy for acute renal failure in critically ill patients – part 2. Animal experiments and clinical implication. Jpn Circ J. 1988;52:1183–90.
158. Tam PY, Huraib S, Mahan B, et al. Slow continuous hemodialysis for the management of complicated acute renal failure in an intensive care unit. Clin Nephrol. 1988;30:79–85.
159. Cruz D, Bobek I, Lentini P, et al. Machines for continuous renal replacement therapy. Semin Dial. 2009;22:123–32.
160. Fliser D, Kielstein JT. Technology insight: treatment of renal failure in the intensive care unit with extended dialysis. Nat Clin Pract Nephrol. 2006;2:32–9.
161. Abi Antoun T, Palevsky PM. Selection of modality of renal replacement therapy. Semin Dial. 2009;22:108–13.
162. Marshall M, Tianmin M, Galler D, et al. Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. Nephrol Dial Transplant. 2004;19:877–84.

163. Vaslaki L, Karátson A, Vörös P, et al. Can sterile and pyrogen-free on-line substitution fluid be routinely delivered? A multicentric study on the microbiological safety of on-line haemodiafiltration. Nephrol Dial Transplant. 2000;15(Suppl 1):74–8.
164. Weber C, Groetsch W, Schlotter S, et al. Novel online infusate-assisted dialysis system performs microbiologically safely. Artif Organs. 2000;24:323–8.
165. Kumar V, Craig M, Depner T, et al. Extended daily dialysis: a new approach to renal replacement therapy for acute renal failure in the intensive care unit. Am J Kidney Dis. 2000;36:294–300.
166. Morath C, Miftari N, Dikow R, et al. Sodium citrate anticoagulation during sustained low efficiency dialysis (SLED) in patients with acute renal failure and severely impaired liver function. Nephrol Dial Transplant. 2008;23:421–2.
167. Marshall MR, Golper TA. Sustained low efficiency or extended daily dialysis. In: Berns SJ, Palevsky PM, Post TW, editors. UpToDate® v17.3. www.uptodate.com. Accessed 30 Sep 2009.
168. Kielstein J, Kretschmer U, Ernst T, et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. Am J Kidney Dis. 2004;43:342–9.
169. Henderson LW. The beginning of clinical hemofiltration: a personal account. ASAIO J. 2003;49:513–7.
170. Henderson LW, Livoti LG, Ford CA, Kelly AB, Lysaght MJ. Clinical experience with intermittent hemodiafiltration. Trans ASAIO. 1973;19:119–23.
171. Henderson LW. The birth of hemodiafiltration. Contrib Nephrol. 2007;158:1–8.
172. Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F. Arteriovenous haemofiltration: a new and simple method for treatment of over-hydrated patients resistant to diuretics. Klin Wochenschr. 1977;55:1121–2. article in German.
173. Zobel G, Ring E, Trop M, Stein JI. Arteriovenous diafiltration in children. Int J Pediatr Nephrol. 1986;7:203–6.
174. Leone MR, Jenkins RD, Golper TA, Alexander SR. Early experience with continuous arteriovenous hemofiltration in critically ill pediatric patients. Crit Care Med. 1986;14:1058–63.
175. Ronco C, Brendolan A, Bragantini L, La Greca G. Treatment of acute renal failure in newborns by continuous arteriovenous hemofiltration. Trans ASAIO J. 1985;41:634–8.
176. Lieberman KV. Continuous arteriovenous hemofiltration in children. Pediatr Nephrol. 1987;1:330–8.
177. Lopez-Herce J, Dorao P, Delgado MA, Espinoza L, Ruza F, Martinez MC. Continuous arteriovenous hemofiltration in children. Intensive Care Med. 1989;15:224–7.
178. Waradt B, Bunchman T. Dialysis therapy for children with acute renal failure: survey results. Pediatr Nephrol. 2000;15:11–3.
179. Goldstein S, Currier H, Graf J, Cosio CC, Brewer ED, Sacheva R. Outcome in children receiving continuous veno-venous hemofiltration. Pediatrics. 2001;107:1309–12.
180. Bunchman TE, Maxvold NJ, Kershaw DB, Sedman AB, Custer JR. Continuous venvenous hemofiltration in infants and children. Am J Kidney Dis. 1995;25:17–25.
181. Hmiel SP, Martin RA, Landt M, Levy FH, Grange DK. Amino acid clearance during acute metabolic decompensation in maple syrup urine disease treated with continuous venovenous hemodialysis with filtration. Pediatr Crit Care Med. 2004;5:278–81.
182. Ricci Z, Ronco C, Picardo S. CRRT in series with extracorporeal membrane oxygenation in pediatric patients. Kidney Int. 2010;77:469–70.
183. Jenkins R, Harrison H, Chen B, Arnold D, Funk J. Accuracy of intravenous infusion pumps in continuous renal replacement therapies. Trans ASAIO J. 1992;38:808–11.
184. Bunchman TE, Gardner JJ, Kershaw DB, Maxvold NJ. Vascular access for hemodialysis or CVVH(D) in infants and children. Nephrol Dial Transplant. 1994;23:314–7.
185. Davenport A, Will EJ, Davison AM. Hyperlactemia and metabolic acidosis during hemofiltration using lactate-buffered fluids. Nephron. 1991;59:461–5.
186. Thomas AN, Guy JM, Kishen R, Garaughty IF, Bowles BJM, Vadgama P. Comparison of lactate and bicarbonate buffered hemofiltration fluids: use in critically ill patients. Nephrol Dial Transplant. 1997;12:1212–17.
187. Zimmerman D, Cotman P, Ting R, Karanicolas S, Tobe SW. Continuous veno-venous hemodialysis with a novel bicarbonate dialysis solution: prospective crossover comparison with lactate buffered solution. Nephrol Dial Transplant. 1999;14:2387–91.
188. Maxvold NJ, Flynn JT, Smoyer WE, et al. Prospective crossover comparison of bicarbonate vs lactate-based dialysate for pediatric CVVHD. Blood Purif. 1999;17:27–9.
189. Parshuram CS, Cox PN. Neonatal hyperkalemic-hypocalcemic cardiac arrest associated with initiation of blood-primed continuous venovenous hemofiltration. Pediatr Crit Care Med. 2002;3:67–9.
190. Hackbarth RM, Eding D, Smith CG, Koch A, Sanfilippo DJ, Bunchman TE. Zero-balance ultrafiltration (Z-BUF) in blood-primed CRRT circuits achieves electrolyte and acid-base homeostasis prior to patient connection. Pediatr Nephrol. 2005;20:1328–33.
191. Brophy PD, Somers MJ, Baum MA, et al. Multicenter evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant. 2005;20:1416–2.
192. Mehta RL, McDonald BR, Aguilar MM, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int. 1990;38:976–81.

193. Bunchman TE, Maxvold NJ, Barnett J, Hutchings A, Benfield MR. Pediatric hemofiltration: normocarb dialysate solution with citrate anticoagulation. Pediatr Nephrol. 2002;17:150–4.
194. Chadha V, Garg U, Warady B, Alon US. Citrate clearance in children receiving continuous veno-venous renal replacement therapy. Pediatr Nephrol. 2002;17:819–24.
195. Meier-Kreische HU, Gitomer J, Finkel K, DuBose T. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. Crit Care Med. 2001;29:748–52.
196. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: a prospective comparison between classic hemofiltration and hemfiltration with dialysis. Crit Care Med. 2000;28:1161–5.
197. Mokrzycki MH, Kaplan AA. Protein losses in continuous renal replacement therapies. J Am Soc Nephrol. 1996;7:2259–63.
198. Braun MC, Welch TR. Continuous venovenous diafiltration in the treatment of acute hyperammonemia. Am J Nephrol. 1998;18:531–3.
199. Falk MC, Knight JF, Roy LP, et al. Continuous veno-venous hemofiltration in the acute treatment of inborn errors of metabolism. Pediatr Nephrol. 1994;8:330–3.
200. Yorgin PD, Eklund DK, al-Uzri A, Whitesell L, Theodorou AA. Concurrent centrifugation plasmapheresis and continuous venovenous hemodiafiltratio. Pediatr Nephrol. 2000;14:18–21.
201. Yorgin P, Ludlow M, Chua A, Alexander S. A technique for rapid exchange of continuous renal replacement therapy. Pediatr Nephrol. 2006;21:743–6.
202. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous hemofiltration on outcomes of acute renal failure: a prospective randomized trial. Lancet. 2000;356:26–30.
203. DiCarlo JV, Alexander SR. Hemofiltration for cytokine-driven illnesses: the mediator delivery hypothesis. Int J Artif Organs. 2005;28:777–86.
204. Honore PM, Joannes-Boyau O, Boer W, Collin V. High-volume hemofiltration in sepsis and SIRS: current concepts and future prospects. Blood Purif. 2009;28:1–11.
205. Goldstein SL, Currier H, Graf JM, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous hemofiltration. Pediatrics. 2001;107:1309–12.
206. Symons JM, Brophy PD, Gregory MJ, et al. Continuous renal replacement therapy in children up to 10 kg. Am J Kidney Dis. 2003;41:984–9.
207. Flores FX, Brophy PD, Symons JM, et al. CRRT after stem cell transplantation: a report from the prospective pediatric CRRT registry. Pediatr Nephrol. 2008;23:625–30.
208. Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: a report of the prospective pediatric CRRT registry. Am J Kidney Dis. 2010;55:316–25.

Part VIII

Special Indications and Techniques of Blood Purification

The Development of CRRT for Infants and Children

38

Claudio Ronco and Zaccaria Ricci

Keywords

Continuous hemofiltration • Acute renal failure • Pediatric dialysis • Perinatal ARF • Pediatric CRRT • Acute kidney injury in infants

Introduction

Acute kidney injury (AKI), or acute renal failure (ARF), in infancy may result from a variety of pathophysiologic events and is characterized by a sudden impairment of renal function with consequent decrease in urine output (<1 mL/kg/h in the newborn) and a parallel increase in blood levels of urea nitrogen, creatinine, and other waste products [1–3].The main cause of AKI/ARF in infancy is renal hypoperfusion due to acute volume depletion, perinatal asphyxia, severe hypotension and/or septic shock. Another frequent cause of AKI in children is acute tubular necrosis (ATN) associated with abdominal or cardiac surgery. Fluid and electrolyte imbalances are frequently present, and metabolic acidosis is often associated with other alterations of intermediary metabolism. All these pathologic conditions are aggravated in children by the small size of the patient and the limited tolerance of homeostatic imbalances. For these reasons, this disorder represents a severe illness in children, and it may become even more severe when it occurs in neonates, especially premature infants.

Prerenal failure accounts for more than one third of the pediatric cases of AKI and requires prevention and adequate homeostatic corrections with a careful fluid challenge [3]. Intrinsic renal failure is mostly linked to acute tubular necrosis and often necessitates renal replacement therapy due to the prolongation of renal insufficiency. Postrenal failure may require surgical removal of the obstruction. In all cases, the presenting signs and symptoms may be dominated or modified by the precipitating disease. Clinical findings related to AKI include pallor (anemia), diminished urine output, edema, (salt and water overload), hypertension, vomiting, and lethargy (uremic encephalopathy), while laboratory abnormalities are typical of a status of renal insufficiency, often requiring substitution of renal function by dialysis (see also Chap. 37).

The characteristics of the syndrome have changed little in the last three decades. The only exceptions are that AKI today is frequently part

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of a multiple organ dysfunction syndrome (MODS), and patients are sicker and more complicated than in previous years.

In this chapter, we will describe our experience and that of others in the management of AKI in infants and children through the development of new devices and new equipment, especially in the area of continuous renal replacement therapies (CRRT) [4]. Our own involvement in the development of CRRT for children was unexpected. Our adult nephrology team had little experience and certainly no prior competence in pediatric dialysis. However, our center in Vicenza is a major cardiac surgery center for children as well as adults. We received frequent requests to assist in the management of infants and children who had AKI after cardiac surgery, and our accumulated experience in the field of adult CRRT, together with a specific interest in bridging engineering and nephrology, made it possible to start the adventure of CRRT in infants and children in the early 1980s [5, 6].

The Birth of CRRT in Infants and Children

During the 1980s, advances in dialysis technology had made intermittent hemodialysis possible even in small patients. This technique however, was difficult and not routinely applied to small children in the critical care setting, especially in infants in whom AKI was frequently associated with severe cardiovascular instability, respiratory problems, and other medical complications which precluded hemodialysis because of the induction of severe hemodynamic instability [7]. As a result, peritoneal dialysis (PD) was used more often for blood purification in infants and produced satisfactory clinical results in most patients [7]. However, PD was technically impossible or undesirable in cases of recent abdominal surgery and/or abdominal skin infection. In addition, severe fluid overload at times could not be effectively treated by PD because of its low ultrafiltration efficiency. In all these conditions, an alternative treatment was needed.

Continuous arteriovenous hemofiltration (CAVH) was a simple method for blood purification and body fluid control originally described by Kramer et al. in 1977 [8]. A small hemofilter was connected to an artery and a vein, and the simple arteriovenous hydrostatic gradient generated by the heart moved the blood through the circuit, producing slow continuous ultrafiltration. Blood purification was mainly achieved by convection. Replacement of ultrafiltrate by substitution solutions contributed to lower solute levels in the blood. No pumps were used in the classic method, and the system operated with low blood flows and low transmembrane pressures [9–14]. Beginning in 1979, CAVH was widely used in our center in Vicenza, Italy in adults as an alternative treatment for critically ill patients in whom HD or PD were contraindicated or precluded. We in the Nephrology Division contributed to the evolution of the technique and the deeper understanding of CAVH, focusing our studies on development of new devices and specific hardware [15–17]. Although we were not a pediatric nephrology division, we had recurrent requests from pediatric surgery for immediate delivery of renal replacement therapy (RRT) in neonates developing AKI after cardiac surgery . Our feeling was that the simplicity, rapid application, and good clinical tolerance demonstrated by CAVH in the adult patient could make it a reliable treatment also for infants and children [5, 18, 19]. In pediatric patients, the technique could offer special advantages in terms of the low priming volume of the extracorporeal circuit, low rate of heparinization [20], low blood flow, and slow continuous removal of isotonic fluid.

In the early 1980s, thanks to a fruitful collaboration with Professor Juan Bosch at Mount Sinai Hospital in New York, and Eng. Luciano Fecondini, the head of Research and Development at Amicon Corporation in Ireland, the idea of pediatric CAVH became a reality [5, 18, 19].

One day in early 1981 in Vicenza, a neonate was brought to our attention who was olguric due to AKI after extensive abdominal surgery. HD could not be performed and PD was impossible because of the large peritoneal breach. We had

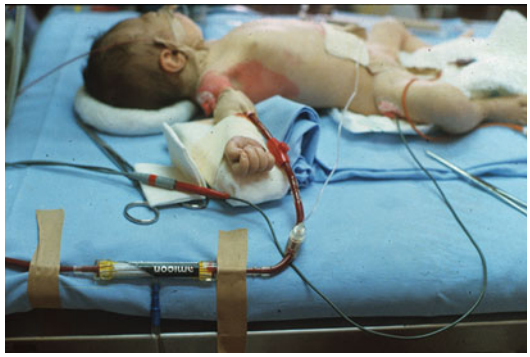

Fig. 38.1 First in the world pediatric patient treated with CAVH. Vicenza, Italy, 1981 (from the author's collection)

four small prototype filters containing only a few hollow fibers intended to be used to separate plasma water from blood in the laboratory. After obtaining the parents' consent, we created a modified CAVH circuit with shortened blood lines and the small filter, connecting the circuit to an artery and a vein. The circuit ran for 48 h, after which it was replaced with another similar circuit that ran for more than 72 h. Heparin and substitution fluids were administered according to fluid balance requirements. Although we were operating in uncharted waters, all the skills learned in the adult patient proved useful in the neonate, and an average ultrafiltration rate of 0.9 mL/min was maintained throughout the 6 days of treatment until renal recovery occurred and the patient survived. In Fig. 38.1 is a photograph of this first in the world pediatric CAVH treatment carried out at the San Bortolo Hospital in Vicenza in 1981.

From that moment, we realized that CAVH in neonates could be done successfully. The profound knowledge of CAVH operations in adults and the possibility of technical developments for new extracorporeal circuits and filters stimulated the production of a new series of devices called "Minifilters".

The Evolution of CRRT in Infants and Children

The success of the initial experience led to an immediate evaluation of the requirements for adequate CAVH in infants: a reliable vascular access, adequate technical devices and supplies, specific extracorporeal circuits, precise ultrafiltration control systems, compatible fluids for replacement, adequate anticoagulation regimens, and accurate monitoring systems to improve quality of management, safety, and performance.

Vascular Access

An adequate vascular access in CAVH was required to generate the arteriovenous hydrostatic gradient moving the blood through the filter [21]. Short, large diameter cannulas were critical to achieve good blood flow while avoiding unnecessary pressure loss. Flexibility without reduction of the inner lumen of the cannula and good clinical tolerance were other important features of the vascular access.

Several vascular access routes were utilized in infants in the early 1980s, including the umbilical vessels used in a neonate treated at Mount Sinai Hospital in New York (Fig. 38.2). Special catheters were used and specific nomograms were designed to assess the length of the cannulas in the umbilical vessels. However, this type of access could not be used for long periods and could not be used at all in patients older than 4–5 days [22, 23]. Brachial artery or femoral artery cannulation represented more reliable vascular access (Fig. 38.3). Surgical isolation of the artery was preferred in order to avoid hematomas or hemorrhagic complications. Flexible Teflon cannulas, 18–20 gauge and 20–25 mm long were generally employed. The cannulas were fixed to the skin to avoid accidental disconnection or unwanted folding with reduction of blood flow. In bigger children, percutaneous cannulation of the above mentioned vessels could be performed with the standard Seldinger technique. Mean arterial pressure in the newborn generally ranged from 35 to 50 mmHg resulting in blood flows ranging from 15 to 50 mL/min [24].

Cannulation of the brachial or femoral artery in infants led in some cases to distal hypoperfusion or even occlusion of the vessels. Although long-term complications were seldom observed, acute occlusion occasionally resulted in proximal propagation

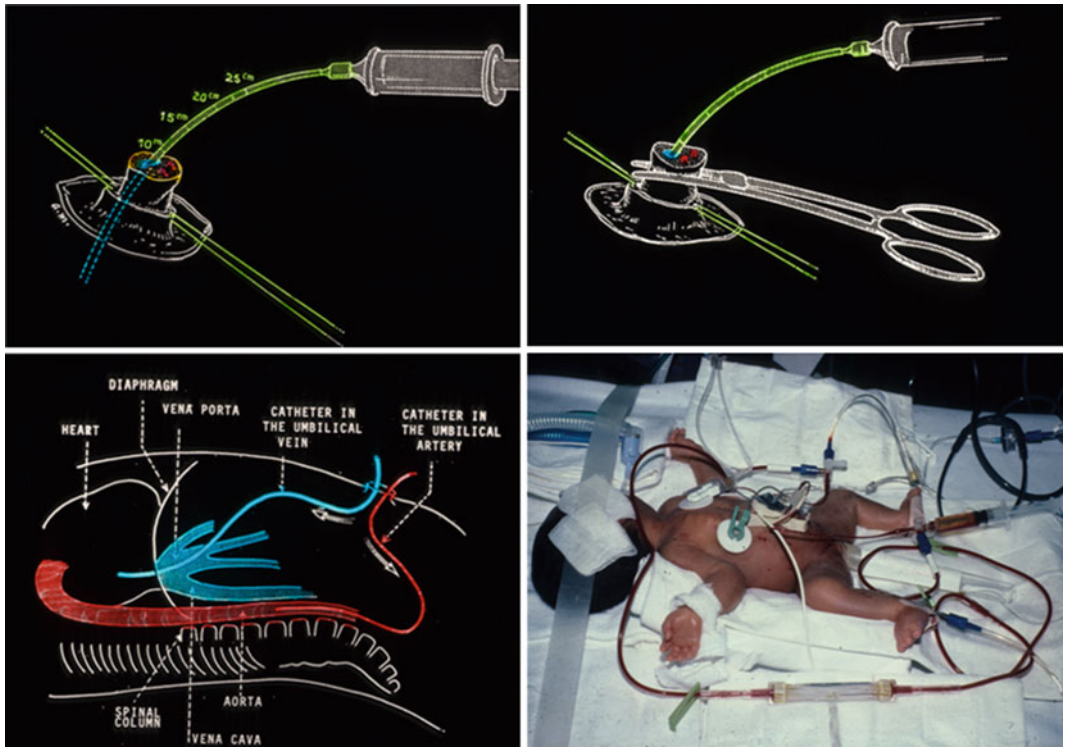

Fig. 38.2 Umbilical vessel access for CAVH in a neonate (Courtesy of J. Bosch, MD, 1987)

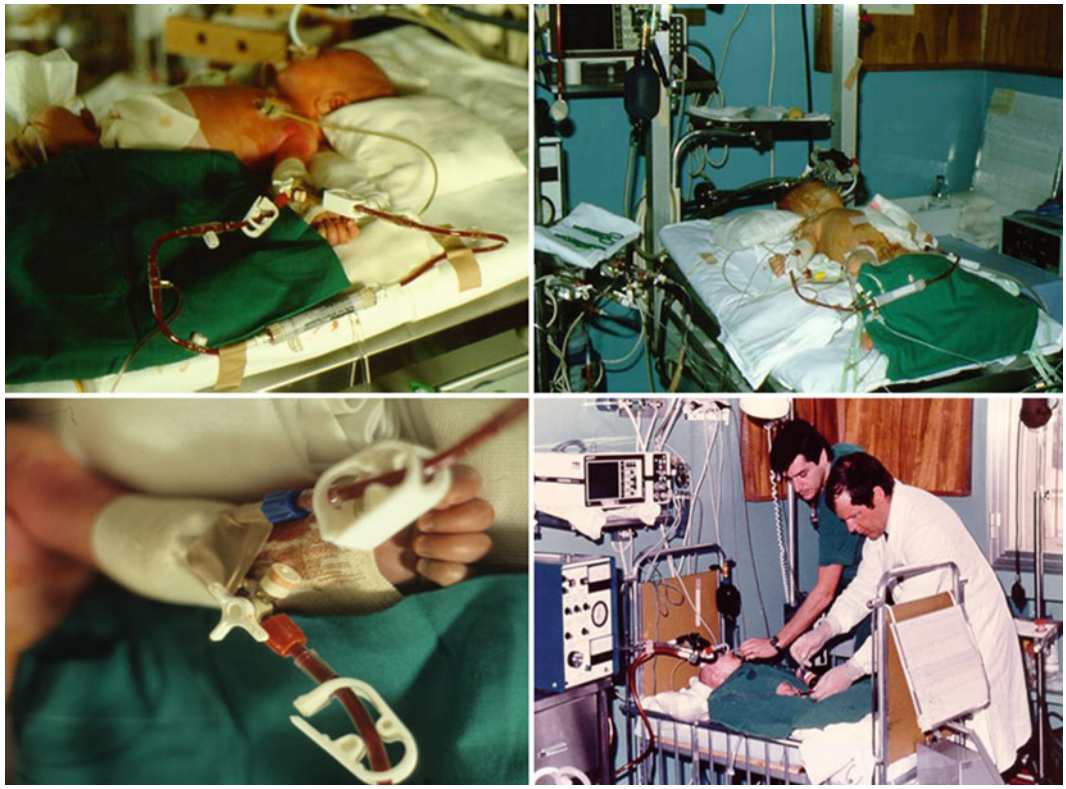

Fig. 38.3 Brachial or femoral artery cannulation for CAVH in a neonate ca 1980s (from the author's collection)

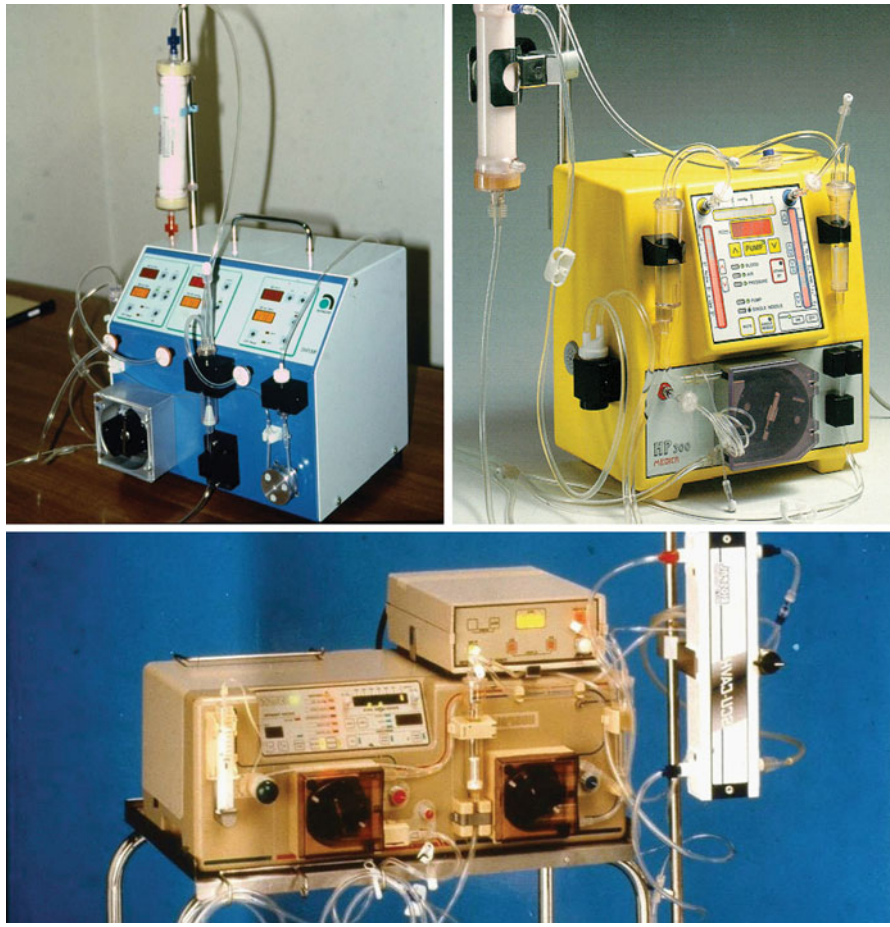

Fig. 38.4 Early CVVH machines, ca 1990 (from the author's collection)

of clot and limb-threatening ischemia. For this reason, perfusion in the extremity and cannulation site was always rigorously monitored.

The jugular or subclavian veins were the most common route for venous return. However, cannulas routinely used for fluid infusion (such as those for parenteral nutrition and central venous pressure measurement) were extremely thin and too long for CAVH. Short lines with large inner diameter (18 gauge) were created from standard blood lines to reduce undesired resistance in the extracorporeal circuit.

In the early 1990s, two central veins, or a double lumen catheter inserted in a single central vein began to be used in conjunction with new blood pumps to perform continuous veno-venous hemofiltration (CVVH) (Fig. 38.4). This innovation presented the advantage of reducing the risk of arterial bleeding while guaranteeing a stable blood flow rate resulting in consistent performance of the treatment. In CVVH, however, the priming volume of the extracorporeal circuit was necessarily increased, and it became advisable in very small patients to start the procedure with a blood primed circuit. Despite the fact that CVVH was a more efficient technique, the use of a blood pump and the more complex layout of the extracorporeal circuit made CVVH somewhat less suitable for infants which delayed the development of the veno-venous approach in infants compared to the treatment for larger children and adults.

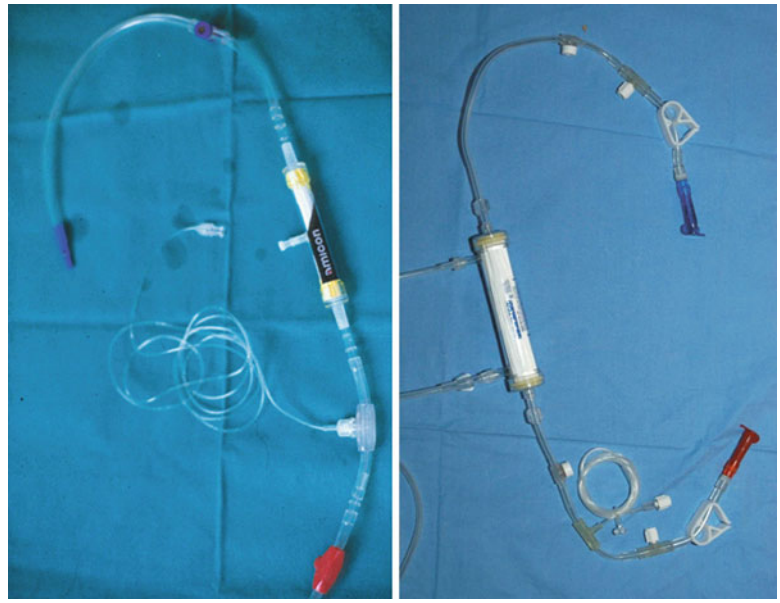

Fig. 38.5 Two early commercially available tubing sets developed for CAVH in infants, ca 1980s (from the author's collection)

Extracorporeal Circuit

Standard pediatric hemodialysis lines (inner diameter 0.3 cm) were initially modified in order to obtain arterial and venous lines adequate for CAVH. Subsequently, blood tubing especially created for CAVH in infants was made commercially available (Fig. 38.5). The arterial line had to be as short as possible in order to avoid an inacceptable pressure drop due to high resistance. Since CAVH operated at low pressures, a loss of 5–10 mmHg could seriously affect the ultrafiltration rate and consequently treatment efficiency. For the same reason, a hemofilter with a very low end-to-end pressure drop was required together with short, large-bore connections between the venous line and the vascular cannula. A port for continuous heparin infusion and another port for arterial blood sampling were incorporated in the arterial line. The sampling port could also be used for pressure measurements or for the use of the filter in a pre-dilutional mode in which replacement fluid was infused before the hemofilter [24–26].

The venous line contained a port for the infusion of replacement solutions and a venous blood sampling port, which could also be used for pressure measurements. At the inlet and outlet of the circuit, wide-bore three-way stopcocks were often placed in order to exclude the patient's circulation during lavage of the filter with heparinized saline solution. Kinking of the arterial and venous lines was carefully avoided during treatment (Fig. 38.6).

The ultrafiltrate line was kept as long as possible in order to maximize the negative pressure exerted on the membrane by the ultrafiltrate column. This pressure definitely contributed to increasing ultrafiltration (Fig. 38.7). The low priming volume (less than 20 mL) further increased clinical tolerance of the treatment. When a blood pump was subsequently added to the circuit to perform CVVH, two veins or a single vein with a double lumen catheter were cannulated, and all the methods employed to increase blood flow during CAVH became less important since a constant blood flow was provided by the pump during CVVH. At blood flows between 20 and 80 mL/min, pressure sensors within the blood lines were required to minimize the risk of damage to the vessels and any possible mechanical complication. New blood lines allowed continuous monitoring of the pre and post filter pressures, thus making possible the continuous evaluation of filter and circuit patency [26].

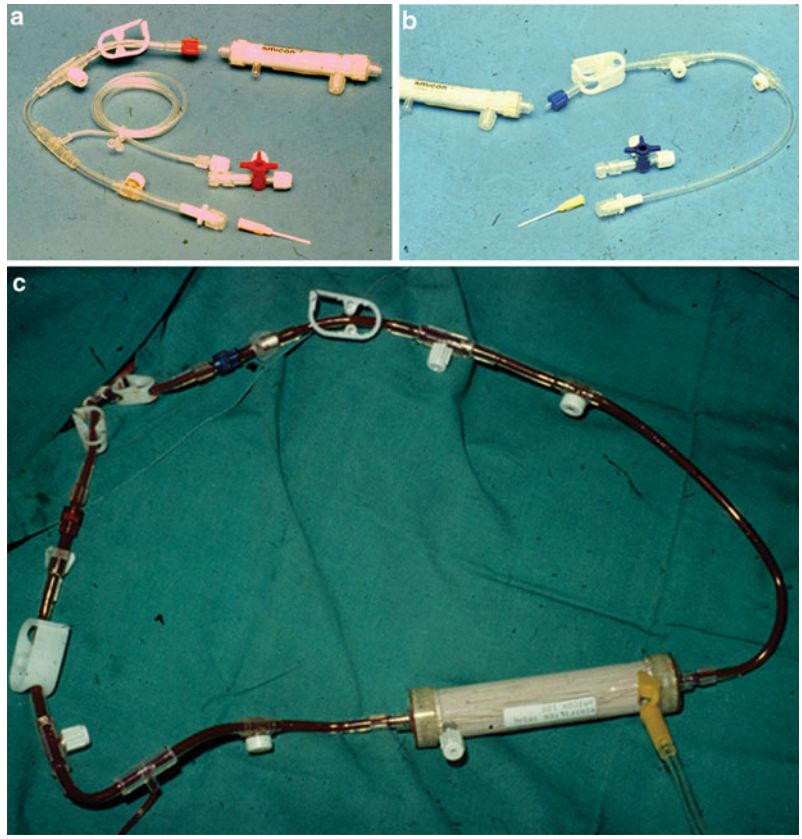

Fig. 38.6 (**a**) The arterial limb of early CAVH circuit tubing developed for use in infants, ca 1980s (from the author's collection). (**b**) The venous limb. Note the presence of short, large-bore stopcocks and connections to the vascular catheters in both arterial and venous limbs (from the author's collection). (**c**) An early CAVH circuit in operation in an infant, ca 1980s (from the author's collection)

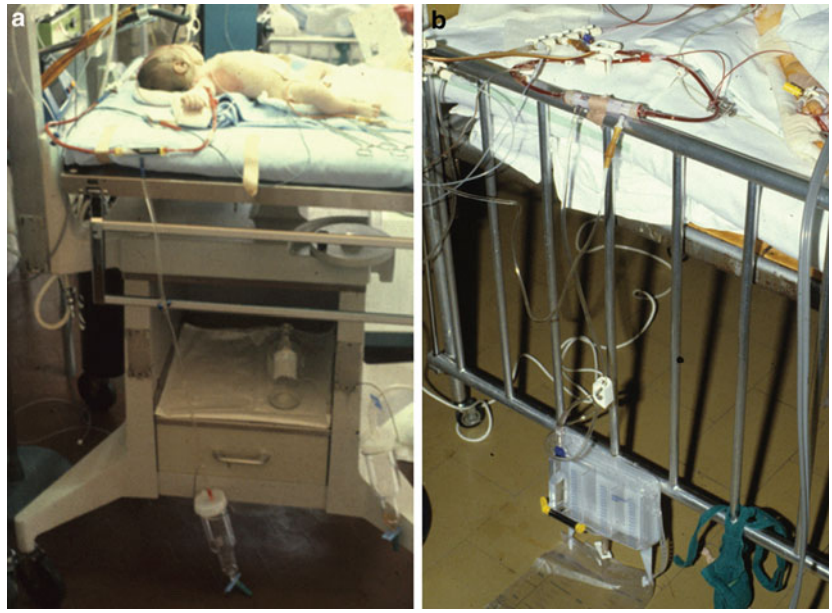

Fig. 38.7 (**a**) and (**b**) Two early infant CAVH circuits in operation, ca 1980s. Note the long ultrafiltrate lines to maximize negative pressure on the membrane and the different ultrafiltrate collection devices (from the author's collection)

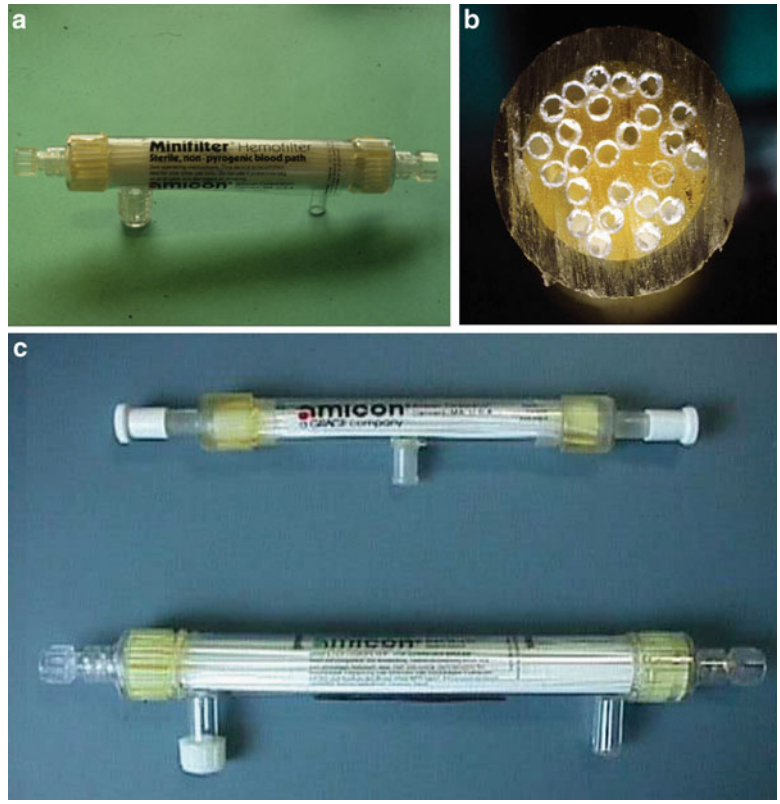

Fig. 38.8 (**a**) and (**c**) Early polysulfone hemofilters developed for use in CAVH in infants (from the author's collection). (**b**) An early hemofilter prototype developed for use in CAVH in infants. Note the large inner diameter of the hemofilter fibers needed to minimize resistance to flow (from the author's collection)

The hemofilter also could be incorporated into extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal (ECCO2R) circuits thus permitting maintenance of an adequate fluid balance during treatment [27]. The minifilter circuit could also be used as a hemoconcentration device after open heart surgery. .

The Search for Specific Filters

The availability of adequate filters was the key to performing CAVH in infants. Small filters designed for standard hemodialysis that were in use in the 1980s were inadequate. In CAVH filters, low priming volumes had to be coupled with a very low resistance in the blood compartment. These conflicting features could not be achieved with standard fibers and designs. A definite improvement came from the development of a new polysulfone hollow fiber with larger inner diameter (500 and subsequently 1100 μm) (Fig. 38.8).

Soon thereafter hemofilters especially made for CAVH in infants and children became commercially available. Our initial clinical experience in the early 1980s was with a polysulfone hollow fiber hemofilter (0.005 m^2 surface area) made by Amicon (Danvers, Mass, USA). A few years later, this prototype was improved by increasing the surface area to 0.015 m^2 and incorporating optimized flow dynamic design. The new filter was called the "Minifilter". This filter however, was in some instances still insufficient to guarantee an adequate amount of ultrafiltrate per day. To meet all possible requirements of efficiency and performance, a newer series of minifilters was then developed by Minntech Corporation called the Minifilter Plus®. These filters were designed to operate with minimal end-to-end pressure drop during CAVH in infants. While variable results had been achieved with other "small" filters available at that time, optimal results were achieved with the Minifilter series (Fig. 38.9) specifically designed for infants

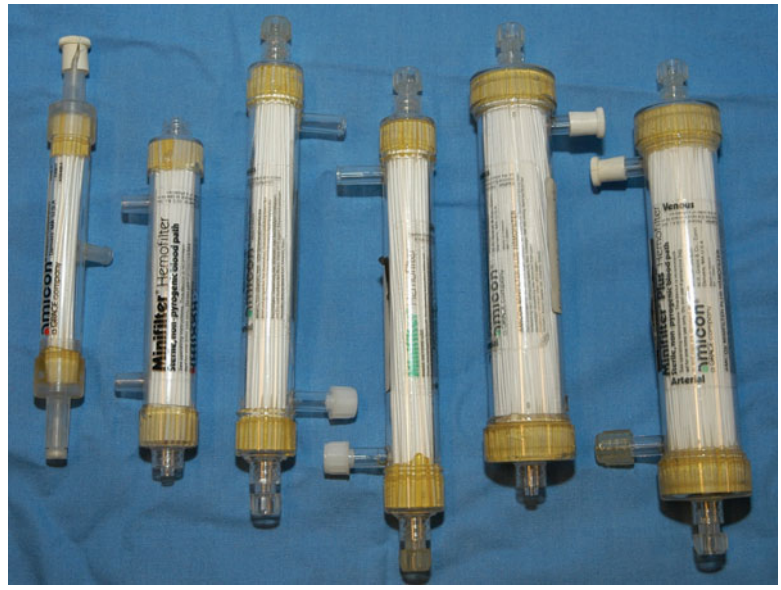

Fig. 38.9 The Minifilter® series. From the author's collection

Table 38.1 Characteristics of the minifilters

	First prototype	Minifilter	Minifilter plus
Overall length (cm)	13	13	17
Effective length (cm)	7	12.7	12.7
Diameter (cm)	1.5	1.7	2.5
Membrane type	Assymm. PSF	Assymm. PSF	Assymm. PSF
Membrane area (cm^2)	50	210	800
Fiber int. diameter (μm)	1100	1100	570
Priming volume (mL)	2.8	7.6	15
Pr drop (50 mL/min) (mmHg)	2.5	3.5	5
Number of fibers	25	60	450
Range of ultraf. (mL/min)	0.2–0.5	1–2.5	1–8

(see Table 38.1). Low resistance was the most attractive feature of the filters, since high flows were obtained even at very low perfusion pressures. When the filters were utilized in clinical conditions, additional factors, such as the negative pressure exerted by the ultrafiltrate column, helped to increase the rate of ultrafiltration. The Minifilters achieved ultrafiltration rates between 0.5 and 1.5 mL/min for TMP values between 20 and 70 mmHg and a blood flow of 20 mL/min with a plateau value at 2.0–2.5 mL/min. At similar pressures, the Minifilter Plus displayed UF rates significantly higher (in the range of 3–4 mL/min) when the blood flow exceeded 50 mL/min.

In such filters, filtration pressure equilibrium (Hydrostatic pressure = oncotic pressure) does not occur, and low filtration fractions are obtained. This permits an extended filter span life and lower heparin requirement compared to that observed in hemofilters for adults [28].

The new Minifilters had two ports in the ultrafiltrate compartment, permitting the use of a countercurrent flow of dialysate. In this case, the treatment was named CAVHDF (Continuous Arterio-Venous Hemo-diafiltration) since both diffusive and convective solute transport mechanisms were employed . Dialysate flows up 10 mL/min could be routinely achieved [29–32].

The Search for Performance

Synthetic polysulfone, polyamide, or AN 69S membranes have been commonly employed in CAVH-CVVH filters. In CAVH, this resulted in an ultrafiltrate with the same composition as plasma water [32].

In our experience with CAVH, no reduction in membrane permeability had been noted after as much as 86 h of treatment. Periodic lavages of the filter with small quantities of heparinized saline helped to prevent the negative effect of protein "concentration polarization" [28–32].

When dialysis fluid was circulated in the filters (CAVHDF-CVVHDF), the combination of diffusive and convective clearance allowed a significant enhancement of small solute clearance [33–39].

Since a remarkable quantity of thermal energy was lost in the hemofilter, it became advisable to monitor the temperature of dialysis or replacement solutions. In CAVHDF in fact, the hemofilter was like a heat exchanger, and hypothermia was a possible complication.

Anticoagulation

Preparation of the filter for CAVH treatment was extremely important for its function and duration during therapy. At the beginning, liposoluble compounds were present in the structure of the fibers to maintain porosity and permeability. These compounds were removed prior to treatment by rinsing the filter with 1,000 mL of heparinized saline solution (5,000 IU of heparin/l of saline). During the washing procedure, the venous line and the ultrafiltration line had to be clamped periodically in order to remove paraffin and air bubbles from the system.

Since the population treated with CAVH was often at risk of bleeding, the main goal of anticoagulation was to achieve an adequate local effect without any systemic consequence. Since heparinization was conducted empirically in the first treatments, whole-blood activated clotting time and partial thromboplastin time were carefully monitored. After the determination of these parameters under baseline conditions, if they were within normal ranges a bolus of heparin was administered (100 IU/kg body weight). After these procedures, a continuous heparin infusion of 5–10 IU/kg body weight/h was generally adequate to maintain effective extracorporeal anticoagulation with minimal systemic effects. Subsequently, with the improved understanding of the rate of heparin metabolism in the newborn, the amount of anticoagulant was adjusted case by case. At infusion rates between 5 and 8 IU /h/kg, maximal anticoagulation was achieved in the filter with minimal effects in the systemic circulation. This anticoagulation generally allowed maintenance of a filter in use for days without clotting of the fibers and consequent need for replacement of the unit.

Periodic lavages of the circuit with saline helped to assess the condition of the filter and to assure the complete absence of clots. To avoid acute fluid overload during this procedure, the patient was excluded from the circuit using the three-way taps.

Substitution Fluids and Fluid Balancing Systems

The removal of large amounts of ultrafiltrate from the patient (1–2 L/day) required the administration of substitution fluid. Depending on the patient's requirements, ultrafiltrate was replaced in part, in whole, or even in excess. The replacement solution was initially administered by manual methods and only subsequently semiautomatic, or completely automatic systems were employed. It was clear that particular care had to be placed in obtaining the scheduled fluid balance because of the high sensitivity of the neonate even to small variations in body fluid balance and composition. We utilized a simple gravimetric control system (EQUALINE®, Medica – Medolla, Italy) as a safe and reliable device for precise fluid balance during CAVH, over a prolonged period of time [33] (Fig. 38.10).

The replacement solution was generally prepared by the pharmacy or simply taken from the bags used for adult hemofiltration. Its composition had to be adapted to the metabolic requirements and to the electrolyte imbalances recorded in the patient. In our experience, replacement solutions containing lactate used for chronic hemofiltration were adequate in the majority of patients. Because

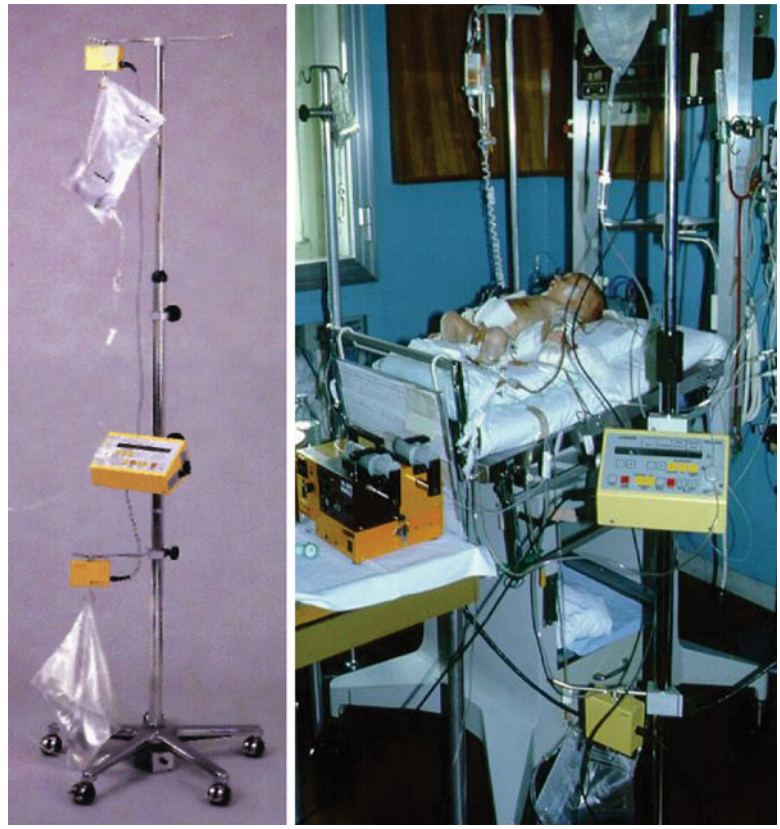

Fig. 38.10 A simple gravimetric control system (EQUALINE®, Medica – Medolla, Italy) employed as a safe and reliable device for precise fluid balance during CAVH, over a prolonged period of time, ca 1980s (from the author's collection)

of lactate intolerance in some infants, bicarbonate containing replacement solutions were sometimes necessary, and in that case calcium and magnesium were separately administered.

The Modern Practice of CRRT in Infants

The indications for RRT in pediatric patients have changed through the years and the present trend is toward a wider spectrum of applications including prevention of fluid accumulation and management of multiple organ dysfunction syndrome (MODS) [40–42]. Up to 20% of all pediatric patients with MODS are represented by children undergoing cardiac surgery, and these patients are most likely to require RRT [43]. The two RRT modalities most frequently used in infants are peritoneal dialysis (PD) and CRRT. PD is relatively easy to perform, does not require heparinization nor vascular access (often complicated in infants) and is generally well tolerated in hemodynamically unstable patients [44]. PD is currently the RRT treatment of choice in neonates, unless specific contraindications are present (i.e. peritonitis, abdominal masses, or bleeding). Nonetheless, one of the main disadvantages of PD in these patients is a relative lack of efficiency, especially in water removal with direct consequences on fluid balance and frequent limitation of parenteral nutrition in particular when the treatment of a highly catabolic patient is required. Given these limitations, the early application of PD in order to achieve the prevention and treatment of fluid overload is presently recommended [45]. In particular, infants and children with specific risk factors for AKI should be considered for the preventive use of PD. Sorof et al. described an extraordinary high survival rate (80%) in a group of infants with post–heart surgery AKI in which PD was started much earlier than in other studies

(time to PD application after surgery: 5–40 h) [46]. Although a very limited experience, this study confirms that prevention of renal failure and/or fluid accumulation directly affects survival in these patients. PD is known to offer a limited depurative performance if compared with extracorporeal techniques [47]. Moreover, in post–heart surgery infants, the application of high dialysate volumes to increase PD clearance is difficult. Adverse alterations of atrial, mean pulmonary artery and systemic pressures have been observed in chronic PD and in children after cardiac surgery [48]. For this reason, a PD exchange volume of 10 mL/kg is commonly prescribed during neonatal renal replacement therapy after cardiac surgery [49]. Prevention of volume overload has prompted some centers to deliver postoperative prophylactic peritoneal dialysis in neonates and infants after complex congenital cardiac surgery [50]. Both ultrafiltration and solute clearance occur rather slowly in patients undergoing PD. Extracorporeal dialysis can be managed with a variety of modalities, including intermittent hemodialysis, and continuous hemofiltration or hemodiafiltration. The choice of dialysis modality to be used is influenced by several factors, including the goals of dialysis, the unique advantages and disadvantages of each modality, and institutional resources. Intermittent dialysis may not be well tolerated in infants because of its rapid rate of solute clearance and in particular in hemodynamically unstable pediatric cardiac surgery patients [51]. These children are generally treated by CRRT that seems to better provide both fluid and solute re-equilibration and proinflammatory mediator removal.

Current Challenges and Future Developments

AKI in Neonates: An "Orphan Disease"

AKI/ARF in infants is a dramatic syndrome requiring careful clinical management. In recent years, in spite of significant advances in technology, a truly pediatric CRRT system has yet to be developed. While some currently available CRRT machines have been equipped with pediatric circuits and lines demonstrating an attempt to comply with the specific requirements of the very small patient, most machines, if not all, are used off label when patients below 15 kg are treated. The small number of cases, together with the limited interest of industry in development of a fully integrated device specifically designed for the pediatric population, have made AKI/ARF in infants and neonates an "orphan disease"

Current CRRT machines present significant limitations for the pediatric population and in some cases, severe complications have occurred.

In current practice, clinical application of dialysis equipment to pediatric technology is now substantially 'adapted' to smaller patients with great concerns about outcomes and side effects of such extracorporeal therapy. In these conditions, whereas adult critically ill patients receive renal support with modern devices and very strict safety features, smaller patients cannot rely on accurate delivery of therapy especially as far as fluid balance is concerned. It is extremely difficult to treat a small infant with a dialysis monitor providing accurate blood flow rates in the range of 10–50 mL/min and hourly ultrafiltration error below 5 mL/h. Since manufacturers of dialysis and CRRT machines do not perform specific tests of treatments in patients smaller than 10–15 kg and safety features for these small patients have not been specifically created, legal concerns may arise when operators decide to prescribe these therapies.

The CA.R.PE.DI.E.M. Project

The Cardio-Renal, Pediatric Dialysis Emergency Machine (CARPEDIEM) project recently developed in Vicenza, was designed in order to create a CRRT system specifically dedicated to newborns and small infants with a weight range of 2.0–9.9 kg and with an approximate body surface area from 0.15 to 0.5 sq meters. In these patients, the total blood volume ranges from 200 mL to 1 L, meaning that total body water content varies from 1 to 5 L. In such conditions, a dedicated machine should include exchange volumes ranging from 30 to 500 mL/h (Fig. 38.11). The CARPEDIEM project has been conceived in Vicenza, Italy, with the collaboration of two

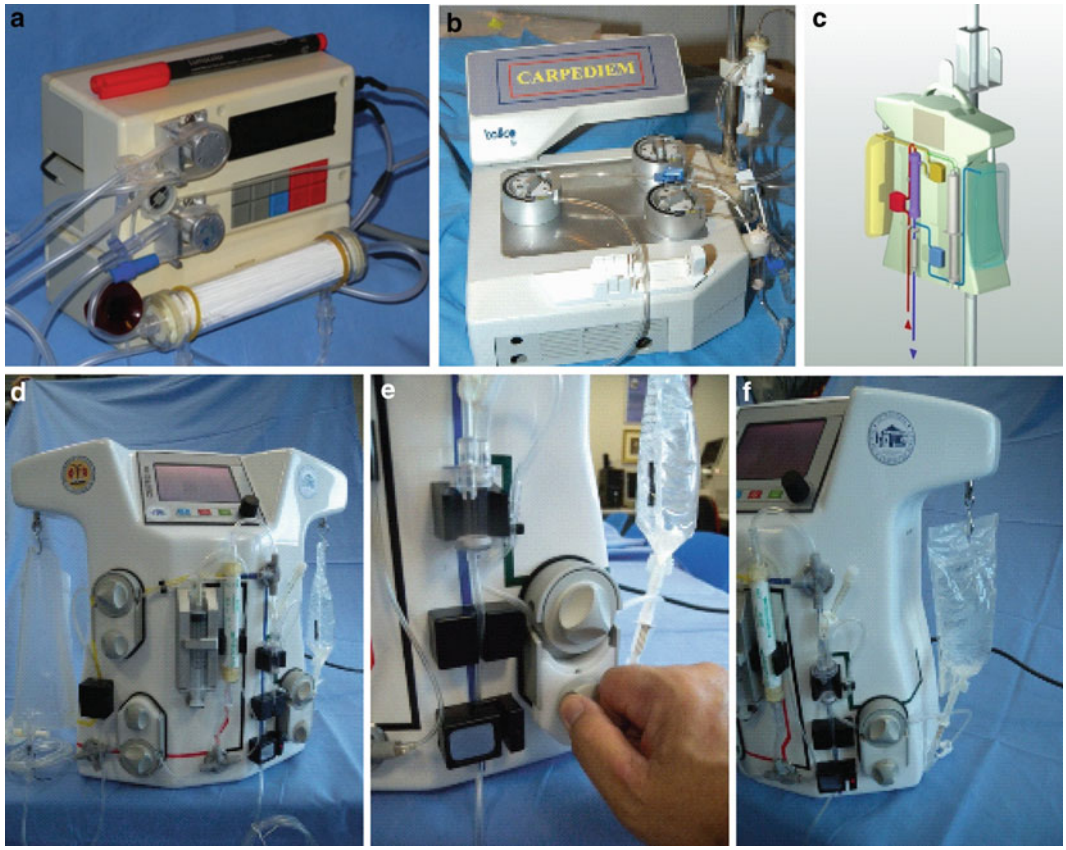

Fig. 38.11 The cardio-renal, pediatric dialysis emergency machine (CARPEDIEM) project: CRRT equipment specifically dedicated to newborns and small infants. (**a** and **b** prototypes from the author's collection) (**c**) first drawing of the new machine. (**d**, **e,** and **f**), overall view and details of the new CARPEDIEM machine

Italian pediatric cardiosurgical centers (Milan and Rome). The system operates with a hemofiltration circuit featuring a very low priming volume (15 mL for the whole circuit including the hemofilter). Low blood flows (20 to 80 mL/min) and very low ultrafiltration rates (UFR = 1–8 mL/min) are performed with an accuracy of fluid balance of 0.1 mL/min. Dedicated technology has been developed for this purpose.

Conclusions

Multiorgan dysfunction remains a deadly syndrome in the care of critically ill patients. Renal replacement has evolved into a complex intervention directed at support of the function of several organs. Today the care of the acute patient has reached a level of complexity that requires a dedicated series of devices and machines and, eventually, their integration into a single device: ECMO, CRRT, hemoperfusion, adsorption, or plasmafiltration and adsorption might be integrated in the future into a single multifunctional machine with a very user-friendly interface. Advances in information technology should allow the fully integrated extracorporeal blood purification system to be connected to all electronic therapeutic devices (from simple syringe pumps to CRRT machines), in order to ultimately lead to an "artificial organ" in a more complete sense. These therapeutic approaches are today carried out safely in children above 10–15 kg but not in neonates. As machines have become more accurate and therapies have improved significantly, the discrepancy between the level of accuracy required in the neonate and that effectively delivered has become manifest. A new generation

of equipment will be required to effectively treat the very small infant. It is hoped that the CARPEDIEM project under development in the very same center (Vicenza) where the story of CRRT in infants began three decades ago will fulfill these requirements.

Acute renal failure is a severe clinical condition that is further complicated in small children by the peculiar problems of these patients. Early diagnosis, prevention, conservative measures, and renal replacement therapies are all part of a common approach that must be undertaken in these high risk patients.

Outcomes may vary significantly depending on the underlying disease, the severity of illness, and the time of intervention. New technological advances are helping the clinician to improve the quality of treatment and diagnosis. A multidisciplinary approach involving all critical care medicine specialties and contributors is needed to achieve the best possible care of these patients.

References

1. Devarajan P. Pathophysiology of pediatric acute kidney injury. In: Ronco C, Bellomo R, Kellum J, editors. Critical care nephrology. 2nd ed. Philadelphia: Sounders-Elsevier; 2009. p. 1581–9.
2. Goldstein S. Epidemiology of pediatric acute kidney injury. In: Ronco C, Bellomo R, Kellum J, editors. Critical care nephrology. 2nd ed. Philadelphia: Sounders-Elsevier; 2009. p. 1589–92.
3. Bunchmann TE. Treatment of acute kidney injury in children: conservative management to renal replacement therapy. In: Ronco C, Bellomo R, Kellum J, editors. Critical care nephrology. 2nd ed. Philadelphia: Sounders-Elsevier; 2009. p. 1592–5.
4. Ronco C, Polaschegg HD. History and development of continuous renal replacement therapy. In: Ronco C, Bellomo R, Kellum J, editors. Critical care nephrology. 2nd ed. Philadelphia: Sounders-Elsevier; 2009. p. 1323–8.
5. Ronco C, Brendolan A, Bragantini L, La Greca G. Treatment of acute renal failure in newborns by continuous arteriovenous hemofiltration. Trans Am Soc Artif Internal Organs. 1985;41:634–8.
6. Trachtman H, Hackney P, Tejani A. Pediatric hemodialysis: a decade's (1974–1984) perspective. Kidney Int. 1986;30:S15–22.
7. Potter DE, San Luis E, Wippler JE, Portale AA. Comparison of continuous ambulatory peritoneal dialysis and hemodialysis in children. Kidney Int. 1986;30:S11–4.
8. Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F. Arteriovenous hemofiltration: a new and simple method for treatment of overhydrated patients resistant to diuretics. Klin Wschr. 1977;55:1121–5.
9. Lauer A, Saccaggi A, Ronco C, Belledonne M, Glabman S, Bosch JP. Continuous artriovenous hemofiltration in the critically ill patient. Ann Intern Med. 1983;99:455–61.
10. Olbricht CJ, Schurek HJ, Stolte H, Koch KM. The influence of vascular access modes on the efficiency of CAVH. In: Sieberth HG, Mann H, editors. Continuous arteriovenous hemofiltration. Basel: Karger; 1985. p. 14–24.
11. Jenkins RD, Harrison HL, Jackson EC, Fink JE. Continuous renal replacement in infants and toddlers. Contrib Nephrol. 1991;93:245–9.
12. La Greca G, Fabris A, Ronco C. CAVH Proceedings of the International Symposium on CAVH, Vicenza. Milano: Wichtig Ed; 1986.
13. Ronco C, Brendolan A, Bragantini L, La Greca G. Self limited dehydration during CAVH. Blood Purif. 1984;2:88–93.
14. Ronco C, Brendolan A, Bragantini L, La Greca G. Studies on blood flow dinamic and ultrafiltration kinetics during continuous arteriovenous hemofiltration. Blood Purif. 1986;4:220–6.
15. Ronco C, Brendolan A, Bragantini L, La Greca G. Continuous arterio-venous hemofiltration. Contr Nephrol. 1985;48:70–8.
16. Bartlett R, Bosch JP, Paganini EA, Geronemus R, Ronco C. Continuous arterio-venous hemofiltration. Trans Am Soc Artif Internal Organs. 1987;38: 345–52.
17. Paganini EP. Acute continuous renal replacement therapy. Boston: Martinus Nijhoff Publishing; 1986.
18. Lieberman KV, Nardi L, Bosch JP. Treatment of acute renal failure in an infant using continuous arteriovenous hemofiltration. J Pediatr. 1985;106:646–9.
19. Ronco C, Brendolan A, Bragantini L, La Greca G. Treatment of acute renal failure in the newborn by continuous arteriovenous hemofiltration. Kidney Int. 1986;29:908–15.
20. Zobel G, Trop M, Muntean W, Ring E, Gleispach H. Anticoagulation for continuous arteriovenous hemofiltration in children. Blood Purif. 1988;6:90–5.
21. Olbricht CJ, Schurek HJ, Tytul S, Muller C, Stolte H. Comparison between Scribner shunt and femoral catheters as vascular access for continuous arteriovenous hemofiltration. In: Kramer P, editor. Arteriovenous hemofiltration. Berlin: Springer Verlag; 1985. p. 57–66.
22. Ronco C, Bosch JP, Lew S. Technical and clinical evaluation of a new hemofilter for CAVH; theoretical concepts and practical applications of a different blood flow geometry. In: La Greca G, Fabris A, Ronco C, editors. Proc Intern Symp on CAVH. Vicenza: Wichtig Ed Milano; 1986.
23. Golper TA, Ronco C, Kaplan AA. Continuous arteriovenous hemofiltration: improvements, modifications and future directions. Semin Dial. 1988;1:50–4.

24. Pallone TL, Peterson J. Continuous arteriovenous hemofiltration, an in vivo simulation. Trans Am Soc Artif Internal Organs. 1987;33:304–8.
25. Ronco C, Brendolan A, Borin D, et al. Continuous arterio-venous hemofiltration in newborns. In: Sieberth H, Mann H, editors. Proc Int Conference on CAVH, Aachen. Basel: Karger; 1985. pp. 76–9.
26. Ronco C, Fecondini L, Gavioli L, Conz P, Dell'Aquila R, Bragantini L, Chiaramonte S, Brendolan A, Crepaldi C, Feriani M, La Greca G. A new blood module for continuous renal replacement therapies. Int J Artif Organs. 1994;17:29–33.
27. Stolar CJ, Snedecor SM, Bartlett RH. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience from the extracorporeal life support organization. J Pediatr Surg. 1991;26:563–71.
28. Pappenheimer Jr AM. Passage of molecules through capillary walls. Physiol Rev. 1953;33:387–423.
29. Geronemus R, Schnaider N. Continuous arteriovenous hemodialysis. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy. Ft. Lauderdale, Paganini E, Geronemus R, editors, 1987. pp. 77–85.
30. Ronco C. Arterio-venous hemodiafiltration (AVHDF): a possible way to increase urea removal during CAVH. Int J Artif Organs. 1985;8:61–2.
31. Ronco C. Continuous renal replacement therapies and the polyamide membrane. Contr Nephrol. 1992;96: 111–23.
32. Ronco C, Brendolan A, Bragantini L, La Greca G. Solute and water transport during continuous arteriovenous hemofiltration. Int J Artif Organs. 1987;10: 179–84.
33. Brendolan A, Ronco C, Crepaldi C, Feriani M, Milan M, Fecondini L, La Greca G. Clinical use of a new fluid balancing system: a useful complement to continuous replacement therapies. J Nephrology. 1993;6:149–52.
34. Ronco C, Burchardi H. Management of acute renal failure in the patient critically ill. In: Dhainaut JF, Pinsky M, editors. Pathophysiologic foundations of critical care. Baltimore: Williams & Wilkins; 1993. pp. 630–76.
35. Ronco C. Continuous arterio-venous hemofiltration: optimization of technical procedures and new directions. In: Horl WH, Schollmeyer P, editors. New perspectives in hemodialysis, peritoneal dialysis, arteriovenous hemofiltration and plasmapheresis. New York: Plenum Press; 1987. pp. 167–81.
36. Zobel G, Ring E, Kuttnig M, Grubbauer HM. Continuous arterio-venous hemofiltration versus continuous veno-venous hemofiltration in critically ill pediatric patients. Contrib Nephrol. 1991;93:257–60.
37. Ronco C, Brendolan A, Bragantini L, La Greca G. Arterio-venous hemodiafiltration associated with continuous arteriovenous hemofiltration. A combined therapy in the hypercatabolic patient. In: La Greca G, Fabris A, Ronco C, editors. Proceedings of the International Symposium on Continuous Arterio-Venous Hemofiltration, Vicenza. Milano: Wichtig Ed; 1986. pp. 171–83.
38. Ronco C. Acute renal failure in the neonate. Treatment by continuous renal replacement therapies. In: Bellomo R, Ronco C, editors. Acute renal failure in the critically ill. Heidelberg: Springer Verlag; 1995. p. 246–65.
39. Ronco C, Parenzan L. Acute renal failure in infancy: treatment by continuous renal replacement therapy. Int Care Med. 1995;21:490–9.
40. Bailey D, Phan V, Litalien C, Ducruet T, Mérouani A, Lacroix J, Gauvin F. Risk factors of acute renal failure in critically ill children: a prospective descriptive epidemiological study. Pediatr Crit Care Med. 2007;8:29–35.
41. 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, 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 multiorgan dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int. 2005;67:653–8.
42. Tantalean JA, Leon RJ, Santos AA, Sanchez E. Multiple organ dysfunction syndrome in children. Pediatric Crit Care Med. 2003;4:181–5.
43. Ricci Z, Carotti A, Parisi F, Grutter G, Di Donato RM, Picardo S. Extracorporeal membrane oxygenation and high-dose continuous veno-venous hemodiafiltration in a young child as a successful bridge to heart transplant for management of combined heart and kidney failure: a case report. Blood Purif. 2010; 29(1):23.
44. Fleming F, Bohn D, Edwards H. Renal replacement therapy after repair of congenital heart disease in children. J Thorac Cardiovasc Surg. 1995;109:322–31.
45. Alkan T, Evin AA, Tu Rkog Lu H, Paker T, Sas Mazel A, Bayer, Ersoy C, Askın D, Aytac A. Postoperative prophylactic peritoneal dialysis in neonates and infants after complex congenital cardiac surgery. ASAIO J. 2006;52:693–7.
46. Sorof JM, Stromberg D, Brewer ED, Feltes TF, Fraser Jr CD. Early initiation of peritoneal dialysis after surgical repair of congenital heart disease. Pediatr Nephrol. 1999;13:641–5.
47. Ricci Z, Morelli S, Ronco C, Polito A, Stazi GV, Giorni C, Di Chiara L, Picardo S. Inotropic support and peritoneal dialysis adequacy in neonates after cardiac surgery. Interact Cardiovasc Thorac Surg. 2008;7(1):116–20.
48. Dittrich S, Vogel M, Daihnert I, Haas NA, Alexi-Meskishvilli V, Lange PE. Acute hemodynamic effects of post cardiotomy peritoneal dialysis in neonates and infants. Intensive Care Med. 2000;26:101–4.
49. McNiece KL, Ellis EE, Drummond-Webb JJ, Fontenot EE, O'Grady CM, Blaszak RT. Adequacy of peritoneal dialysis in children following cardiopulmonary bypass surgery. Pediatr Nephrol. 2005;20:972–6.
50. Golej J, Kitzmueller E, Hermon M, Boigner H, Burda G, Trittenwein G. Low-volume peritoneal dialysis in 116 neonatal and paediatric critical care patients. Eur J Pediatr. 2002;161:385–9.
51. Flynn JT. Choice of dialysis modality for management of pediatric acute renal failure. Pediatr Nephrol. 2002;17:61–9.

Extracorporeal Liver Replacement Therapy for Pediatric Patients

39

Claus Peter Schmitt and Franz Schaefer

Keywords
Extracorporeal liver replacement • Pediatric patients • Acute liver failure

Acute liver failure (ALF) is a rare but life-threatening disorder in children. The spectrum of etiologies varies with age: Metabolic disorders predominate in infants, followed by neonatal hemochromatosis. In older children ALF is caused by viral hepatitis in 40% and by drug intoxication in 10%, while the etiology remains obscure in almost 50% of cases [1]. While one third of children recover with supportive management [2], the other two third require emergency liver transplantation. Likewise, the majority of children with acute-on-chronic liver failure and those with progressive chronic liver disease require liver transplantation. Since organ availability is limited and considerable bridging time may be required, extracorporeal liver support therapies are increasingly applied.

Four different artificial liver support systems are currently applied: the Molecular Adosrbents Recirculating System (MARS), Prometheus dialysis, plasmapheresis combined with hemodialysis (PP/HD), and single pass albumin dialysis (SPAD). MARS and Prometheus are approved medical devices applied in many countries in Europe, Asia, Latin America, and Australia. In the USA, MARS has recently been approved for drug overdosing.

All technologies have a limited elimination capacity of water soluble and protein-bound toxins and can only be applied for a limited period of time. None of the systems has been evaluated in prospective randomized trials in children and adolescents. Randomized controlled trials in adults have mostly compared liver dialysis systems to "standard medical therapy" without active toxin removal, while a few small-sized studies performed head-on comparisons of MARS and Prometheus.

The four different liver support systems are based on different technical approaches to remove protein-bound toxins. These encompass 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). While no single system appears generally superior to another, it is important to know the specific advantages and shortcomings of each technology in order to select the most

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appropriate liver support system available in a given critical care unit setting.

Indications for Extracorporeal Liver Support

The liver plays a key role in maintaining 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 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 only if a curative therapy, i.e., usually liver transplantation, or significant recovery of liver function can be expected (Table 39.1).

The policies at which degree of liver dysfunction extracorporeal liver support is initiated vary markedly among treatment centers. The following criteria should be taken into account in the decision to start extracorporeal liver support therapy: presence of hepatic encephalopathy stage 2 or higher, cerebral pressure and perfusion, hepatic cardiopathy and cardiocirculatory stability, coagulopathy (INR > 1.5–2.8), presence of hepatorenal failure, plasma bilirubin concentrations (>5–20 mg/dL), plasma ammonium levels and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (>1500 U/L). In addition to absolute numbers, the dynamics of liver dysfunction need to be considered.

Table 39.1 Indications for liver replacement therapy

- Acute liver failure
  - Bridging to liver transplantation
  - Post LTX in case of primary dysfunction
  - Liver dysfunction after hepatobiliary surgery
  - Acute intoxication
  - Acute hepatitis
- Secondary liver dysfunction (sepsis, systemic inflammatory response syndrome, multiorgan dysfunction syndrome)
- Acute-on-chronic liver failure (biliary atresia, progressive familial intrahepatic cholestasis …)
- Hepatic pruritus (biliary atresia, PFIC, ARPKD …)

In face of the limited efficacy of extracorporeal liver support, the high risk of life-threatening complications of ALF, and the usually excellent tolerability of the procedures, an early start of treatment appears justified particularly in patients exhibiting rapid disease progression.

The scientific evidence for an improved outcome of extracorporeal liver support is still limited, mainly due to the relatively low incidence of ALF and the still limited availability of advanced technologies. Studies comparing MARS and the Liver Dialysis Device Biologic DTT (see below) to standard medical therapy in adults suggest superiority of liver dialysis [3–6].

The indication for liver dialysis, efficiency and risk factors should be evaluated prior to and after each treatment by thorough clinical examination, including assessment of coma scale and hepatic encephalopathy scores, and by regular measurement of liver and dialysis-related biochemical parameters. These include bilirubin, ammonium, blood count, INR, PTT, fibrinogen, activated clotting time, bile acids, albumin, liver enzymes, CrP, creatinine, urea, electrolytes including phosphate, and acid base status. Factor VII, the coagulation factor with the shortest half-life (~4 h), is a sensitive parameter to assess liver synthesis.

Anticoagulation therapy is needed in about 40% of patients and should be administered if endogenous activated clotting time is below 160 s. Besides 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 indicated in case of coagulation failure. Hepatic citrate metabolism should be monitored closely; accumulation of citrate leads to metabolic acidosis and the "citrate lock" phenomenon, i.e., dissociation of ionized and total calcium levels. A second i.v. line is required for the calcium infusion; otherwise clotting of the venous dialysis catheter line is likely to occur.

Liver support therapy should be withheld in patients with circulatory failure and in case of critical progression of the underlying disease or fatal complications precluding a positive outcome. Treatment should also be discontinued in case of allergic reactions to components of the extracorporeal circuit.

Molecular Adsorbent Recirculating System (MARS)

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. 39.1).

Two different types of MARS filters are available; the adult system with 2.1 m² and the MARSmini filter set with 0.6 m² filter surface area. The extracorporeal volumes are 152 and 57 mL plus blood lines; the MARSmini system is recommended for patients with 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 (25) mL/min with MARS (MARSmini) at 200 and 100 mL/min blood flow rate and 500 and 30 mL/min dialysate flow rate 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 [7]. Due to its molecular cutoff around 50 kD proteins such as albumin, coagulation factors and immunoglobulins are not removed with MARS.

The blood flow rate should be around 3–5 mL/min/kg body weight, and the albumin dialysate flow rate should equal the blood flow rate. The sum of the secondary dialysate turnover and ultrafiltration rate should not exceed 20% of the blood flow rate. The secondary dialysate flow rate should be at least twofold 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 adsorber systems are saturated, or if required continuously with system exchanges every 8 h. The 8 h limit is given by the 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. In addition to the general recommendations given above, MARS should not be applied or discontinued in children with active bleeding. The coagulation status often deteriorates during MARS therapy. The underlying mechanisms include progressive

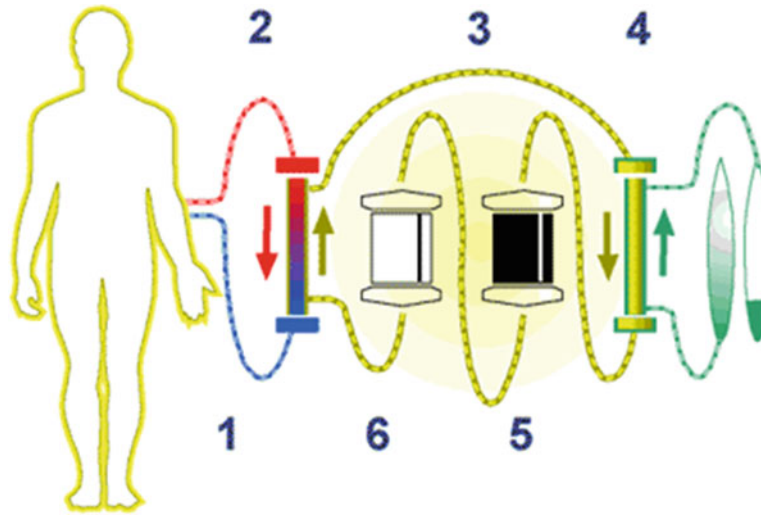

Fig. 39.1 MARS is a combination of a blood circuit with a polysulfone filter (1,2) which dialyses against a primary circuit containing 20% albumin (3) and a secondary conventional hemodialysis circuit to remove water soluble toxins (4). While water soluble compounds are removed from the primary dialysate 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

failure of hepatic protein synthesis, mechanical platelet sequestration during blood passage through the filter, and membrane-induced immune-mediated coagulation factor consumption [8–10]. Hence, it should be emphasized that MARS therapy does not preclude the need for plasma protein supplementation.

Prometheus (Fractionated Plasma Separation and Adsorption)

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 (Fig. 39.2). 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 consequently 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 somewhat be reduced by exchanging the hemodialysis filter by an appropriate pediatric size high-flux filter. 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 4–8 h, maximal time 10 h per session.

Combined Plasma Exchange and Hemodialysis

Sequential plasma exchange and conventional high-flux hemodialysis is an alternative to MARS and Prometheus which can be performed with conventional hemodialysis machines and filters. The filter surface area should roughly equal patient body surface area. The standard plasma exchange volume is 150% per session but can be adapted according to individual needs and must

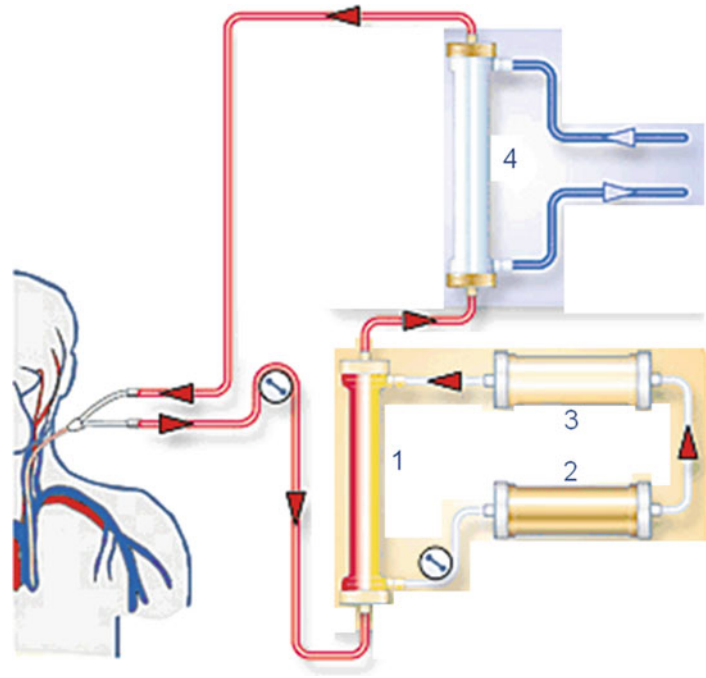

Fig. 39.2 Prometheus separates plasma via an albumin permeable polysulfone filter (1) which is purified by a neutral resin exchanger (2) adsorbing albumin-bound substances and by an anion exchanger (3) retaining negatively charged toxins. In a subsequent circuit a conventional high-flux polysulfone dialyzer (4) eliminates water soluble toxins. (© by Fresenius Medical Care Deutschland, GmbH)

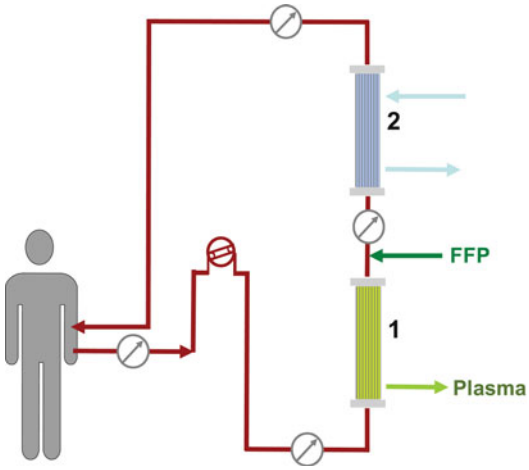

Fig. 39.3 Plasmapheresis and hemodialysis for liver support therapy can be performed simultaneously with a plasma separator and a conventional high-flux filter configured serially. The combination of two BM25 dialysis machines (Edwards) is shown. Pressure measurements are placed at indicated positions (*crossed circles*). Variations may be required when other systems are combined

be replaced by fresh frozen plasma. Iso-oncotic albumin can be considered only in the rare scenario of ALF with a still intact plasmatic coagulation status.

In emergency ALF situations with a need for rapid clearance of both albumin-bound and water soluble toxins such as ammonium and associated coagulation failure, it is possible to perform simultaneous plasmapheresis and hemodialysis, which can be accomplished by a single blood circuit passing serially through two dialysis machines encorporating a plasma and a high-flux hemodialysis filter system. Joint system pressure monitoring is feasible (Fig. 39.3). While dialysis machines have not been approved for such combinations, clinical experience is good.

The plasma turnover rate should not exceed 20% of the blood flow rate. If a relatively high blood flow rate is achieved, plasmapheresis can be accomplished within 2 h. Hemodialysis should be continued until water soluble toxins, in particular ammonium levels, are in the normal range. 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 encephalopathy. The advantage of combining hemodialysis and plasma exchange with fresh frozen plasma is that both efficient toxin elimination and volume- and nitrogen-neutral substitution of plasma proteins can be achieved.

Single Pass Albumin Dialysis (SPAD)

Single Pass Albumin Dialysis is a continuous veno-venous 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. With regard to the cost–efficacy relation, 4–5% dialysate albumin concentration is usually considered adequate. The blood flow rate can be adjusted as recommended for standard CVVHD (blood flow rate 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 20–60 mL/kg/h of albumin dialysate flow, which is feasible in small children where 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) [11] and with hemodiafiltration (Fig. 39.4). 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.

The Liver Dialysis Device ("Biologic DTT")

Liver Dialysis (HemoCleanse, Lafayette, Indiana, USA) removes blood from a single lumen multi-holed central venous catheter using a push–pull technique. Simultaneously, a 2 L suspension of powdered activated charcoal and cation exchange resin is pumped from a sorbent bag through the dialysate side of a flat-plate cellulose membrane dialyzer with a 5 kD cutoff. Prospective randomized trials have indicated improved

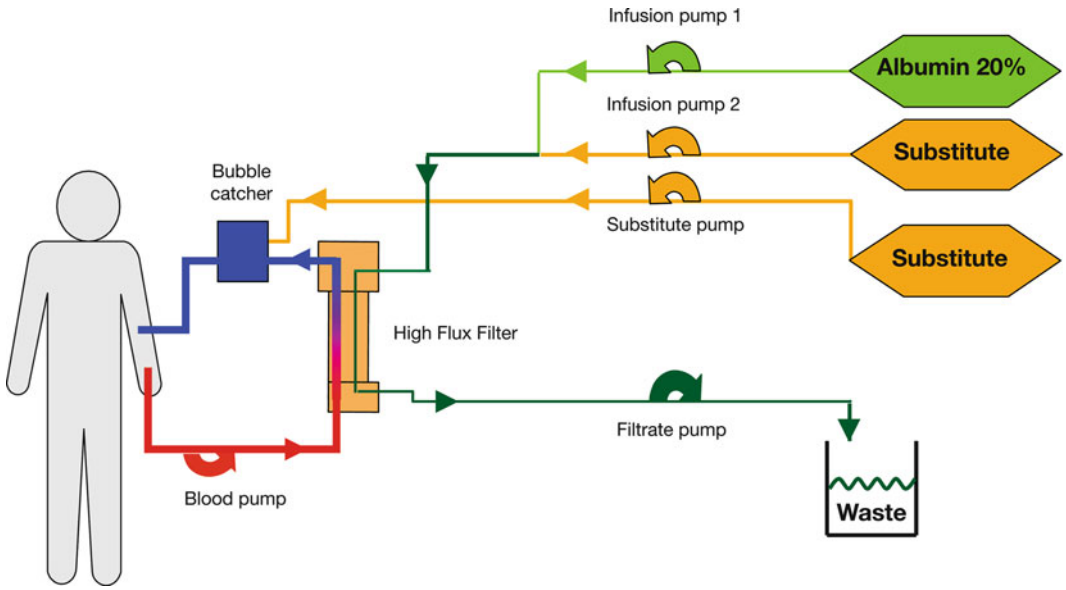

Fig. 39.4 Scheme of a single pass albumin hemodiafiltration. Albumin solution (usually 4–5%) passes through a high-flux filter, which allows for ultrafiltration replaced by substitution fluid and net ultrafiltration in volume overloaded children. Of note, using the BM25 dialysis machine (Edwards) in this setting, removal is composed of the net ultrafiltration and the albumin dialysate flow. The latter is determined by the speed of the two infusion pumps

neurological status and blood pressure in patients with ALF and acute-on-chronic liver failure, and improved outcome [12, 13]. Risks associated with the use of the device include bleeding, disseminated intravascular coagulation due to platelet activation, and clotting of the device. The system is currently being redesigned with immobilized charcoal in a block to improve purification capacity and tolerability.

Bioartificial Devices

The promising aim of bioartificial devices is to provide both liver detoxification and synthetic functions by the use of physical and chemical procedures and cell hosting bioreactors. HepatAssist and the Extracorporeal Liver Assist Device (ELAD) 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. So far the safety of the systems, but not improved outcomes, has been demonstrated [14, 15].

Pediatric data are lacking. At the present time bioartificial devices are certainly not yet ready for routine clinical use.

Comparison of Liver Support Systems

The major advantage of MARS, Prometheus, and SPAD is the removal of protein-bound substances without administration of exogenous protein. Plasmapheresis replaces plasma by 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. MARS and Prometheus are usually performed for 6–8 h but can be extended and even be applied continuously. 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 compared MARS and Prometheus with standard medical therapy. The removal of an array of toxins with MARS has repeatedly been demonstrated. Likewise, several studies reported improved mean arterial pressure, systemic vascular resistance, cardiac output, cerebral flow, renal function, and hepatic encephalopathy during MARS therapy [3, 16–21]. A small randomized prospective controlled study suggested improved short-term survival in patients with acute-on-chronic liver failure treated with MARS as compared to standard medical therapy [4]. Two large RCTs (FULMAR and MARS RELIEF) are currently underway which will hopefully allow concluding whether MARS improves patient outcomes as compared to standard medical therapy.

Efficient detoxification has also been demonstrated with the Prometheus system [22, 23]. An ongoing prospective randomized trial (HELIOS) is comparing patient outcomes with Prometheus versus standard medical treatment.

Several studies have compared MARS and Prometheus in adult ALF patients. Taken together, purification capacity is somewhat higher with Prometheus, while superior cardiovascular stability may be achieved with MARS [24, 25].

SPAD is a technically simple liver support system, which is feasible in small children. Several case reports including three pediatric patients suggest dose- and time-dependent clearance efficacy of SPAD with respect to bilirubin, thyroxine, and copper and, at least in vitro, of inflammatory cytokines such as TNF-alpha and IL-6 but uncertain survival benefits as compared to standard medical treatment [26–30]. Experimental comparison of SPAD and MARS yielded conflicting findings: both similar to slightly better [31] and inferior efficacy of SPAD was found [32]. A single center retrospective comparison of SPAD and MARS in 57 liver failure patients suggested similar safety and detoxification capacity [33]. Of note, MARS was performed with 500 mL of recirculating 20% albumin, the mean duration was 10.9 ± 4.5 h, and the albumin flow rate 200 mL/min. SPAD was performed against 4000 mL of 5% albumin dialysate, duration was 5.5 ± 07 h, and dialysate flow rate 12 mL/min.

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 [34]. 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 bleedings [8, 9, 35]. Consumptive coagulopathy induced by preexisting bleeding from predilection sites may further aggravate coagulation deficiency. Fresh frozen plasma and blood infusion often is insufficient and associated with volume and protein overload; plasma exchange should be initiated in these children. Table 39.2 gives a summary of specific features of the different extracorporeal liver support systems.

Surprisingly, neither MARS nor Prometheus have been compared with combined hemodialysis and plasma exchange, the most readily available and least expensive extracorporeal liver support therapy. Preliminary clinical observations in seven children, including an intraindividual comparison in five children, suggest better bilirubin removal and, not surprisingly, much better control of coagulation status with the combined technique as compared to intermittent MARS therapy. The MARSmini system appeared particularly limited in this comparison [36]. In the light of our comparative experience we strongly suggest testing the efficacy and safety of new devices against an active comparator such as combined hemodialysis and plasma exchange.

Table 39.2 Advantages and disadvantages of extracorporeal liver support systems (for detailed explanations and scientific evidence please see text)

	MARS	Prometheus	SPAD	PP/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
Disadvantages	Bleeding risk, additional plasma substitution is associated with volume and nitrogen load High costs and work load (system exchange q. 8–12 h)	Bleeding risk, additional plasma substitution is associated with volume and nitrogen load High costs and work load (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 (PP) Infectious and allergic risks related to exogenous protein load

References

1. Cochran JB, Losek JD. Acute liver failure in children. Pediatr Emerg Care. 2007;23(2):129–35.
2. 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.
3. 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.
4. Heemann U, Treichel U, Loock J, Philipp T, Gerken G, Malago M, Klammt S, Loehr M, Liebe S, Mitzner S, Schmidt R. Stange J albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology. 2002;36(4 Pt 1):949–58.
5. Khuroo MS, Farahat KL. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transplant. 2004;10(9):1107–8.
6. Ash SR. Extracorporeal blood detoxification by sorbents in treatment of hepatic encephalopathy. Adv Ren Replace Ther. 2002;9(1):3–18.
7. 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.
8. Faybik P, Bacher A, Kozek-Langenecker SA, et al. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. Crit Care. 2006;10(1):2.
9. 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.
10. Doria C, Mandalà L, Smith JD, et al. Thromboelastography used to assess coagulation during treatment with molecular adsorbent recirculating system. Clin Transplant. 2004;18(4):365–71.
11. 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.
12. Ash SR, Blake DE, Carr DJ, Carter C, Howard T. Makowka L clinical effects of a sorbent suspension dialysis system in treatment of hepatic coma (the BioLogic-DT). Int J Artif Organs. 1992;15(3):151–61.
13. Ash SR, Blake DE, Carr DJ, Carter C, Howard T. Makowka L neurologic improvement of patients with hepatic failure and coma during sorbent suspension dialysis. ASAIO Trans. 1991;37(3):M332–4.
14. Demetriou AA, Brown Jr RS, Busuttil RW, Fair J, McGuire BM, Rosenthal P, Am Esch 2nd JS, 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.
15. 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.
16. 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.
17. 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.
18. Novelli G, Rossi M, Pretagostini M, Pugliese F, Ruberto F, Novelli L, Nudo F, Bussotti A, Corradini S, Martelli S. Berloco PB One hundred sixteen cases of acute liver failure treated with MARS. Transplant Proc. 2005;37(6):2557–9.
19. Hassanein TI, Tofteng F, Brown Jr RS, 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.
20. 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.
21. 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 Transplant. 2001;7(8): 709–12.
22. Rifai K, Ernst T, Kretschmer U, Bahr MJ, Schneider A, Hafer C, Haller H, Manns MP. Fliser D prometheus – a new extracorporeal system for the treatment of liver failure. J Hepatol. 2003;39(6):984–90.
23. Skwarek A, Grodzicki M, Nyckowski P, Kotulski M, Zieniewicz K, Michalowicz B, Patkowski W, Grzelak I, Paczkowska A, Giercuszkiewicz D, Sa ko-Resmer J, Paczek L. Krawczyk M the use of prometheus FPSA system in the treatment of acute liver failure: preliminary results. Transplant Proc. 2006;38(1):209–11.
24. 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.
25. Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M, Holzer H. Schneditz D in vivo quantification of liver dialysis: comparison of albumin dialysis and fractionated plasma separation. J Hepatol. 2005;43(3):451–7.
26. 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):e51–6.
27. 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):E55–8.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. Meijers BK, Verhamme P, Nevens F, et al. Major coagulation disturbances during fractionated plasma separation and adsorption. Am J Transplant. 2007; 7(9):2195–9.
36. 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 Mar 18. [Epub ahead of print].

Dialytic Therapy of Inborn Errors of Metabolism

40

Philippe Jouvet and Franz Schaefer

Keywords
Dialytic therapy • Inborn errors • Nutritional management • Pharmacological management

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. 40.1). 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 IEMs who are admitted to the NICU and PICU, respectively [3]. In the other

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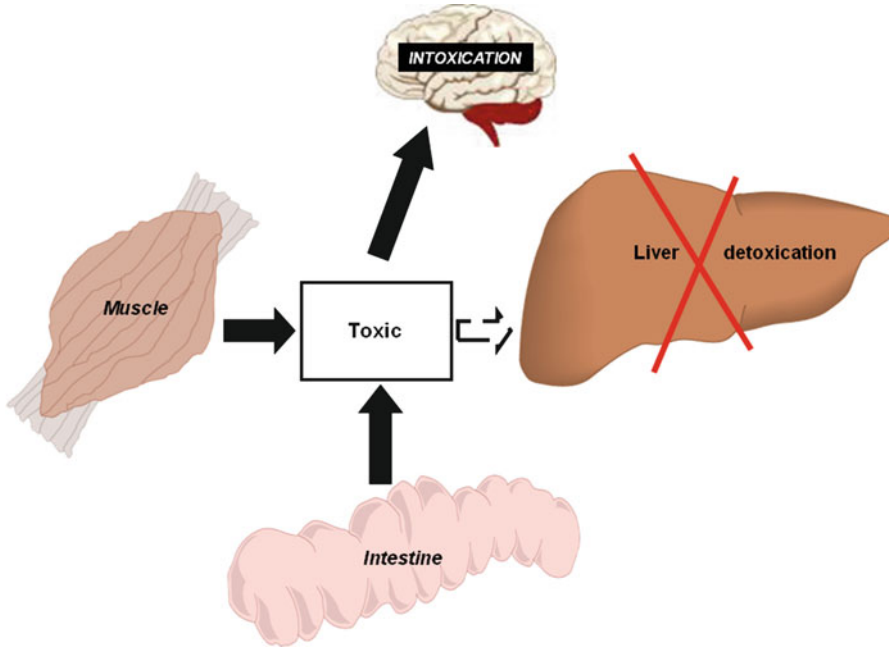

Fig. 40.1 Endogenous intoxication model: the toxic metabolite produced by the intestine and muscle amino acid catabolism (NH_3, propionic acid, etc., depending on the inborn error of metabolism) is not metabolized by the liver, resulting in toxic accumulation and brain damage (Courtesy of D. Rabier (Biochemical Laboratory, Necker Hospital, France))

cases, the first challenge is to quickly diagnose treatable disorders so as to ensure prompt treatment and recovery. 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. Each attack can follow a rapid course that ends in either spontaneous improvement or unexplained death, despite supportive measures in the ICU. 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.

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 [4].

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 40.1. 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.

Table 40.1 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 disease. It can be replaced by an amino acid chromatography, if available, in an emergency situation

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 40.2 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 [5].

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 lacking physiological or alternative pathway substrates, and (3) rapid removal of the small, water-soluble neurotoxic metabolites by dialysis.

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 one quarter of normal saline solution is preferable to physiological saline solution in patients with hyperammonemia, since ammonia scavenging drugs contain large amounts of sodium [6]. When a central line is inserted, concentrated solutions of glucose are infused (>1,000 kcal/m^2/d) which may require the addition of insulin infusion so as to avoid hyperglycemia. When the diagnosis is confirmed, nutritional support should be started,

Table 40.2 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	With ketosis	Organic aciduria (MMA, PA), MSUD
		Without ketosis	FAO[a]
	Hyperammonemia	Normal glucose	Urea cycle defects
		Hypoglycemia	FAO[a]
	Hypoglycemia	With acidosis	MSUD
			FAO[a]
	Hyperlactatemia	Without acidosis	FAO[a]
		Normal glucose	MCD
		Hypoglycemia	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	MSUD
			OTC
		Hemiplegia or hemianopsia	MSUD
			OTC
			MMA
			PA
		Extrapyramidal signs	MMA
		Stroke-like	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 to dialysis

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 1,500 kcal/m^2/d. 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 40.3). 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 [7].

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 [4]. 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.

Table 40.3 Specific treatments of inborn errors of metabolism

Drug	Effect	Indication(s)	Dose	Administration route
Sodium benzoate	Ammonia removal	$NH_3 > 200$ µmol/L	250–500 mg/kg/d	IV
Phenylbutyrate	Ammonia removal	$NH_3 > 200$ µmol/L	600 mg/kg/d	IV or p.o.
Arginine	Ammonia removal	$NH_3 > 200$ µmol/L	300 mg/kg/d	IVC
Carglumic acid	Ammonia removal	NAGS defect, MMA, PA, FAO, and $NH_3 > 200$ µmol/L	25–50 mg/kg/6 h	p.o.
Carnitine	Primary or secondary deficiency compensation	Organic aciduria FAO	100 mg/kg/d	IVC or p.o.
Vitamin B12	Enzyme cofactor	MMA	1–2 mg/d	IM
Metronidazole	Decreased toxin production by intestine bacteria	MMA, PA	20 mg/kg/d	p.o.
Biotin	PC cofactor	PA	10–20 mg/d	IV or p.o.
Riboflavin	Cofactor of acyl CoA dehydrogenase	FAO	20–40 mg/d	IV or p.o.

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 for a particular disease

IV intravenous, *IVC* continuous intravenous infusion, *NAGS* N-acetylglutamate synthase, *MMA* methylmalonic acidemia, *PA* propionic acidemia, *FAO* fatty acid oxidation defect, *PC* pyruvate carboxylase

Hyperammonemic Disorders

In hyperammonemic disorders, increasing serum ammonia level or values persistently above 300–500 µmol/L are usual indications for dialysis [8, 9]. Since rapid toxin 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 terminated when ammonia blood levels are below 100 µmol/L.

In hyperammonemic metabolic crises, experimental evidence suggests that ammonium is more efficiently removed by extracorporeal techniques than by PD [10, 11]. PD is of limited efficacy in hyperammonemic patients, with normalization of blood ammonia levels in no less than 24 h, continued dialysis requirements over 1–5 days on average, and a failure to decrease ammonia levels in individual cases [11–19]. Better results are obtained using continuous venovenous extrarenal therapies (CERT) including continuous hemofiltration and continuous hemodialysis, by which blood ammonia was typically reduced 50% within 4–8 h and by >90% within 10 h, and which usually could be discontinued within 24 h [16, 20–23]. The most efficient toxin removal is achieved by the use of intermittent hemodialysis (iHD), which reliably decreased blood ammonia concentrations by 75% within 3–4 h [11, 14, 15, 24–26]. However, repeated hemodialysis sessions or a switch to CERT are usually required due to rebound hyperammonemia [11, 14]. Hence, *continuous venovenous 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:

$$\text{Clearance}\left(\text{mL}/\text{min}\right) = \text{blood flow}\left(\text{mL}/\text{min}\right) * \left(C_{pre} - C_{post}\right) / C_{pre},$$

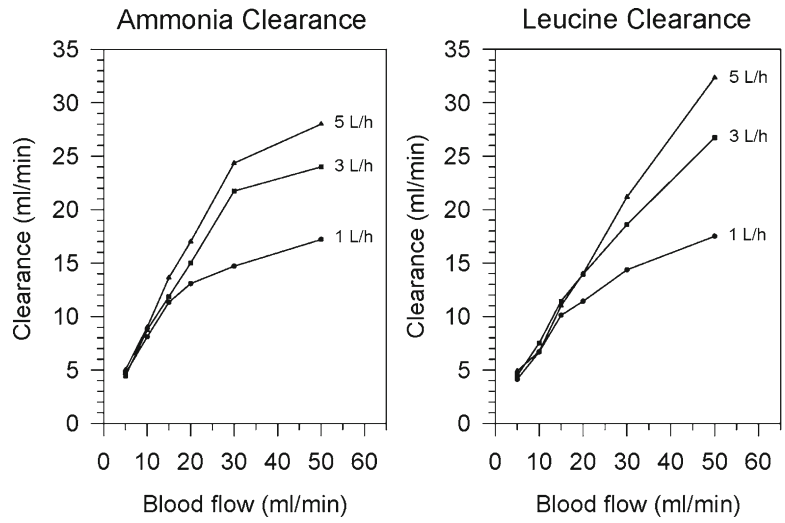

Fig. 40.2 Effect of blood and dialysate flow rate on ammonium and leucine removal by hemodialysis in a neonatal setting (simulation study using Baxter BM25 device and Bellco Spiraflo HFT02 dialyzer) (Source: Reprinted with permission from [11])

where C_{pre} and C_{post} are the pre- and post-dialyzer metabolite blood concentrations.

Maple Syrup Urine Disease (MSUD)

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 [27]. 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 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 [13, 17, 28]. More recently, 100–150% higher BCAA removal rates have been demonstrated experimentally with continuous extracorporeal blood purification techniques compared to PD (Fig. 40.2) [11, 29]. In clinical practice, CERT resulted in better leucine clearance than PD [21, 22, 30]. In children, iHD provided higher leucine clearance and required shorter sessions than CERT (5.4 ± 0.6 h vs. 17.1 ± 6.0 h) [27]. A leucine clearance ≥50 mL min^{-1}.1.73 m^{-2} resulted in a similar kinetic profile both with CERT and iHD [27, 31]. 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 nonprotein-bound small-molecular-weight solutes such as urea or creatinine [31]. This suggests that leucine clearance can be estimated from the creatinine clearance.

Organic Aciduria

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 [32]. CERT or iHD are preferred (in these authors' experience).

Others

The other inherited metabolic diseases are not usual indications for dialysis. Extracorporeal removal therapy is sometimes initially instituted because an endogenous 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/m² 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 femoral 5-French single-lumen catheters (e.g., Medcomp 5 Fr, 3.0 in.) can be inserted. 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 made 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. 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 operated 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. 40.2). 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 BM25.

The major complications to consider when dialyzing neonates or small infants with metabolic crises are *clotting* of the extracorporeal system and *hemodynamic instability*, 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 to 120–150 s. We use an initial bolus of 1500 IU/m² followed by continuous infusion of 300–600 IU/m²/h. Anticoagulation should be monitored by hourly ACT measurements. Coagulation requirements are inversely related to the blood flow rate.

Hypotensive episodes and osmotic dysequilibrium occur less frequently than in neonates and infants dialyzed for renal failure, since dialysis is usually isovolemic and the accumulated metabolites are osmotically less active than the urea accumulated in uremia. However, hemodynamic instability, leading to reduced cerebral perfusion pressure, is common in patients with a prolonged duration of hyperammonemia due to urea cycle disorders.

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 toxin clearance should be reduced and mannitol infused.

Recently, it has been suggested that moderate hypothermia (34°C) could be considered in order to decrease metabolic activity in severe hyperammonemia [33]. This effect was attributed to a slowing of metabolic ammonia generation. However, since there is only one case report published, the usefulness of therapeutic hypothermia relative to efficient toxin removal is difficult to judge.

Clinical Outcomes

Metabolic encephalopathy due to inborn errors of metabolism represented 2% of admissions to a pediatric and neonatal ICU serving a national reference center for metabolic diseases. The mortality rate of these patients was 28.6% [3]. In MSUD patients with neonatal onset who were dialyzed, good neurologic development is usually achieved [30]. 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 [34]. 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 [35–37]. 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.

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.

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. 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. pp. 973–83.

5. Fernandes J, Saudubray J, Van den Berghe G, Walter J. Inborn metabolic diseases. Diagnosis and treatment. Heidelberg: Springer; 2006.
6. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138 Suppl 1:S30–9.
7. Gebhardt B, Dittrich S, Parbel S, Vlaho S, Matsika O, Bohles H. N-carbamylglutamate protects patients with decompensated propionic aciduria from hyperammonaemia. J Inherit Metab Dis. 2005;28(2):241–4.
8. 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.
9. 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.
10. 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.
11. Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant. 1999;14(4):910–18.
12. Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. J Pediatr. 1980;97(6):893–900.
13. Saudubray JM, Ogier H, Charpentier C, Depondt E, Coude 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.
14. 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.
15. 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.
16. 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):612–17.
17. 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.
18. Siegel NJ, Brown RS. Peritoneal clearance of ammonia and creatinine in a neonate. J Pediatr. 1973;82(6): 1044–6.
19. 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.
20. Ring E, Zobel G, Stockler S. Clearance of toxic metabolites during therapy for inborn errors of metabolism. J Pediatr. 1990;117(2 Pt 1):349–50.
21. 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.
22. 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.
23. 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.
24. Rajpoot DK, Gargus JJ. Acute hemodialysis for hyperammonemia in small neonates. Pediatr Nephrol. 2004;19(4):390–5.
25. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int. 1994;45(3):903–6.
26. 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.
27. Phan V, Clermont MJ, 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.
28. 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.
29. 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.
30. Jouvet P, Jugie M, Rabier D, Desgres J, Hubert P, Saudubray JM, 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.
31. Jouvet P, Hubert P, Saudubray JM, Rabier D, Jouvet P, Hubert P, et al. 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.
32. 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. 2009;97(3):286–90.
33. Whitelaw A, Bridges S, Leaf A, Evans D. Emergency treatment of neonatal hyperammonaemic coma with mild systemic hypothermia. Lancet. 2001;358(9275): 36–8.

34. 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.
35. 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.
36. 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.
37. 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. pp. 1685–97.

Pediatric Therapeutic Apheresis

41

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Keywords
Apheresis • Pediatric • Therapeutic apheresis

Introduction

The term "apheresis" is derived from a Greek word meaning "removal." In its most general sense, apheresis refers to techniques for large-scale removal of selected components of the blood. "Plasmapheresis" refers to removal of plasma, "erythrocytapheresis" to removal of red blood cells, and "leukapheresis" to removal of white blood cells. In the first part of this chapter we (SLG, DFF, HCK) will give an overview of apheresis techniques in general as currently practiced in the United States, describe some of the issues that are unique to the application of apheresis techniques in pediatrics, and will review indications for use of apheresis in patients with kidney disease. The latter portion of the chapter (GK) is devoted to an in-depth description of low-density lipoprotein (LDL) apheresis, a specialized application of apheresis technology, as it is currently practiced in Europe.

Although the majority of this chapter will be devoted to automated apheresis used for *therapeutic* purposes, the technique of apheresis is commonly used in other situations. The original automated cell separators were designed in the 1960s for *donor* apheresis, specifically for drawing transfusable single-donor platelet products from normal volunteer donors. It remains true today that the majority of automated apheresis procedures performed in the United States are donor procedures, to produce either platelets or plasma. Furthermore, the term "apheresis" need not be restricted to procedures that use automated cell separator instruments. Manual apheresis procedures using syringes, tubing, stopcocks, and blood bags can be designed to perform whole blood

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exchanges in neonates with hyperbilirubinemia, to perform therapeutic phlebotomies for adults with idiopathic hemochromatosis, to harvest whole blood from donors to provide T-cell infusions or even to prepare small volumes of plasma or packed red blood cells for neonates. In most cases, however, the automated cell separators offer significant advantages over manual procedures in speed, sterility, and overall safety.

Automated Apheresis Technology

Principle of Separation

Since apheresis technology is based on the use of automated cell separators, it is helpful to understand how these instruments work. The basic task of automated cell separators is to separate red blood cells, buffy coat, and plasma while maintaining sterility such that one or more of the components can be returned to the patient or donor. In most instruments, this separation is accomplished by mechanical centrifugation. It is also possible to separate plasma from cells by filtration across a membrane, but machines based on this principle are used predominantly for collecting plasma from adult donors or in the intensive care unit setting for treatment of sepsis-associated microangiopathies [1]. Centrifugal devices separate whole blood into components on the basis of density differences, while membrane separators work on the basis of differences in particle size.

The configuration of the centrifugal separation chamber differs among instrument manufacturers, but all have certain design requirements in common. All apheresis systems have single use disposable plasticware that will maintain sterility during centrifugation and that incorporates safety features such as air traps to prevent embolism, filters to prevent reinfusion of aggregates, pressure monitors for access pressure, and a means to infuse an anticoagulant to prevent clot formation in the extracorporeal circulation. All automated separators have an obligate extracorporeal volume (ECV) and an obligate extracorporeal red cell mass (ECRCM), which must be in the instrument's tubing during the apheresis procedure. ECV and ECRCM vary depending on both the type of apheresis device used and the type of procedure being performed. For example, using the COBE Spectra, the ECV and ECRCM for the leukapheresis set are 285 and 114 mL, respectively, but they are 170 and 68 mL for the plasma/RBC exchange procedure. The temporary loss of these volumes, typically 200–400 mL as shown in Table 41.1, is usually well tolerated by adults, but volume and red cell balance must be taken into careful consideration when automated apheresis is performed in small children, especially if the ECV represents >10–15% of the patient's blood volume

The Apheresis Process

Number of Vascular Access Points

Cell separators are designed to perform "discontinuous" or "continuous" procedures, and some

Table 41.1 Extracorporeal volumes of centrifugal separators for plasmapheresis

			During procedure run	
Type of cell separator	Name of separator	Apheresis procedure	Volume (CV) (mL)	Red cells (ECRCM) (mL)
Continuous flow	COBE Spectra	Plasma/RBC exchange	170	68
	COBE Optia	Plasma[a]/RBC exchange	185	10
Baster/Fenwall	Plasma	Plasma/RBC exchange	393	68
	CS-3000 + Fresenius AS 104	Plasma/RBC exchange	150	90
Discontinuous flow	Hemonetics V50 and MCS	Plasma/RBC exchange	284 (125 mL bowl)[b]	87.5
			515 (225 mL bowl)[b]	180

[a]Plasma exchange only available in the United States at this time
[b]ECV for a patient hematocrit of 40%; the lower the hematocrit, the larger is the ECV

can be modified to do both. Discontinuous apheresis procedures consist of cycles of three separate phases: drawing blood, separating the components, and returning. Since the drawing of blood and returning of blood are done in distinct phases, discontinuous procedures require only one point of vascular access. For this reason, they are often called "single arm" procedures. In contrast, "continuous" apheresis procedures carry out the drawing, separation, and returning of blood simultaneously and continuously. This requires two points of vascular access, one for drawing and one for returning, and thus these procedures are called "two arm procedures." One feature of continuous procedures is that there is no cyclic removal and administration of volume to the patient, a decided advantage when the ECV of the machine makes up a significant fraction of the patient's blood volume. For therapeutic apheresis in pediatrics, especially for children younger than 10 years old, the safety advantages of a continuous circuit are the main consideration, and one must accept the need for "two arms." In contrast, the "single arm" procedures are well suited to donor procedures in healthy adults who can tolerate a small fluctuation in their blood volume, and who would prefer to have only one venipuncture.

Quantification of Removal

Plasmapheresis is the most commonly indicated apheresis treatment for kidney disease. The general rationale for plasmapheresis is to remove, safely and efficiently, those soluble substances in the plasma that might play a role in the patient's disease process, for example, the pathogenic antiglomerular basement membrane antibody in patients with Goodpasture syndrome. Plasmapheresis is not as selective as dialysis (see comparison below) since whole plasma is removed. As plasma is removed from the patient, a replacement fluid must be given to maintain intravascular volume and oncotic pressure. This replacement fluid becomes admixed with the patient's plasma, and some of it is subsequently removed as the plasmapheresis proceeds. At the start of a plasmapheresis, most of what is removed

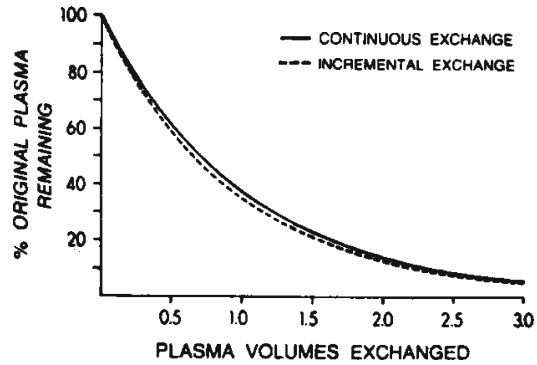

Fig. 41.1 The percentage of the patient's initial plasma still remaining in circulation, on the vertical axis, as a function of the volume of plasma removed during plasmapheresis, on the X-axis. The volume of plasma removed is expressed as a multiple of the patient's baseline plasma volume

is the patient's plasma, whereas at the end of the plasmapheresis, much of what is removed is replacement fluid. The relationship of the amount of plasma removed (expressed as multiples of the patient's plasma volume) in a plasmapheresis to the fraction of the original plasma remaining is given in Fig. 41.1 [2]. A plasmapheresis procedure that removes a volume equal to the patient's plasma volume 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 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 resynthesis and degradation [2].

Control of Volume and Red Cell Mass

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 worthwhile. 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 a 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.

Anticoagulation

An anticoagulant must be added to the blood as it enters the extracorporeal circuit in order to prevent clotting in the machine's tubing. Sodium citrate is the most commonly used anticoagulant for apheresis; sodium citrate is the anticoagulant in blood products as well. It acts to chelate calcium to prevent in vitro activation of the clotting cascade. When infused into the patient, the citrate may cause transient hypocalcemia. The severity of this side effect depends on the rate of infusion, the capacity for hepatic metabolism of citrate, and the patient's state of calcium homeostasis (i.e., baseline hypocalcemia or hypoparathyroidism). In many apheresis protocols, the rate of citrate infusion to the patient is the limiting safety factor in determining how rapidly blood can be drawn and returned, and ultimately how long the procedure will last.

The symptoms of reduced ionized calcium related to citrate [3] are usually referred to as "citrate toxicity." The mildest and most common symptoms are perioral or hand and foot tingling and paresthesias. Some patients experience nausea, an unusual taste in the mouth, or lightheadedness. More severe hypocalcemia may lead to tremors, twitching, muscular spasm, tetany, seizures, arrhythmias, and hypotension related to myocardial dysfunction [4–6]. Patients undergoing apheresis should be monitored for early signs of citrate toxicity either by clinical questioning or measurement of ionized calcium levels. In small children or sedated or unconscious patients who cannot verbalize their discomfort, frequent vital signs including blood pressure and EKG monitoring are necessary.

Prevention of hypocalcemia can also be achieved using a regional anticoagulation protocol, adapted from continuous renal replacement therapy protocols [7], in which a calcium chloride (8 g/L of NS) is infused in the return line at 1.5–2 times the blood pump rate in mL/h. For example, if the blood pump rate is 60 mL/min, the calcium chloride rate would be 90 mL/h. In general, mild symptoms can be relieved by reducing the rate of citrate infusion or by stopping the procedure temporarily until symptoms subside. Oral calcium supplements are often used to treat mild subjective symptoms although their efficacy has not been proven. For severe reactions, such as seizures, tetany, or EKG changes, it is advisable to terminate the procedure altogether and administer parenteral calcium supplements.

Heparin alone, or in combination with sodium citrate, can also be used as the anticoagulant for apheresis procedures. The patient will usually receive the equivalent of a therapeutic dose of heparin during the procedure and would be expected to have an elevated activated clotting time (ACT) and an anticoagulant effect afterward. Some centers that use heparin as the anticoagulant monitor the degree of heparinization during the procedure and adjust the infusion rate. The reason to use a combination of citrate and heparin is to reduce the net dose of citrate required to prevent clotting in the machine, reduce the dose of citrate delivered to the patient, and permit the blood processing to speed up. The decision to use heparin must take into account the effect of the apheresis procedure on the coagulation system, and the patient's underlying risk for hemorrhage.

Procedures

There are three basic therapeutic apheresis procedures: plasmapheresis, erythrocytapheresis, and leukapheresis. These three procedures are modified in various ways for the therapeutic goal at hand and for safety considerations in small children.

Plasmapheresis

Plasmapheresis involves separation of the plasma from the cellular elements of blood, collecting the patient's plasma into a waste bag, and returning to the patient his own cells mixed with a fluid to replace the discarded plasma. The replacement fluid must contain colloid to maintain the patient's intravascular oncotic pressure. When 5% albumin is used as the only replacement fluid, the plasmapheresis procedure can be performed with minimal concern for transfusion-transmitted infectious disease or transfusion-associated lung injury (TRALI) [8]. Removal of plasma and replacement with 5% albumin will result in depletion of most plasma proteins including immunoglobulins and the components of the coagulation cascade. As shown in Fig. 41.1, plasmapheresis of one plasma volume will reduce the levels of coagulation proteins by about 70%, which can be associated with a fibrinogen level below 100 mg/dL and prolongation of the PT and aPTT but not usually with clinical bleeding. If the rate of hepatic regeneration of these lost coagulation factors is normal, a schedule of plasmapheresis procedures every other day generally does not require exogenous replacement with fresh frozen plasma (FFP). However, if daily plasmapheresis is necessary or if the patient has a concomitant coagulopathy, the replacement fluids must include FFP. If the pre-plasmapheresis fibrinogen level is less than 100 mg/dL, FFP should also be included as part of the replacement fluids. If FFP is used as the replacement fluid, the patient's plasma proteins and coagulation parameters will remain within normal limits. Plasmapheresis using FFP as replacement fluid is more properly termed "automated plasma exchange."

Plasmapheresis with Staphylococcal Protein A Immunoadsorption

Since plasmapheresis removes all plasma proteins and requires a large volume of replacement fluids, selective removal of specific plasma constituents is an attractive therapeutic approach. Selective removal can be accomplished by immunologic, chemical, or physical means depending on the specific pathogenic substance to be targeted. One example is specific removal of immunoglobulin G (IgG) using immunoadsorption columns. The advantages of immunoadsorption columns over simple plasmapheresis are as follows: (1) large quantities of replacement fluids are not needed, (2) removal is targeted to antibodies and does not affect other plasma constituents, and (3) there is a potential for greater overall efficiency because a larger volume of plasma may be treated than by simple plasmapheresis.

Two techniques have been developed to remove IgG and IgG-containing circulating immune complexes from plasma after it has been separated from the cellular elements by plasmapheresis. The staphylococcal protein A-silica column (Prosorba® column, Fresenius HemoCare, Inc., Redmond, WA) utilizes a solid phase of silica gel beads to which staphylococcal protein A has been bound. The staphylococcal protein A binds human IgG selectively, permitting other plasma proteins to pass through into the column eluate and to be returned to the patient. While this is theoretically attractive as a means of achieving specific removal of IgG, the amount of IgG actually removed is limited by the binding capacity of the column, which is about 2 g of human IgG. The clinical value of immunoadsorption is limited, and is often attributed to "immunomodulation" rather than quantitative removal of IgG. The Prosorba column has been approved by the FDA for the treatment of ITP [9, 10] and rheumatoid arthritis [11, 12].

A variation of this technique, staphylococcal protein A-agarose column (Immunosorba® column, Excorim AB, Lund, Sweden) which was recently acquired by Fresenius HemoCare, employs the intermittent renewal of two staphylococcal A columns to increase the quantity of IgG removed. One column is stripped and regenerated while a second column is in use, and then the flow of plasma is diverted to the newly stripped column when the first column is saturated. This is the only column which has regulatory approval in the United States for the treatment of patients with hemophilia A and B with inhibitors [13–15]. However, the use of both protein A immunoadsorption column techniques has

been reported in patients with kidney diseases, such as, hemolytic uremic syndrome (HUS), Goodpasture syndrome, rapidly progressive glomerulonephritis (RPGN) including lupus nephritis, nephrotic syndrome, and kidney allograft rejection [16–32].

As will be discussed later in this chapter, column technology is also available for use in conjunction with plasmapheresis for selective removal of plasma lipids, with return of the remaining plasma proteins. Two such techniques are available in the United States for the treatment of hyperlipidemia, primarily in adults [33–35]. In pediatric practice, this therapy is indicated for rare congenital hyperlipidemia syndromes that are associated with extremely elevated plasma lipid or cholesterol levels and premature atherosclerosis. While standard plasmapheresis can also be used to remove blood lipids, the specialized techniques and equipment currently in use in Europe to treat these children using low-density lipoprotein (LDL) apheresis will be described later in this chapter.

Erythrocytapheresis

Erythrocytapheresis involves separation of the plasma from the cellular elements, collecting primarily the patient's red cells into the waste bag and returning the patient's own plasma mixed with donor-packed red blood cells. This technique can be of great value for hemoglobinopathies, and occasionally for diseases caused by intra-erythrocytic parasites such as malaria. The principal applications of erythrocytapheresis are in sickle cell disease. The pheresis machines can be programmed to calculate the volume of packed red blood cells needed to achieve a desired post-procedure hemoglobin S level, as long as the patient's pre-procedure hematocrit, hemoglobin S, and packed red cell hematocrit concentrations are known. The patient's total hemoglobin can also be raised without a large volume of intravascular fluid. Common indicators for erythrocytapheresis in sickle cell disease include emergent preparation for surgery, severe acute chest syndrome, or cerebrovascular event. Typically, a post-procedure hemoglobin S of 25% is desired in these acute situations. Erythrocytapheresis may also be used to deliver chronic transfusion therapy in sickle cell disease for primary or secondary stroke prevention, and for other indications which require chronic transfusion therapy. The typical post-procedure hemoglobin S concentration is 15% in this chronic situation, with a schedule of treatments every 4–6 weeks to maintain hemoglobin S less than 30–40%. The principal advantage of erythrocytapheresis in this setting is that iron overload associated with regular RBC transfusions can he reduced or prevented [36, 37].

Leukapheresis

Leukapheresis involves separation of the whole blood into three fractions: plasma, red cells, and white cells from the buffy coat. The plasma and red cells are returned, and only the leukocyte fraction is retained as a leukocyte product. With the standard leukapheresis procedure using the automated cell separators, a replacement fluid is not needed since both donor and therapeutic leukapheresis are collection procedures, not exchange procedures. For any leukapheresis procedure, a replacement fluid may be needed to compensate for the volume of leukocytes and red cells removed in the waste or collected product, especially in small children. This technique can be applied as therapeutic leukocyte depletion to patients with hyperleukocytosis from leukemia as a rapid means of reducing blood viscosity associated with extremely high peripheral white blood cell counts [38–40]. In, general, two blood volumes are processed, and the procedure may he expected to remove approximately 50% of the circulating platelets along with the leukocytes [41]. Variations of this leukapheresis technique can be used to harvest peripheral blood mononuclear cells from an allogeneic or autologous donor, as sources of either hematopoietic stem cells for stem cell transplantation [42–48], dendritic cells, T-lymphocytes for donor lymphocyte infusions [49–53], and other cell-based therapies. Another variation of the leukapheresis procedure is termed "photopheresis," in which the mononuclear cells harvested by leukapheresis are treated with a photoactivatable chemical (a psoralen),

subjected to irradiation under ultraviolet-A light (UVA), and returned to the patient. This therapy is used for cutaneous T-cell lymphoma [54–59] and may have broader applications as immunologic therapy for other autoimmune diseases [60, 61], solid organ graft rejection [62, 63] including kidney allograft rejection [62, 63], and graft-versus-host disease [54, 64, 65].

Plateletpheresis

Plateletpheresis involves separation of the whole blood from healthy donors into three fractions: platelet-poor plasma (PPP), platelet-rich plasma (PRP), and red cells. The PRP is retained as a single-donor platelet concentrate (more accurately termed "apheresis platelets") while the PPP and red cells are returned to the donor. This is the single most frequent application of apheresis technology. Plateletpheresis is indicated as a therapeutic procedure to remove excess platelets from the circulation in patients with symptomatic thrombocytosis [66–70].

Comparison of Apheresis and Dialysis

Both plasmapheresis and hemodialysis are therapeutic techniques involving extracorporeal circuits for selective removal of components of the blood. For this reason, apheresis and dialysis are sometimes confused, and are occasionally considered as alternative therapeutic options in a patient with kidney disease. In fact, plasmapheresis has been performed safely and efficiently using hemodialysis equipment after modification of the procedure [71, 72]. However, the fundamental mechanisms and clinical utility of plasmapheresis and dialysis are entirely different.

Plasmapheresis employs centrifugation to separate whole plasma from the cellular components of blood. Whether the therapeutic goal is to reduce levels of pathogenic immunoglobulins, lipids, paraproteins, or other substances in the plasma, whole plasma is removed during plasmapheresis, and the proteins of the clotting cascade, normal immunoglobulins, and other plasma proteins are lost. The efficiency of plasmapheresis in removing these substances depends primarily on the volume of plasma removed, but also on their distribution between intra- and extravascular compartments, rate of equilibration between compartments, and other metabolic characteristics [72].

On the other hand, dialysis employs a semipermeable membrane and a dialysis fluid to alter the solute concentrations and free water content of the patient's plasma. Ions, salts, small molecules, and free water may be removed, but the plasma proteins are unaffected. Thus, dialysis is suitable for treating the electrolyte disturbances, waste product accumulation, water intoxication, and volume overload of kidney failure. Dialysis can also be used to remove toxins if the toxin molecule is small enough and dialyzable, whereas plasmapheresis is suited to removal of antibodies and other pathogenic proteins and lipids, and to large-scale replacement with FFP. Plasmapheresis can be used to remove some toxins, especially if they are predominantly bound to proteins in the plasma. Plasmapheresis does not alter the electrolyte content of plasma, and has only very transient effects on the plasma levels of small molecules such as urea or ammonia. Plasmapheresis can be used to a limited extent to treat fluid overload, but the fluid removed is plasma from the intravascular space not free water or extravascular fluid. The differences between plasmapheresis and dialysis are summarized in Table 41.2.

Pediatric Issues

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

Most children smaller than 30 kg will not have antecubital veins with large enough diameter to

Table 41.2 Comparison of therapeutic apheresis with dialysis

	Plasmapheresis	Dialysis
Targets for removal	Antibodies, plasma proteins, soluble elements of plasma	Electrolytes, free water
Principle of separation	Centrifugation	Semipermeable membrane
Extracorporeal volume	250–400 mL	80–350 mL
Indications	Autoimmune disease Coagulation defect Metabolic disease	Kidney failure, toxin removal
Treat fluid overload	Limited	Effective
Treat coagulopathy	Yes	No
Treat electrolyte imbalance	No	Yes

permit successful use of peripheral venous access for apheresis procedures. The access for drawing blood into the cell separator is the most critical, requiring a vein large enough to admit a 16-gauge steel needle and resilient enough to withstand a flow rate as high as 2 mL/kg/min. A 20-gauge flexible IV catheter can be used for returning. A double lumen catheter is usually used for smaller patients or patients with unusable veins so that both draw and return can use the same central access. It is preferable to draw from the proximal ports and reinfuse at the distal point to minimize recirculation, although in practice the better functioning port is usually chosen for the drawing access. The length, gauge, and positioning of the tip of the catheter will depend on the child's size. However, the wall of the catheter must be resilient enough to withstand the negative pressure generated during the apheresis procedure. In practice, catheters designed for use in dialysis also work well for apheresis procedures, but the softer single and double lumen catheters, such as the Broviac catheter, commonly used in oncology patients and in intensive care units, are not suitable as the draw line, although they can be used for returning.

Extracorporeal Volume

Extracorporeal volume is the most important consideration in adapting apheresis instruments designed for adults to use in children. The ECV for cell separators in clinical use varies from 200 to 400 mL depending on the machine and the procedure to be performed as shown in Table 41.1.

Table 41.3 Formulae [73] for estimation of total blood volume (*BV*, in liters) and plasma volume (*PV*, in liters) based on the patient's height (*H*, in meters), weight (*W*, in kilograms), and venous hematocrit (*Hct*, in percent)

Male
$BV = 0.3669 \times H^3 + 0.03219 \times W + 0.6041$
Female
$BV = 0.3561 \times H^3 + 0.03308 \times W + 0.1833$
$PV = BV \times (1 - Hct/100)$

Unless specific measures are taken to compensate for this volume, the patient's blood volume will be depleted by this amount during the apheresis procedure. While an adult may easily tolerate the temporary loss of 200–400 mL of whole blood, this ECV may be too much for a small child. As a general guideline, modification of the procedure in the interest of patient safety is required if the ECV exceeds 15% of the patient's total blood volume (TBV) and should he considered if the ECV exceeds 10% of the TBV.

The ECV for an apheresis procedure is a fixed specification of the instrument and tubing, and can be determined precisely. The patient's TBV, however, must be estimated in order to plan the apheresis procedure. The TBV estimate is a basic parameter for the algorithms that control the pumps on an automated apheresis instrument. The traditional formula used by most pediatricians to estimate TBV is 70–75 cm^3/kg. More complex, empirically derived formulae [73] for blood volume estimation that take into account gender, weight, and height are shown in Table 41.3. These formulae are programmed into the software of some automated apheresis instruments. While

these formulae may be more accurate than a weight-based TBV estimate in adults, they may yield overestimates of TBV in children, especially prepubertal males.

Blood Priming

In addition to the ECV, there is an obligate ECRCM, a volume of packed red blood cells which must be held in the apheresis instrument in order to achieve the separation of plasma from red cells. Two decisions arise with respect to this ECRCM. First, can the patient tolerate the temporary loss of this red cell mass during the procedure? The answer to this question depends not only on the patient's total blood volume, but also on the patient's hematocrit and cardiovascular and pulmonary reserve. Second, can the patient tolerate the bolus of fluid which is associated with returning the red cells, or "rinsing back" the red cells from the machine to the patient at the end of the apheresis procedure? The answer to this question also depends on a clinical assessment of the patient's blood volume, cardiopulmonary reserve, and kidney function.

The procedure modifications that compensate for the ECV and ECRCM for young children undergoing apheresis are often referred to as "priming." While it is possible to prime the apheresis instrument by filling all of the tubing with red blood cells at a predetermined hematocrit before starting, priming is usually accomplished by infusing additional red cells or fluids at the start of the procedure during the time that the machine is filling with blood 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 in one of the references [74].

In general, the method of priming for an apheresis procedure affects the patient's blood volume during the procedure and also the final amount of fluid administered at the end of the procedure. The patient's ability to tolerate volume depletion, loss of red cell mass, and volume overload must be assessed as part of the planning before the procedure is started. For children weighing <20 kg or for patients who are anemic or hemodynamically unstable, red cell priming is usually indicated. From a practical standpoint, this means that half to one unit of packed red cells must be ordered and available before the apheresis procedure can be started.

Anticoagulation (Dose)

The need for anticoagulation to prevent clotting in the extracorporeal circuit was discussed above. For apheresis procedures in pediatrics, one must pay particular attention to the dose 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 higher flow rates than adults, when the rate is expressed on a per kilogram basis. Using typical values as an example, a 70-kg adult undergoing plasmapheresis with flow rates of 90–120 mL/min experiences blood draw rates in the range of 1.3–1.7 mL/kg/min, but a 20-kg child undergoing plasmapheresis using a central line that permits a flow of 40 mL/min experiences a draw rate of 2.0 mL/kg/min. Thus, the dose rate of anticoagulant, citrate, heparin, or a combination will be higher in the child than in the adult. For many apheresis protocols, the dose rate of citrate is the limiting parameter for how fast the procedure can be run. Procedure modifications including calcium supplementation based on regional citrate anticoagulation protocols used in CRRT [7] to prevent citrate toxicity are commonly used in pediatric plasmapheresis.

Hypothermia

Children and adults experience some degree of hypothermia during apheresis procedures because of cooling of blood in the extracorporeal circuit.

This side effect may be more pronounced in younger children since the flow rate per kilogram is higher than for adults, as discussed above. A blood warmer is commonly incorporated into the return line in most pediatric apheresis procedures. Depending on the model used, the warmer increases the ECV by 20–50 mL.

Cooperation

The aspects of apheresis that children tolerate least well are the needles, the need to remain seated and still, the restriction of one or both arms, the operation of the blood pressure cuff, and boredom. The apheresis staff must be expert in phlebotomy and IV placement to gain the trust and cooperation of young patients. The staff must also be able to provide age-appropriate explanations of what is going on, and should encourage parental involvement wherever possible. Space and resources to provide distracting entertainment for children undergoing apheresis are a necessity. With a sensitive and experienced apheresis staff, it is rare that children are so frightened, inconsolable, or uncooperative that sedation must be used.

Application to Kidney Diseases

The evidence that demonstrates the clinical efficacy of apheresis-based treatments is compelling in some disease states and marginal in others. For this reason, the Journal of Clinical Apheresis has published, most recently in 2010 [75], a categorized listing of the indications for therapeutic apheresis. The indications are placed into one of four categories, as shown in Table 41.4, based on the strength of evidence that therapeutic apheresis is effective for that disease process. Although this system of categories is imperfect, it is helpful in guiding clinical decisions about the use of apheresis. When therapeutic apheresis is applied to diseases of the kidney, either plasmapheresis or plasma exchange is most commonly indicated. The kidney diseases for which therapeutic apheresis may be indicated are shown in Table 41.5, along with commonly used treatment schedules. Of course, these schedules must be individualized based on the patient's clinical condition. It is important to establish at the start of a course of apheresis how the success or failure of the therapy will be monitored and judged. This is often difficult to determine with certainty, because

Table 41.4 Categories of the indication for therapeutic apheresis by evidence of effectiveness (American Society of Apheresis, Ref. [75])

Category	Description
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 Example: plasma exchange in Guillain–Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment Example: plasma exchange as a standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease
III	Optimum role of apheresis therapy is not established. Decision making should be individualized Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure
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 Example: plasma exchange for active rheumatoid arthritis

Table 41.5 Application of plasmapheresis to kidney disease

		Typical treatment plans		
Diagnosis	ASFA category	Volume treated	Frequency	Duration/endpoint
TTP	I	1–1.5 FFP or cryopoor plasma	Daily	Normalized LDH and platelet count
HUS, atypical	I (anti-factor H antibody) II (complement mutations) IV (diarrhea associated)	1–1.5 FFP or cryopoor plasma	Daily	Normalized LDH and platelet count
Goodpasture syndrome	I	1–1.5 5% albumin	Every other day for six treatments	Reduction in anti-GBM antibody/cessation of pulmonary hemorrhage
Rapidly progressive glomerulonephritis with antibodies (ANCA)	I	1–1.5 5% albumin FFP when pulmonary hemorrhage is present	Daily or every other day	6–9 procedures
SLE	II (CNS disease)	1–1.5 5% albumin	Daily or every other day	3–6 treatments
Lupus nephritis	IV	1–1.5 5% albumin	Three times a week	3–6 treatments
Recurrent FSGS	I	1–1.5% Albumin/FFP	Daily × 3 then every other day	Minimum nine treatments until resolution/improvement or resolution of proteinuria, taper treatments on individual basis
Kidney allograft rejection (antibody-mediated)	I	1–1.5 5% albumin	Daily or every other day	Six treatments minimum, consider more if donor-specific antibodies still elevated
Thrombocytopenia-associated multiorgan Failure (TAMOF), sepsis	III	1–1.5 5% albumin/plasma	Daily or every other day	2–14, assess for resolution of MOF, improvement in platelet count

many diseases do not have a discrete identifiable marker with which to follow clinical response to treatment.

Apheresis and ACE Inhibitors

One unusual interaction of medications with apheresis therapy is relevant to the care of patients with kidney disease. Antihypertensive agents of the angiotensin-converting enzyme (ACE) inhibitor class have been associated with an atypical and potentially severe reaction occurring shortly after the start of apheresis procedures. The symptoms include flushing and hypotension in most patients, and abdominal cramping, diarrhea, nausea, and diaphoresis in some. The reactions were first reported in patients taking ACE inhibitors who underwent staphylococcal protein A column therapy, but have been associated with plasmapheresis [76] and other therapies involving extracorporeal circuits. The postulated mechanism of these reactions is that during an apheresis procedure elevated levels of bradykinin are generated. In most apheresis patients this is inconsequential because of rapid degradation of bradykinin by kininase II. However, if the patient is receiving ACE inhibitors, the degradation mechanism may be blocked by the drug, and the vasodilatory and gastrointestinal effects of bradykinin give rise to the symptoms. Many ACE inhibitors have been implicated, and it is recommended that ACE inhibitors be withheld at least 24 h before an apheresis procedure.

Low-Density Lipoprotein (LDL) Apheresis

Background

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary metabolic disease due to inactivating mutations in the low-density lipoprotein receptor (LDLR) gene. This results in grossly elevated plasma LDL cholesterol. Clinical manifestations are severe and include premature atherosclerosis and a high risk of myocardial infarction before the age of 30. Because lipid-lowering drug therapy often is insufficient, LDL apheresis has been a mainstay of FH treatment for the past 20 years. LDL apheresis in combination with drug therapy lowers LDL cholesterol plasma levels by 40–70%, and earlier treatment is more likely to prevent the complications of premature atherosclerosis. Pediatric reports are scarce and often refer to patients above the age of 10 years, despite the fact that treatment is recommended below this age. Different techniques for LDL apheresis are available, including chemoadsorption, precipitation, cascade filtration, and direct adsorption. However, most commercial systems are not suitable for children below 10 years due to large extracorporeal volume requirements. The following section will review the experience and technique with LDL apheresis in the pediatric population.

Homozygous familial hypercholesterolemia (FH) affects one subject per million inhabitants. It is characterized by grossly elevated LDL cholesterol plasma levels (>15.5 mmol/L). Clinical signs and symptoms include tuberous xanthomas over the extensor surfaces, thickened Achilles tendons, and stenosis of the carotid artery and aortic valve developing during the first 10 years of life. Untreated, this results in myocardial infarction and/or sudden death due to cardiovascular complications during the first or second decade of life [77, 78]. Brown and Goldstein discovered that FH is caused by mutations within the LDL receptor gene [79]. The LDL receptor is essential for uptake of LDL into the cells by receptor-mediated endocytosis. This occurs mainly in hepatocytes and accounts for the clearance of about 70% of all plasma circulating LDL [79]. The gene for the LDLR is located on chromosome 19, and more than 800 different mutations have been described ([80], http://www.ucl.ac.uk/fh). Heterozygous patients rarely develop clinical signs during childhood other than elevated LDL cholesterol plasma levels, but left untreated, their relative risk of death is increased three- to fourfold [81].

Treatment options for FH are limited. Conventional cholesterol-lowering therapy includes dietary interventions, intestinal bile-acid or cholesterol binding agents (cholestyramine), specific

cholesterol absorption inhibitors (ezetimib), and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMGCoA-reductase-inhibitors, statins). However, in FH patients cholesterol-lowering drug therapy often is not sufficient to lower the plasma LDL cholesterol level to recommended levels below 100–140 mg/dL. In FH patients resistant to dietetic and drug therapy, extracorporeal cholesterol elimination by LDL apheresis is indicated. LDL apheresis lowers cholesterol by approximately 50% long term [82] and has been proven effective to prevent future cardiovascular events [83, 84].

Indication for LDL Apheresis

The diagnosis of FH should be validated. The American Heart Association has published a set of diagnostic criteria and LDL apheresis indications focused on cardiovascular risk reduction in high-risk pediatric patients [85].

In patients with HF LDL apheresis is indicated if the following take place:

- A LDLR deficiency is demonstrated functionally or genetically. These patients have LDL cholesterol plasma levels above 15 mmol/L and face a high risk of cardiovascular morbidity and mortality already in childhood. Therefore LDL apheresis is indicated as prophylaxis for these devastating complications.
- Plasma cholesterol cannot be lowered below 160 mg/dL despite dietetic and medical therapy.
- In heterozygous FH LDL apheresis is only indicated as a secondary treatment option; most patients will respond to drug therapy.

LDL Apheresis Technique

For extracorporeal removal of cholesterol, direct absorption from whole blood can be obtained (Fig. 41.2). In most systems, plasma is separated from the cellular blood components by membrane or centrifuge separation. The separated plasma then passes through the absorber unit, in which LDL is removed by different methods,

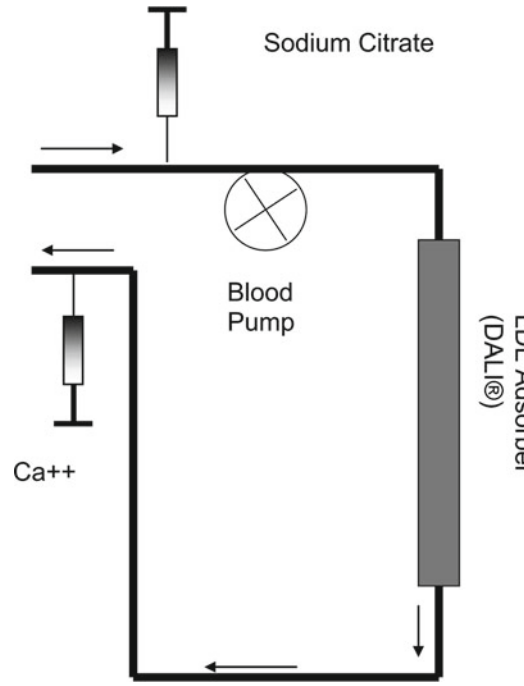

Fig. 41.2 Scheme of LDL apheresis using direct absorption technique without prior separation of plasma from the cellular blood components

before the cleared plasma is given back to the patient without major volume change (Fig. 41.3). The disadvantage of membrane-plasma separation is the limited capacity of the plasma filter membrane. However, with modern plasma filters, this is no longer a significant clinical problem in LDL apheresis. With centrifuge plasma separation, the amount of plasma generated is not limited.

For membrane-plasma separation, a plasma filter with a membrane surface of 0.2 m^2 is recommended for children of 10–20 kg body weight, and 0.5 m^2 for children >20 kg, assuming the treatment is designed to process approximately 1.5 times the plasma volume (see Table 41.3 and Ref. [73] for plasma volume determination).

Venous Access

Venous access can be obtained by peripheral veins, central-venous catheter (dialysis catheter) or arteriovenous fistula. The blood flow needed is

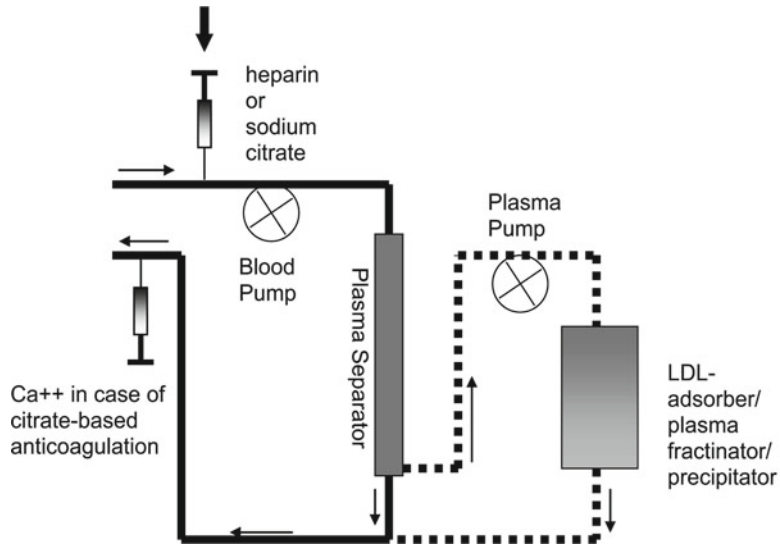

Fig. 41.3 Scheme of LDL apheresis using techniques after separation of plasma from the cellular blood components

considerably lower than in hemodialysis, but should be more than 10 mL/min even in small children. In older children, blood flow of 60–80 mL/min is sufficient. Peripheral veins are the preferred access in adult patients. Several studies have shown that peripheral access is sufficient in more than 50% of adolescent patients [82, 86]. However, because both antecubital veins often must be used, patients become totally dependent on the assistance of hospital or apheresis personal or accompanying persons for sniffing, eating, and almost all activities during the procedure. This is reported to be discomforting, especially with longer duration of treatment [82]. The antecubital veins should not be used for blood sampling or infusions unrelated to LDL apheresis. For these reasons, an arteriovenous fistula or central line might be advantageous with respect to both patient comfort and treatment adherence. In our experience, patients have discontinued treatment due to discomfort associated with bilateral antecubital venipuncture and taping for the LDL apheresis procedure. Due to the long treatment period expected with FH, an arteriovenous fistula is the preferred access.

Anticoagulation

For anticoagulation the same medications are principally applicable as for hemodialysis or plasma separation. However, in membrane-plasma separation a higher level of anticoagulation is needed as in hemodialysis. The choice of anticoagulation is influenced by the method of LDL apheresis: for dextran-sulfate absorption (Liposorber®, Fa Kaneka) no citrate anticoagulation is needed, whereas for the cascade filtration (CascadeFlow®, Fa. ASHAI Kassei Kurray) and direct adsorption (DALI®, Fa Fresenius, Germany) citrate anticoagulation is recommended. The anticoagulation is aimed at sufficient anticoagulation in the external blood circuit with the best biocompatibility, and without activation of the coagulation system, complement system, or cellular blood components. Use of citrate-based anticoagulation has been shown to have the advantage of inhibition of calcium-dependent complement activation [87], albeit this was not confirmed in other studies [88]. For control of anticoagulation, measurement of activated clotting time or ionized calcium in case of citrate anticoagulation should be immediately available.

LDL Apheresis Systems

Different techniques for removal of LDL are available (Table 41.6). When choosing an LDL apheresis system, the size of the child, i.e., his/her circulating blood volume should be calculated, as many commercially available systems require

Table 41.6 Technical data of the LDL apheresis systems used in pediatric patients

System	Plasma separation	V blood (mL)	V plasma (mL)	Anticoagulation	Pt. size
Dextran-sulfate (Liposorber®)	Yes	170	230	Heparin	>20 kg
Dextran-sulfate (Liposorber®) custom made [16]	Yes	65	100	Heparin	10–20 kg
Heparin-induced extracorporeal LDL precipitation (H.E.L.P.®)	Yes			Heparin	>30 kg
Double/cascade filtration (CascadeFlow®)	Yes	165	180	Citrate	>20 kg
Direct adsorption (DALI®)	No			Citrate	

large priming volumes. The extracorporeal blood volume should not exceed 5–7% of circulating blood volume. In children below the age of 6 years priming of the extracorporeal circuit is often performed using albumin [89]. However, this is not ideal due to increased costs, risk of adverse events, and increased risk of transmitted infections. Most published pediatric series report on use of the Liposorber®-system, but cascade filtration and direct absorption have also been described, whereas precipitation techniques are infrequently used in pediatric patients.

Chemoadsorption (Liposorber®, Fa. Kaneka)

The Liposorber®-System adsorbs LDL to dextran-sulfate-cellulose from plasma separated from the cellular blood components. The mechanism of adsorption is the result of electrostatic forces between negatively charged sulfate-groups on dextran-sulfate and positively charged Apo B of LDL and Lp(a). Immunoglobulins, HDL, and albumin are adsorbed by this system at a very low level (http://www.liposorber.com/physician/prescribe/prescribe.htm) [83, 86, 89–91]. The commercially available system uses two dextran-sulfate columns, which are alternately being loaded and regenerating. The ECV of the system is 400 mL; therefore this system cannot be used safely in small children. Because bradykinin can be generated in the plasma filter as well as in the dextran-sulfate columns, bradykinin-related symptoms can be observed when transition time is too short for bradykinin inactivation. Furthermore, ACE inhibitors decrease bradykinin inactivation and should therefore not be used with dextran-sulfate adsorption or stopped at least 24 h before treatment.

Dextran-sulfate columns can be run with a pediatric blood pump monitor and a volume-regulated plasma dialysis device (BM-25, Fa. Baxter) using a custom-made tubing system (Päd. Lipidapherese-Set I09.4, Fa Meise, Germany). With such a system, the volume of the extracorporeal circuit can be reduced to 60 mL in the blood compartment and 100 mL in the plasma compartment, making this system suitable for children of 10–20 kg without the need of priming with albumin [92] (Fig. 41.4).

Double/Cascade Filtration

The double/cascade filtration (CascadeFlow EX 50 W Lipidfilter (Fa ASAHI Kasei Kuraray, Tokyo, Fa DIAMED Cologne)) depletes plasma components nonspecifically according to their size. After separation from the cellular blood components, plasma is run on a plasma fractionator (ethylene vinyl alcohol copolymer) that retains LDL by 98% and fibrinogen by 69% (data given by manufacturer [93]), which is discarded. The reduction in fibrinogen might exclude patients with low fibrinogen plasma levels. For anticoagulation, citrate is used. The system has a priming volume of 165 mL blood and 180 or 240 mL plasma according to the size of the plasma fractionator used. Therefore it is suitable for children above about 20 kg body weight. However, due to its lack of specificity, this technique is reported to be used decreasingly [86].

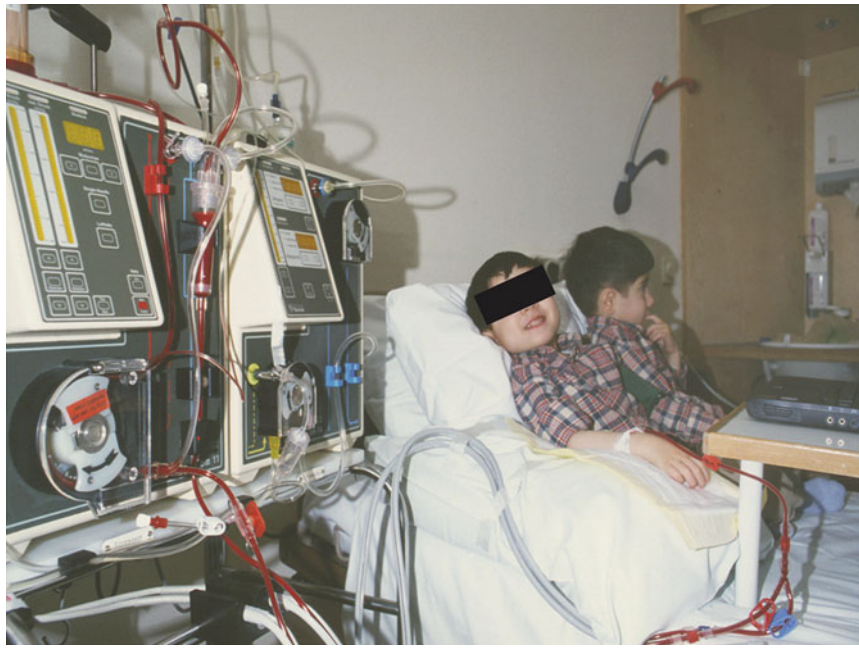

Fig. 41.4 *LDL apheresis unit with dextran-sulfate column (Liposorber®) in small children*. The photos shows 3.5-year-old children during the LDL apheresis using a custom-made tubing on a BM25 balanced blood pump with the Liposorber® system. Venous access by single needle to a Cimino fistula

Precipitation Techniques

In heparin-induced extracorporeal LDL precipitation (H.E.L.P.® Fa Braun, Melsungen, Germany, http://www.help-therapie.de) LDL, Lp(a), and fibrinogen are precipitated from plasma by heparin in acidic buffer with a pH of 5.12 (sodium acetate). The cleared plasma then passes a heparin adsorber (DEA mod. polyamide, fill volume 150 mL, adsorption capacity ≥ 300.000 IE heparin). This is followed by a single pass dialysis with a cellulose membrane (ultrafilter SMC 1.8, 1.84 m² surface, fill volume 117 mL, max. TMP 600 mmHg) for removing the sodium acetate and normalizing the pH. The system is complex but the procedure is well tolerated (<3% adverse events) [94]. However, published pediatric experience is not available. In contrast to the dextran-sulfate adsorption, H.E.L.P. additionally reduces fibrinogen plasma levels. This system may not be usable in patients with low fibrinogen levels. Co-medication with ACE inhibitors is possible. Due to its large extracorporeal volume, the system is not recommended for patients <30 kg body weight. The H.E.L.P. system also removes complement. Therefore the indication in patients with low C3 or C1 esterase inhibitor deficiency should be thoroughly evaluated. For anticoagulation, no citrate must be used. An initial heparin bolus of 2,000 IE/m^2 body surface often is sufficient.

Whole Blood Apheresis

Direct adsorption of lipoproteins on whole blood is obtained with the DALI®-system (Fa Fresenius Medical Care, Germany [95]). This technique lowers both LDL and Lp(a). The system does not need plasma separation. The blood is run over the adsorber unit, which contains negatively charged polyacrylate ligands immobilized on polyacrylamide. The DALI adsorber is available in five different sizes (300, 500, 750, 1,000, and 1,250 mL). Anticoagulation is performed by citrate. The DALI system is reported to be increasingly used in France [86].

Infrastructure for Pediatric LDL Apheresis

The application of LDL apheresis in children and adolescents needs specific structural conditions and staff qualification. The physician should be trained in pediatric extracorporeal therapies as well as in intensive care medicine, because acute life-threatening complications can occur. The unit should also have emergency equipment. The nursing staff must be experienced in maintaining extracorporeal circuits in children. It is recommended that at least one physician and one to two nurses are present during the entire procedure. The availability of social workers, teachers, or play therapists may increase pediatric patient tolerance of apheresis, especially if the patient is immobilized due to blood lines in both antecubital veins. For control of anticoagulation, measurement of activated clotting time or ionized calcium in case of citrate anticoagulation should be immediately available. Pediatric dialysis units offer qualified staff and appropriate equipment, but due to high costs, in most countries health insurance systems must authorize LDL apheresis in the individual patient prior to the start of treatment.

LDL Apheresis Treatment Results

Plasma Cholesterol

Despite different characteristics of the currently available techniques, efficacy in lowering plasma cholesterol levels is similar. One single treatment session with the processing of 1.5× plasma volume lowers plasma LDL cholesterol by 50–80% [82, 86, 90, 96, 97]. In the long term, patients have 18–52% lower average plasma LDL cholesterol levels with a treatment frequency of once every 1–2 weeks [82]. The average LDL cholesterol level is calculated as the mean of the LDL cholesterol plasma concentrations before and after the LDL apheresis session. However, recommended targets are often not met.

Atherosclerotic Lesions

In general, a late start of LDL apheresis in FH patients is associated with more severe involvement of the aortic valve and less response to treatment. Atherosclerotic involvement of the aortic valve often is detectable by 6 years of age and shows no or little regression on therapy. Therefore, initiation of LDL apheresis is recommended below the age of 8 years [85] or even 6 years [84]. If the patient has established atherosclerotic lesions, a mean plasma cholesterol <140 mg/dL was found to be associated with regression of the lesions in adult patients [81]. LDL cholesterol was the main determinant for the effect of LDL apheresis. In pediatric FH patients on LDL apheresis followed with angiography every 2 years, Stefanutti reported no development of atherogenic lesions in those free of it at start of treatment. In about 50% of patients lesions were already present before LDL apheresis started. These lesions regressed or stabilized and no increase was observed with biweekly or weekly apheresis sessions aiming at a posttreatment LDL cholesterol of 70–100 mg/dL [84]. After a mean observation period of 12.6 ± 6 years, all FH patients of the pediatric series of Palcoux [86] were alive with normal physical and pubertal development; these patients began LDL apheresis treatment at a mean age of 8.5 years. Cardiac disorders were observed in five children during the treatment period, three of them experiencing angina pectoris. In the series of Hudgkins with biweekly treatment, which resulted in a 48% lowering of baseline plasma cholesterol levels, 60% of patients showed atherosclerotic disease of the coronary artery or aorta or aortic valve on angiography. The lesions progressed in one third of the patients [90].

Xanthomas/Xanthelasmas

Xanthomas or xanthelasmas may develop rapidly and are of significance for the body image of the adolescent patient. On adequate apheresis

Table 41.7 Adverse events reported during LDL apheresis in pediatric patients

System	Hudgins [90] Dextran-sulfate cellulose	Stefanutti [84] Dextran-sulfate cellulose	Coker [82] Dextran-sulfate cellulose direct adsorption	Palcoux [86] Dextran-sulfate cellulose
Vascular access	4.7	2	4.5	6/21
Hypotension	2.9	2	0.2	2/21 pts
Nausea	1.0	0.2	0.2	n.r
Inconvenience		n.r.		1/21 pts
Anaphylactic reactions	n. r.	n.r.	n.r.	9/27 pts

n.r. not reported, *pts* patients

therapy, the xanthomas and xanthelasmas are reported to resolve completely or decrease in size within 2 years [85]. Even after 12 years, these lesions may resolve [86].

Adverse Events

LDL apheresis in general is well tolerated. In many series including our own, adverse events occurred more often during the development of an apheresis capability in the unit with limited prior experience. In our own series with two FH twins starting weekly LDL apheresis at the age of 3.5 years, a high level of adverse events was recorded (14%) during the first 75 treatment episodes, mainly due to venous access problems and mild hypotension (6.7%): much lower rates were seen with further follow-up. Adverse events can be minimized by careful selection of apheresis modality according to extracorporeal volume and adherence to exclusion criteria. The most commonly reported adverse events are related to hypotension and venous access problems (Table 41.7). Furthermore, anaphylactic reactions were observed in 9 of 27 patients in the series of Palcoux [86]. Most of these patients used whole blood adsorption techniques, but anaphylactic reactions are also found in dextran-sulfate cellulose systems due to bradykinin liberation. In some patients development of iron deficiency has been described ([98], Klaus unpublished), necessitating iron supplements.

LDL Apheresis Recommendations

LDL apheresis is indicated in FH patients not responsive to medical treatment. In summary, the following recommendations are suggested (for details, see text):

- Start LDL apheresis at age below 6–8 years.
- Vascular access by peripheral antecubital veins in adolescents, if tolerated; Cimino fistula in younger subjects.
- Adequately equipped unit and trained staff including psychosocial support is necessary.
- Selection of modality by adjusted extracorporeal volume and local experience.
- Initial treatment frequency: every 2 weeks.
- Reduction in LDL cholesterol should be aimed at the lowest level possible, at least 60% reduction per session.
- In patients with established atherosclerotic lesions, mean LDL cholesterol should be <100 mg/dL.
- If targets are not met, frequency should be increased to weekly sessions.

References

1. Nguyen TC, Han YY, Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. Crit Care Med. 2008;36(10):2878–87.

2. Chopek M, McCullough J. Protein and biochemical changes during plasma exchange. Washington: AABB Press; 1980.
3. Strauss R, McLeod B. Adverse reactions to therapeutic apheresis. Bethesda: AABB Press; 1996.
4. Dzik WH, Kirkley SA. Citrate toxicity during massive blood transfusion. Transfus Med Rev. 1988;2(2): 76–94.
5. 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.
6. Szymanski IO. Ionized calcium during plateletpheresis. Transfusion. 1978;18(6):701–8.
7. Bunchman TE, Maxvold NJ, Barnett J, Hutchings A, Benfield MR. Pediatric hemofiltration: Normocarb dialysate solution with citrate anticoagulation. Pediatr Nephrol. 2002;17(3):150–4.
8. 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(Suppl 5):S137–43.
9. Snyder Jr HW, Cochran SK, Balint Jr JP, et al. Experience with protein A-immunoadsorption in treatment-resistant adult immune thrombocytopenic purpura. Blood. 1992;79(9):2237–45.
10. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88(1):3–40.
11. Furst D, Felson D, Thoren G, Gendreau R. Immunoadsorption for the treatment of rheumatoid arthritis: final results of a randomized trial. Prosorba Trial Investigators. Ther Apher. 2000;4(5):363–73.
12. Hughes LB, Moreland LW. New therapeutic approaches to the management of rheumatoid arthritis. BioDrugs. 2001;15(6):379–93.
13. 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.
14. Nilsson IM, Freiburghaus C. Apheresis. Adv Exp Med Biol. 1995;386:175–84.
15. Uehlinger J, Button GR, McCarthy J, Forster A, Watt R, Aledort LM. Immunoadsorption for coagulation factor inhibitors. Transfusion. 1991;31(3):265–9.
16. Bohmig GA, Regele H, Saemann MD, 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.
17. Braun N, Kadar JG, Risler T. Therapeutic immunoadsorption – its role in clinical practice. Transfus Sci. 1998;19(Suppl):65–9.
18. Bueno Jr D, Sevigny J, Kaplan AA. Extracorporeal treatment of thrombotic microangiopathy: a ten year experience. Ther Apher. 1999;3(4):294–7.
19. Bygren P, Freiburghaus C, Lindholm T, Simonsen O, Thysell H, Wieslander J. Goodpasture's syndrome treated with staphylococcal protein A immunoadsorption. Lancet. 1985;2(8467):1295–6.
20. Dantal J, Bigot E, Bogers W, 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.
21. Esnault V, Bignon JD, Testa A, Preud'homme JL, Vergracht A, Soulillou JP. Effect of protein A immunoadsorption on panel lymphocyte reactivity in hyperimmunized patients awaiting a kidney graft. Transplantation. 1990;50(3):449–53.
22. Esnault VL, Besnier D, Testa A, et al. Effect of protein A immunoadsorption in nephrotic syndrome of various etiologies. J Am Soc Nephrol. 1999;10(9): 2014–17.
23. Haas M, Bohmig GA, Leko-Mohr Z, et al. Perioperative immunoadsorption in sensitized renal transplant recipients. Nephrol Dial Transplant. 2002;17(8): 1503–8.
24. Hickstein H, Korten G, Bast R, Barz D, Nizze H, Schmidt R. Immunoadsorption of sensitized kidney transplant candidates immediately prior to surgery. Clin Transplant. 2002;16(2):97–101.
25. Hiesse C, Kriaa F, Rousseau P, et al. Immunoadsorption of anti-HLA antibodies for highly sensitized patients awaiting renal transplantation. Nephrol Dial Transplant. 1992;7(9):944–51.
26. Juckett M, Perry EH, Daniels BS, Weisdorf DJ. Hemolytic uremic syndrome following bone marrow transplantation. Bone Marrow Transplant. 1991;7(5): 405–9.
27. Mastrangelo F, Pretagostini R, Berloco P, et al. Immunoadsorption with protein A in humoral acute rejection of kidney transplants: multicenter experience. Transplant Proc. 1995;27(1):892–5.
28. Matic G, Bosch T, Ramlow W. Background and indications for protein A-based extracorporeal immunoadsorption. Ther Apher. 2001;5(5):394–403.
29. Mittelman A, Bertram J, Henry DH, et al. Treatment of patients with HIV thrombocytopenia and hemolytic uremic syndrome with protein A (Prosorba column) immunoadsorption. Semin Hematol. 1989;26(2 Suppl 1): 15–18.
30. Pretagostini R, Berloco P, Poli L, et al. Immunoadsorption with protein A in humoral rejection of kidney transplants. ASAIO J. 1996;42(5): M645–8.
31. Snyder Jr HW, Mittelman A, Oral A, et al. Treatment of cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein A immunoadsorption of plasma. Cancer. 1993;71(5):1882–92.
32. Watson PR, Guthrie Jr TH, Caruana RJ. Cisplatin-associated hemolytic-uremic syndrome. Successful treatment with a staphylococcal protein A column. Cancer. 1989;64(7):1400–3.
33. Parhofer KG, Geiss HC, Schwandt P. Efficacy of different low-density lipoprotein apheresis methods. Ther Apher. 2000;4(5):382–5.
34. Schmaldienst S, Banyai S, Stulnig TM, et al. Prospective randomised cross-over comparison of three LDL-apheresis systems in statin pretreated

patients with familial hypercholesterolaemia. Atherosclerosis. 2000;151(2):493–9.
35. Vella A, Pineda AA, O'Brien T. Low-density lipoprotein apheresis for the treatment of refractory hyperlipidemia. Mayo Clin Proc. 2001;76(10):1039–46.
36. 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.
37. Kim HC, Dugan NP, Silber JH, et al. Erythrocytapheresis therapy to reduce iron overload in chronically transfused patients with sickle cell disease. Blood. 1994;83(4):1136–42.
38. Stemmler J, Wittmann GW, Hacker U, Heinemann V. Leukapheresis in chronic myelomonocytic leukemia with leukostasis syndrome: elevated serum lactate levels as an early sign of microcirculation failure. Leuk Lymphoma. 2002;43(7):1427–30.
39. Rowe JM, Lichtman MA. Hyperleukocytosis and leukostasis: common features of childhood chronic myelogenous leukemia. Blood. 1984;63(5):1230–4.
40. Maurer HS, Steinherz PG, Gaynon PS, et al. The effect of initial management of hyperleukocytosis on early complications and outcome of children with acute lymphoblastic leukemia. J Clin Oncol. 1988; 6(9):1425–32.
41. Steeper TA, Smith JA, McCullough J. Therapeutic cytapheresis using the Fenwal CS-3000 blood cell separator. Vox Sang. 1985;48(4):193–200.
42. Benito AI, Gonzalez-Vicent M, Garcia F, et al. Allogeneic peripheral blood stem cell transplantation (PBSCT) from HLA-identical sibling donors in children with hematological diseases: a single center pilot study. Bone Marrow Transplant. 2001;28(6): 537–43.
43. Diaz MA, Garcia-Sanchez F, Lillo R, Vicent MG, Vicario JL, Madero L. Large-volume leukapheresis in pediatric patients: pre-apheresis peripheral blood CD34+ cell count predicts progenitor cell yield. Haematologica. 1999;84(1):32–5.
44. Goldman JM, Horowitz MM. The international bone marrow transplant registry. Int J Hematol. 2002; 76(Suppl 1):393–7.
45. Gorlin JB, Humphreys D, Kent P, 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.
46. Marson P, Petris MG, Messina C, et al. Peripheral blood stem cell collection in pediatric oncohematology. Experience with patients weighing less than 15 kg. Minerva Pediatr. 2000;52(3):129–35.
47. Sevilla J, Gonzalez-Vicent M, Madero L, Diaz MA. Peripheral blood progenitor cell collection in low-weight children. J Hematother Stem Cell Res. 2002;11(4):633–42.
48. 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.
49. Collins Jr RH, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol. 1997;15(2):433–44.
50. Drobyski WR, Hessner MJ, Klein JP, et al. T-cell depletion plus salvage immunotherapy with donor leukocyte infusions as a strategy to treat chronic-phase chronic myelogenous leukemia patients undergoing HLA-identical sibling marrow transplantation. Blood. 1999;94(2):434–41.
51. Drobyski WR, Keever CA, Roth MS, et al. Salvage immunotherapy using donor leukocyte infusions as treatment for relapsed chronic myelogenous leukemia after allogeneic bone marrow transplantation: efficacy and toxicity of a defined T-cell dose. Blood. 1993;82(8):2310–18.
52. Gasparetto C, Gasparetto M, Morse M, et al. Mobilization of dendritic cells from patients with breast cancer into peripheral blood stem cell leukapheresis samples using Flt-3-Ligand and G-CSF or GM-CSF. Cytokine. 2002;18(1):8–19.
53. Mandanas RA, Saez RA, Selby GB, Confer DL. G-CSF-mobilized donor leukocyte infusions as immunotherapy in acute leukemia relapsing after allogeneic marrow transplantation. J Hematother. 1998;7(5):449–56.
54. Zic JA, Miller JL, Stricklin GP, King Jr LE. The North American experience with photopheresis. Ther Apher. 1999;3(1):50–62.
55. Rook AH, Suchin KR, Kao DM, et al. Photopheresis: clinical applications and mechanism of action. J Investig Dermatol Symp Proc. 1999;4(1):85–90.
56. Knobler R, Jantschitsch C. Extracorporeal photochemoimmunotherapy in cutaneous T-cell lymphoma. Transfus Apher Sci. 2003;28(1):81–9.
57. Knobler R, Girardi M. Extracorporeal photochemoimmunotherapy in cutaneous T cell lymphomas. Ann N Y Acad Sci. 2001;941:123–38.
58. Knobler R. Extracorporeal photochemotherapy – Present and future. Vox Sang. 2000;78(Suppl 2): 197–201.
59. Greinix HT, Volc-Platzer B, Rabitsch W, 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.
60. Shinoda T. Photopheresis and leukocytapheresis: cytapheresis treatment against immune-mediated diseases. Ther Apher. 2002;6(4):245–6.
61. Schneider M. Plasma- and lymphapheresis in autoimmune diseases. Z Rheumatol. 1996;55(2):90–104.
62. Costanzo-Nordin MR, Hubbell EA, O'Sullivan EJ, et al. Photopheresis versus corticosteroids in the therapy of heart transplant rejection. Preliminary clinical report. Circulation. 1992;86(Suppl 5):II242–50.
63. Meiser BM, Kur F, Reichenspurner H, et al. Reduction of the incidence of rejection by adjunct immunosuppression with photochemotherapy after heart transplantation. Transplantation. 1994;57(4):563–8.
64. Rossetti F, Dall'Amico R, Crovetti G, et al. Extracorporeal photochemotherapy for the treatment

of graft-versus-host disease. Bone Marrow Transplant. 1996;18(Suppl 2):175–81.
65. Dall'Amico R, Rossetti F, Zulian F, et al. Photopheresis in paediatric patients with drug-resistant chronic graft-versus-host disease. Br J Haematol. 1997;97(4): 848–54.
66. Adami R. Therapeutic thrombocytapheresis: a review of 132 patients. Int J Artif Organs. 1993;16(Suppl 5):183–4.
67. Baron BW, Mick R, Baron JM. Combined plateletpheresis and cytotoxic chemotherapy for symptomatic thrombocytosis in myeloproliferative disorders. Cancer. 1993;72(4):1209–18.
68. Liumbruno G, Centoni PE, Ceretelli S, Sodini ML. Rapid reduction of platelet numbers in thrombocytosis. Ther Apher. 2000;4(5):374–6.
69. Renner D, Queisser U, Martinez C, Queisser W. Treatment of excessive thrombocythemia in chronic myeloid leukemia by thrombocytopheresis and intravenous Thio-TEPA. Onkologie. 1987;10(5):324–6.
70. Ullrich H, Kadar J, Waxenberger Y, et al. Therapeutic thrombocytapheresis in patients with myeloproliferative diseases with the cell separators Fresenius AS 104 and Cobe Spectra: biocompatibility and safety. Beitr Infusionsther. 1992;30:311–14.
71. Gerhardt RE, Ntoso KA, Koethe JD, Lodge S, Wolf CJ. Acute plasma separation with hemodialysis equipment. J Am Soc Nephrol. 1992;2(9):1455–8.
72. Price CA. Therapeutic plasma exchange in a dialysis unit. ANNA J. 1987;14(2):103–8.
73. Nadler S, Hidalgo J, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224.
74. Kim HC. Therapeutic pediatric apheresis. J Clin Apher. 2000;15(1–2):129–57.
75. Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice – Evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25(3): 83–177.
76. Owen HG, Brecher ME. Atypical reactions associated with use of angiotensin-converting enzyme inhibitors and apheresis. Transfusion. 1994;34(10):891–4.
77. Thompson GR. LDL apheresis. Atherosclerosis. 2003;167(1):1–13. Review.
78. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003;168(1):1–14. Review.
79. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986; 232(4746):34–47. Review.
80. Leigh SE, Foster AH, Whittall RA, Hubbart CS, Humphries SE. Update and analysis of the University College London low density lipoprotein receptor familial hypercholesterolemia database. Ann Hum Genet. 2008;72(Pt 4):485–98.
81. Masaki N, Tatami R, Kumamoto T, Izawa A, Shimada Y, Takamatsu T, Katsushika S, Ishise S, Maruyama Y, Yoshimoto N. Ten-year follow-up of familial hypercholesterolemia patients after intensive cholesterol-lowering therapy. Int Heart J. 2005;46(5): 833–43.
82. Coker M, Ucar SK, Simsek DG, Darcan S, Bak M, Can S. Low density lipoprotein apheresis in pediatric patients with homozygous familial hypercholesterolemia. Ther Apher Dial. 2009;13(2):121–8.
83. Mabuchi H, Koizumi J, Shimizu M, Kajinami K, Miyamoto S, Ueda K, Takegoshi T. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. Am J Cardiol. 1998;82(12):1489–95.
84. Stefanutti C, Vivenzio A, Di Giacomo S, Mazzarella B, Bosco G, Berni A. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion. 2009;49(7):1461–70. Epub 2009 Mar 23.
85. 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; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; 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: endorsed by the American Academy of Pediatrics. Circulation. 2006;114(24):2710–38. Epub 2006 Nov 27. Review.
86. Palcoux JB, Atassi-Dumont M, Lefevre P, Hequet O, Schlienger JL, Brignon P, Roussel B. Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years. Ther Apher Dial. 2008;12(3):195–201.
87. Böhler J, Schollmeyer P, Dressel B, Dobos G, Hörl WH. Reduction of granulocyte activation during hemodialysis with regional citrate anticoagulation: dissociation of complement activation and neutropenia from neutrophil degranulation. J Am Soc Nephrol. 1996;7(2):234–41.
88. Gabutti L, Ferrari N, Mombelli G, Keller F, Marone C. The favorable effect of regional citrate anticoagulation on interleukin-1beta release is dissociated from both coagulation and complement activation. J Nephrol. 2004;17(6):819–25.

89. Stefanutti C, Di Giacomo S, Vivenzio A, Colloridi V, Bosco G, Berni A, Rabbone I, Cerutti F, Bertolini S. Low-density lipoprotein apheresis in a patient aged 3.5 years. Acta Paediatr. 2001;90(6):694–701.
90. Hudgins LC, Kleinman B, Scheuer A, White S, Gordon BR. Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia. Am J Cardiol. 2008;102(9):1199–204.
91. De Silvestro G, Tison T, Vicarioto M, Bagatella P, Stefanutti C, Marson P. The Italian Registry of Pediatric Therapeutic Apheresis: a report on activity during 2005. J Clin Apher. 2009;24(1):1–5.
92. Soufi M, Kurt B, Schweer H, Sattler AM, Klaus G, Zschocke J, Schaefer JR. Genetics and kinetics of familial hypercholesterolemia, with the special focus on FH-Marburg) .W556R. Atheroscler Suppl. 2009; 10(5):5–11.
93. Geiss HC, Parhofer KG, Donner MG, Schwandt P. Low density lipoprotein apheresis by membrane differential filtration (cascade filtration). Ther Apher. 2000;3(3):199–202.
94. Seidel D, Armstrong VW, Schuff-Werner P. The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. I. Evaluation of safety and cholesterol-lowering effects during the first 12 months. HELP Study Group. Eur J Clin Invest. 1991;21(4):375–83.
95. Bosch T, Gahr S, Belschner U, Schaefer C, Lennertz A, Rammo J, for the DALI Study Group. Direct adsorption of low-density lipoprotein by DALI-LDL-apheresis: results of a prospective long-term multicenter follow-up covering 12,291 sessions. Ther Apher Dial. 2006;10(3):210–18.
96. Uauy R, Zwiener RJ, Phillips MJ, Petruska ML, Bilheimer DW. Treatment of children with homozygous familial hypercholesterolemia: safety and efficacy of low-density lipoprotein apheresis. J Pediatr. 1992;120(6):892–8.
97. Zwiener RJ, Uauy R, Petruska ML, Huet BA. Low-density lipoprotein apheresis as long-term treatment for children with homozygous familial hypercholesterolemia. J Pediatr. 1995;126(5 Pt 1):728–35.
98. Eminoglu TF, Yenicesu I, Tumer L, Okur I, Dilsiz G, Hasanoglu A. Lipid apheresis applications in childhood: experience in the University Hospital of Gazi. Transfus Apher Sci. 2008;39(3):235–40.

Extracorporeal Therapy for Drug Overdose and Poisoning

42

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Keywords
Drug overdose • Poisoning • Extracorporeal therapy

Introduction

Poisoning continues to be a significant cause of morbidity and mortality. The 2008 Annual Report of the American Association of Poison Control Centers (AAPCC) published information on 2,491,049 human exposure cases of poisoning, half of them being children younger than 6 years [1]. Prescription drugs, over the counter medications, illicit drugs, and common household substances can all be responsible for poisoning. As per the 2008 Annual Report, the top four most frequently involved substances in all human exposures were analgesics (13.3%), cosmetics/personal care products (9.0%), household cleaning substances (8.6%), and sedatives/hypnotics/antipsychotics (6.6%). Most (82.8%) poison exposures were unintentional, and suicidal intent was suspected in 8.7% of cases. In 10.6% of exposures (263,942 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 is a significant burden on health care. In 2008, approximately one-fourth of all cases received treatment in a health care facility. While half of them were treated and released without admission, 93,096 (15.6%) had to be admitted for critical care management. Treatment in a health care facility was provided in a higher percentage of exposures that involved pharmaceutical substances (26.4%) compared with non-pharmaceutical substances (14.1%), and exposures to pharmaceuticals resulted in more severe outcomes. Although children younger than 6 years were involved in the majority of exposures, fortunately they comprised just 2.0% of the exposure-related fatalities.

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

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identification and determination of blood concentration of the toxic substance
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. Elimination of poison by manipulation of urinary pH
7. Removal of poison by extracorporeal therapies

It is important to note that a large group of patients can be managed by approaches 1–6 with excellent results. Nonetheless, some of these standard therapies such as usage of ipecac syrup, gastric lavage, and forced alkaline diuresis have recently come under intense scrutiny and fallen out of favor [2]. For detailed information regarding use of oral sorbents, specific antidotal therapies, supportive care, and forced alkaline diuresis, the reader is referred to standard emergency medicine and toxicology texts [3–5].

This chapter will mainly focus on a specific category of poisoned patients in whom active removal of the toxic substance through the use of extracorporeal therapies is deemed necessary. Patients in this category can be divided into three subgroups:

1. Patients intoxicated with poisons that cause direct tissue damage (*vide infra*)
2. Patients intoxicated with poisons that do not cause direct tissue damage, but patient's ability to metabolize or excrete the toxic substance is compromised
3. Patients intoxicated with poisons in which active poison removal is considered to avoid prolonged supportive care and its associated complications

For practical purposes, the toxic substance (poison or a drug) 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 aspirin, acetaminophen, and methyl alcohol can cause direct tissue damage despite provision of intensive supportive care [3, 6–8]. In patients poisoned with this group of chemicals, use of specific antidote (if available) and/or active removal of the poison by extracorporeal therapies is necessary to prevent irreversible tissue damage. The second group of poisons such as barbiturates and other common sedative/hypnotic drugs do not have any direct tissue damaging effect but cause harm indirectly due to respiratory compromise or hypotension. These patients can be treated with specific antidote (if available) and supportive care, provided they will metabolize and/or excrete the poison in a reasonable time.

Extracorporeal Therapies for Active Poison Removal

To be worthwhile, the rate of poison removal by an extracorporeal method must be significantly greater than the spontaneous rate of elimination by hepatic and/or renal excretion, unless the intrinsic clearance is impaired by the disease process, and extracorporeal method is the only means of providing useful clearance. According to the 2008 annual report of the AAPCC, out of 93,096 patients admitted for critical care management, only 2,177 (<2.5%) were treated with hemodialysis while hemoperfusion was carried out in merely 27 patients [1]. The reason for such restricted usage of extracorporeal therapies despite the fact that techniques such as hemodialysis are highly efficient in removal of small molecular weight chemicals from circulation is that in relatively few cases, such as poisoning with methanol, ethylene glycol, valproic acid, carbamazepine, acetylsalicylic acid, and lithium, does the extracorporeal removal have a significant impact on patient outcome.

Since poisons achieve their toxic effects on target organs via the blood stream, it seems logical that their elimination from the blood should result in amelioration of the patient's condition. Accordingly, changes in the serum drug 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. To better understand these perplexities, the nephrologist ought to be well versed with the basic concepts of drug kinetics 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.

General Pharmacokinetic Concepts and Principles of Extracorporeal Therapy

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 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.

$$V_d\,(\text{Liters}) = 0.6\ \text{L/kg} \times \text{body weight}\,(\text{kg}) \quad (42.1)$$

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:

$$X(\text{mg}) = V_d(\text{L}) \times C_p(\text{mg/L}) \quad (42.2)$$

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 determines 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. Thus, even if hemodialysis session extracts most of the drug present in blood flowing through the circuit, the amount of drug removed represents a small percentage of the total body drug burden. Volumes of distribution of some of the common substances involved in poisoning are listed in Table 42.1. It is important to note that these values for V_d are derived from 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.

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. Protein binding limits the amount of free drug available for removal across dialysis membranes. Highly protein-bound substances are therefore not amenable to therapy with extracorporeal modalities. However, at toxic levels the protein binding sites are usually saturated, resulting in higher percentage of unbound fraction that can be effectively removed by dialysis therapy. In addition, albumin can be added to the dialysate 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 [9].

Table 42.1 Properties of substances frequently involved in poisonings

Substance	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Preferred extracorporeal modality
Acetaminophen	151	0.95	25	MARS
Aminoglycoside	*	0.2–0.3	<5	HD
Amphotericin B	924	4.0	90	–
Benzodiazepine	*	0.3–6.6	85–98	–
Carbamazepine	228	0.8–1.6	75	HDF[a], PP
Digoxin	765	5–8	20–30	–
Ethanol	46	0.7	0	–
Ethylene glycol	62	0.6	0	HD, HF
Indomethacin	327	0.12	99	–
Isopropyl alcohol	60	0.7	0	HD, HF
Lithium	7	0.5–0.9	0	HF, HD
Methanol	32	0.7	0	HD, HF
Methotrexate	456	0.76	45–50	HP
Narcotic	*	3–16	*	–
Phenobarbital	232	0.7–1.0	40–60	HD, HP
Phenytoin	252	0.55	90	–
Salicylate	138	0.1–0.2	80–90	HD, HF
Theophylline	*	0.4–0.7	55	HD, HP
Tricyclic antidepressants	*	6–50	90–97	? PP
Valproate	144	0.19–0.23	90	HDF[a], PP

MARS Molecular adsorbent recirculating system, *HD* hemodialysis, *HF* hemofiltration, *HP* hemoperfusion, *HDF* hemodiafiltration, *PP* plasmapheresis

[a]Addition of albumin to the dialysate has been shown to enhance the elimination of carbamazepine and valproate [10, 11]

*Variable depending on specific drug

?Questionable efficacy

This technique has been shown to be very efficient in enhancing the clearance of valproic acid and carbamazepine [10, 11]. 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.

Membrane Transport

Transport across dialyzer membrane can occur by diffusion or by convection. Diffusive transport is the average of the random motion of the huge number of individual molecules with a net movement down their concentration gradient. As the random motion of smaller molecules is faster than those of larger molecules, small molecules diffuse and equilibrate faster than large molecules. Concentration gradient and membrane surface area are the two other major determinants of diffusive transport. During convective transport, dissolved molecules are carried along with the fluid (solvent drag). The transport of the molecules across the membrane is limited by the membrane pore size. The ratio of the substance concentration in the filtrate to its plasma concentration is known as sieving coefficient which along with ultrafiltration rate is the major determinant of convective transport.

Lipid Solubility

Lipid solubility affects the accumulation of drug in lipid-rich tissues such as adipose tissue and 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 (nonpolar) phase to aqueous (polar) phase concentration of its nonionized form. Lipid-soluble drugs can accumulate extensively in the adipose tissue and act as reservoir with poor accessibility due to decreased vascular perfusion.

Ionization

Nonionized 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 nonionized. An acid is increasingly ionized as the pH rises above its pK, and a base is increasingly ionized as pH falls below its pK. pH gradients across cell membranes can affect the extent of diffusion by trapping the ionized form on one side. In stomach and kidney, where large pH gradients exist (or can be induced) with respect to plasma, this has therapeutic implications.

Intercompartmental Transfer

In a single compartment model, a change in plasma level would reflect similar change in levels throughout body. Unfortunately, most substances in the body are distributed in multiple compartments and movement across these compartments is variable and dependent on several factors. Knowledge of these parameters is crucial in understanding the relationship between blood level and drug removal during extracorporeal therapies [12].

Drug Removal

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:

$$C = Q_b \times (A - V)/A \qquad (42.3)$$

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 as 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

$$C = E/P \times Q_e \qquad (42.4)$$

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 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 (42.2). 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 h, 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.

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:

$$\text{Half-life } (t\,½) = 0.693/K_e$$
$$K_e = [\log(C_{peak}) - \log(C_{trough})]/t_{interval} \qquad (42.5)$$

where K_e is the elimination rate constant, 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:

$$C = 0.693 \times V_d/t\,½ \qquad (42.6)$$

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.

Specific Toxicological Issues in Neonates and Young Infants

The implications and management of poisoning in newborns and young infants requires 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 [13]. 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 P-450–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.

Modalities of Extracorporeal Therapy

Hemodialysis

Hemodialysis is widely available and has been used for detoxification purposes for a long period of time. To be effectively removed by hemodialysis, a substance must have favorable pharmacokinetic profile such as small molecular weight (<500 Da; currently available high-efficacy dialyzers can provide useful clearance for molecular weights up to 2,000 Da), should be water soluble with a small V_d (<1 L/kg), without significant protein binding, and rapid equilibration with the plasma water compartment. In addition the substance must be nonionized so that it can easily diffuse across the dialysis membrane. For drugs such as methanol, ethylene glycol, aspirin, and lithium which have these pharmacokinetic characteristics, hemodialysis is an effective treatment for drug clearance.

Hemodialysis has been commonly used for alcohol (methanol, ethylene glycol, isopropyl alcohol) and salicylate poisoning. Methanol has a low molecular weight, is water soluble, and has a V_d of 0.6 L/kg. In addition, methanol is metabolized to more toxic substances such as formaldehyde and formate that are also dialyzable. Historically, a plasma concentration of 50 mg/dL has been used as a threshold for the need for dialysis in both ethylene glycol and methanol poisonings [6, 14, 15]. Adjunctive management has traditionally included correction of acidosis and administration of ethanol which competitively inhibits the metabolism of methanol by alcohol dehydrogenase [16]. Similar use of hemodialysis and ethanol could be considered for ethylene glycol, while hemodialysis alone would be useful for isopropyl alcohol and severe ethanol intoxication. However, the availability of fomepizole, a safe and effective inhibitor of alcohol dehydrogenase, has altered the indications for HD [17–20]. While HD continues to be a useful and often necessary adjunct in the treatment of toxic alcohol poisonings, an elevated blood concentration of the alcohol alone is no longer considered sufficient to require HD.

Although highly protein bound, salicylates have very low V_d and are amenable to removal by hemodialysis. The decision to perform hemodialysis is usually made on clinical parameters rather than plasma salicylate concentration. Clinical indications for hemodialysis include the presence of coma, seizures, cerebral or pulmonary edema, renal failure, refractory acid–base disturbances, or clinical worsening despite treatment. While sole reliance on the plasma salicylate concentration is not advised, serious consideration for hemodialysis, however, should be given to acutely poisoned patients with salicylate concentrations of at least 100 mg/dL or chronic patients with salicylate concentrations of at least 60 mg/dL [21].

While hemodialysis has a long track record for safety, it is associated with many potential complications that are outlined elsewhere in the text. In particular, one must be aware that the dialysis process may remove other drugs, such as antibiotics and cardiomimetics. Thus, these drugs must be delivered distal to the dialyzer and will perhaps require higher doses to be effective.

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. Due to its continuous nature, CRRT is beneficial in the removal of drugs that distribute in multiple compartments with slow equilibration. 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. Lithium is a substance known to have a large volume of distribution due to its intracellular distribution. Although it is not highly protein bound, its large V_d coupled with its slow transcellular diffusion, makes CRRT the preferred modality for its elimination [22–24]. In addition, patients with hemodynamic instability may benefit from a slower form of dialysis.

Hemoperfusion

In hemoperfusion, blood is percolated through a cartridge packed with activated charcoal or other resin coated with a semipermeable membrane [25]. Typical cartridges have 150–300 g of activated charcoal or 650 g of resin. Substances are adsorbed onto the charcoal or polystyrene resin despite protein binding, making this modality a better choice for highly protein-bound poisons [26]. These cartridges can also absorb lipid-soluble substances and 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. Most cartridges come sterilized, and must be flushed with saline prior to use.

Complications with hemoperfusion have been well documented and include platelet depletion and clotting in the cartridge. Other substances such as calcium, glucose, and white cells can be depleted during hemoperfusion. As with any extracorporeal therapy, desirable drug levels of other therapeutic agents may require increased dosing. Cartridges can become saturated and must be changed every 4–6 h. 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. The cartridges are not freely available in all hospitals and modern dialyzers with highly porous membranes and large surface area may give clearance rates approaching those achieved with hemoperfusion.

Peritoneal Dialysis

In peritoneal dialysis, the clearance kinetics are dependent on intrinsic characteristics of the

membrane and the mesenteric circulation, and not amenable to significant external adjustments. In cases with intoxication, peritoneal dialysis is only 10–25% as effective as hemodialysis and further more its efficacy is compromised if the patient is hypotensive. Thus the role of peritoneal dialysis in detoxification is limited to situations where other modalities are contraindicated or not possible due to lack of vascular access.

Molecular Adsorbents Recirculating System (MARS)

The Molecular Adsorbents Recirculating System (MARS) is a relatively new method of extracorporeal decontamination, which 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 [27]. MARS may be of interest in the setting of poisons that have a predilection for liver toxicity, as the system is capable not only of removing certain hepatotoxins, but also reducing hyperbilirubinemia, restoring hemodynamics, diminishing hepatic encephalopathy, and improving renal function [27]. MARS has been used to maintain patients in liver failure during the peritransplant period [28–30]. The existing data for MARS in general are encouraging, but the evidence base is limited [31].

Plasmapheresis

Plasmapheresis is the extracorporeal blood purification technique used for removal of large molecular weight substances from plasma such as pathogenic autoantibodies, immune complexes, and endotoxins. 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% [32], which under normal conditions corresponds to removal of 40–60 mL of plasma/kg over 2–3 h [33]. While evidence-based indications on the role of plasmapheresis in the management of intoxications is lacking, several publications (mostly case-reports) have reported its successful usage in the treatment of phalloid mushroom intoxication, tricyclic-antidepressant (amitriptyline), L-thyroxin, phenbromate, verapamil, diltiazem, carbamazepine poisoning, and some heavy metals such as mercury intoxications [34–42]. It is important to note that plasmapheresis is most useful for drugs with a low V_d and a high protein binding. Accordingly, it has been suggested that plasmapheresis should be considered only when plasma protein binding of a substance is greater than 80% and V_d is less than 0.2 L/kg [43].

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. 42.1). The list of toxic substances that have been subjected to extracorporeal therapies is quite long and information is available on more than 200 substances [44]. 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-acytylcysteine, flumazenil, fomepizole, and Fab have significantly changed the clinical management plans, on several occasions it is not possible to identify the small group of patients who will fail to respond to intensive supportive care alone and the decision to institute extracorporeal therapy is based on clinical judgment.

Some of the broad criteria as suggested by Winchester et al. [45] and Rosenbaum et al. [46] for initiating extracorporeal therapy are provided in Table 42.2. 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.

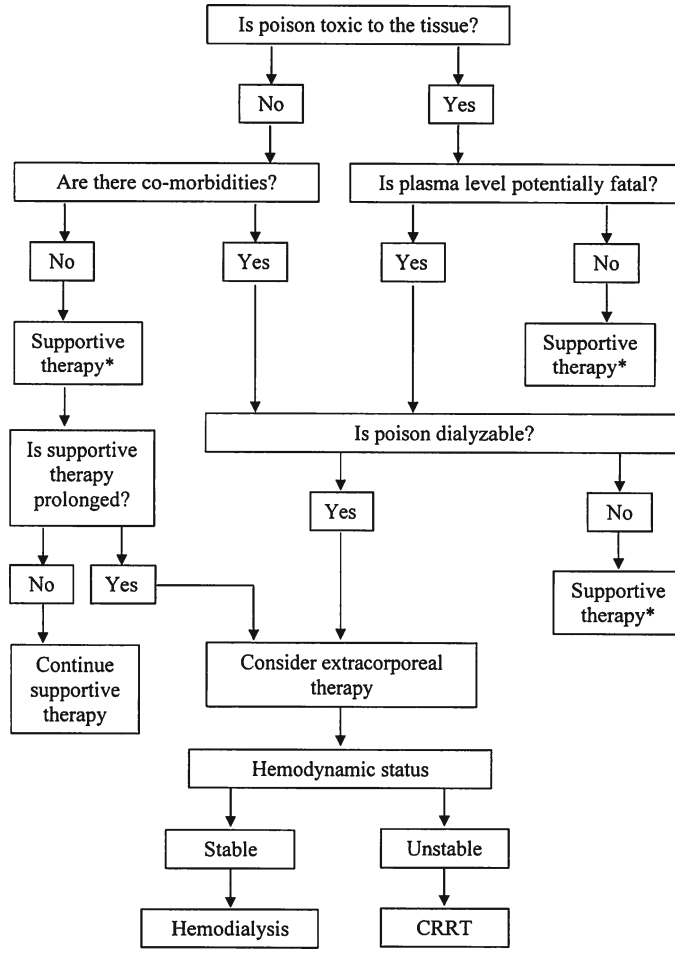

Fig. 42.1 Simplified approach to a patient with poisoning (*specific antidote to be used when available; choice of particular extracorporeal therapy is based on the type of poison and patient's hemodynamic status). *CRRT* continuous renal replacement therapies, *MARS* molecular adsorbents recirculating system

Table 42.2 Criteria for extracorporeal therapy (Modified from Refs. [31, 32])

• 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 vasocative therapy
• Poisoning by agents with delayed toxicity (e.g., paraquat)

References

1. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Giffin SL. 26th Annual Report of the American Association of Poison Control Centers (AAPCC; http://www.aapcc.org). Accessed 25 Jan 2010.
2. Krenzelok EP. New developments in the therapy of intoxications. Toxicol Lett. 2002;127:299–305.
3. Salhanick SD, Shannon MW. Acetaminophen. In: Borron SW, Burns M, Shannon MW, editors. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia: WB Saunders; 2007.
4. Harrington AM, Clifton GD. Toxicology and management of acute drug ingestion in adults. Pharmacotherapy. 1995;1(2):182–200.
5. Garrettson LK, Geller RJ. Acid and alkaline diuresis. When are they of value in the treatment of poisoning? Drug Saf. 1990;5(3):220–32.

6. Gonda A, Gault H, Churchill D, Hollomby D. Hemodialysis for methanol intoxication. Am J Med. 1978;64(5):749–58.
7. Hill JB. Salicylate intoxication. N Engl J Med. 1973; 288:1110–3.
8. Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. Arch Intern Med. 1981;141: 380–5.
9. Patzer J. Principles of bound solute dialysis. Ther Apher Dial. 2006;10:118–24.
10. 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.
11. Askenazi DJ, Goldstein SL, Chang IF, Elenberg E, Feig DI. Management of a sever carbamazepine overdose using albumin enhanced continuous venovenous hemodialysis. Pediatrics. 2004;113(2):406–9.
12. 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.
13. Routledge PA. Pharmacokinetics in children. J Antimicrob Chemother. 1994;34:19–24.
14. Jacobson D, Jansen H, Wiik-Larsen E, Bredesen JE, Halvorsen S. Studies on methanol poisoning. Acta Med Scand. 1982;212:5–10.
15. Pappas SC, Silverman M. Treatment of methanol poisoning with ethanol and hemodialysis. Can Med Assoc J. 1982;126(12):1391–4.
16. Hirsch DJ, Jindal KK, Wong P, Fraser AD. A simple method to estimate the required dialysis time for cases of alcohol poisoning. Kidney Int. 2001;60(5):2021–4.
17. Brent J. Fomepizole for the treatment of methanol poisoning. N Engl J Med. 2001;344(6):424–9.
18. Borron SW. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. Lancet. 1999; 354:831.
19. Hovda KE. Fomepizole may change indication for hemodialysis in methanol poisoning: prospective study in seven cases. Clin Nephrol. 2005;64:190–7.
20. Megarbane B. Current recommendations for treatment of severe toxic alcohol poisonings. Inten Care Med. 2005;31(2):189–95.
21. Temple A. Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med. 1981;141: 364–9.
22. Lebanc M, Raymond M, Bonnardeaux A, Isenring P, Pichette V, Geadah D, Quimet D, Ethier J, Cardinal J. Lithium poisoning treated by high-performance continuous arteriovenous and venovenous hemodiafiltration. Am J Kidney Dis. 1996;27(3):365–72.
23. van Bommel EF, Kalmeijer MD, Ponssen HH. Treatment of life-threatening lithium toxicity with high-volume continuous venovenous hemofiltration. Am J Nephrol. 2000;20(5):408–11.
24. Riegel W. Use of continuous renal replacement therapy for detoxification? Int J Artif Organs. 1996;19(2): 111–2.
25. Chang TMS. Coated charcoal hemoperfusion. Life Supprt Syst. 1984;2:99–106.
26. Kawasaki CI, Nishi R, Uekihara S, et al. How tightly can a drug be bound to a protein and still be removable by charcoal hemoperfusion in overdose cases? Clin Toxicol. 2005;43:95–9.
27. Sen S, Jalan R. The role of the molecular adsorbents recirculating system (MARS) in the management of liver failure. Perfusion. 2004;19:43–8.
28. Choi JY, Bae SH, Yoon SK, et al. Preconditioning by extracorporeal liver support (MARS) of patients with cirrhosis and severe liver failure evaluated for living donor liver transplantation – a pilot study. Liver Int. 2005;25(4):740–5.
29. Hommann M, Kasakow LB, Geoghegan J, et al. Application of MARS artificial liver support as bridging therapy before split liver retransplantation in a 15-month-old child. Pediatr Transplant. 2002;6(4): 340–3.
30. Steiner C, Mitzner S. Experiences with MARS liver support therapy in liver failure: analysis of 176 patients of the International MARS registry. Liver. 2002;22:20–5.
31. Brown Jr RS. MARS preconditioning for living donor liver transplantation: panacea or placebo? Liver Int. 2005;25(4):692–5.
32. Kale-Pradhan PB, Woo MH. A review of the effects of plasmapheresis on drug clearance. Pharmacotherapy. 1997;17(4):684–95.
33. El-Ghariani K, Unsworth DJ. Therapeutic apheresis-plasmapheresis. Clin Med. 2006;6(4):343–7.
34. Binimelis J, Bassas L, Marruecos L, et al. Massive thyroxine intoxication: evaluation of plasma extraction. Intens Care Med. 1987;13:33–8.
35. Siebenlist D. Plasma separation in verapamil poisoning. Dtsch Med Wochenschr. 1990;115:797.
36. Kuhlmann U, Schoenemann H, Muller T, Keuchel M, Lange H. Plasmapheresis in life-threatening verapamil intoxication. Artif Cells Blood SubImmobil Biotechnol. 2000;28:429–40.
37. Gutschmidt HJ. Successful plasmapheresis in severe diltiazem poisoning. Dtsch Med Wochenschr. 1995; 120:81–2.
38. Gambi D, Oggioni R, Mangani V, Librenti M, Manescalchi F, Tulli G. Acute carbamazepine poisoning treated with plasmapheresis. Description of a clinical case. Minerva Anestesiol. 1993;59:547–52.
39. Duzova A, Baskin E, Usta Y, Ozen S. Carbamazepine poisoning: treatment with plasma exchange. Hum Exp Toxicol. 2001;20:175–7.
40. Nenov VD, Marinov P, Sabeva J, Nenov DS. Current applications of plasmapheresis in clinical toxicology. Nephrol Dial Transplant. 2003;18(Suppl 5):v56–8.
41. Kolsal E, Tekin IO, Piskin E, Aydemir C, Akyuz M, Mehmet A, Cabuk H, Eldes N, Numanoglu V. Treatment of severe amitriptyline intoxication with plasmapheresis. Journal of Clin Apheresis. 2009;24: 21–4.
42. Emet M, Aslan S, Cakir ZG, Uyanik A, Uzkeser M, Hacimuftuoglu A, Emre H. Plasmapheresis is useful

in phenprobamate overdose. Amer Jour Emer Med. 2009;27:e621–2.
43. Sketris IS, Parker WA, Jones JV. Plasmapheresis: its effect on toxic agents and drugs. Plasma Ther Transfus Technol. 1984;5:305–17.
44. Winchester JF. Dialysis and hemoperfusion in poisoning. Adv Ren Replace Ther. 2002;9(1):26–30.
45. Winchester JF, Gelfand MC, Knepshield JH, et al. Dialysis and hemoperfusion of poisons and drugs – update. Trans Am Soc Artif Intern Organs. 1977;23:762–842.
46. Rosenbaum JL, Kramer MS, Raja RM, et al. Current status of hemoperfusion in toxicology. Clin Toxicol. 1980;17:493–500.

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