Management of Peritoneal Dialysis in Children

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Alicia M. Neu, Bradley A. Warady, and Franz Schaefer

Introduction

Peritoneal dialysis (PD) is the most frequently prescribed maintenance dialysis therapy for children with kidney failure worldwide, particularly in infants and very young children [1–3]. Technical advances and increasing efforts to minimize risk for infection and cardiovascular disease, the leading causes of morbidity and mortality, have contributed to improvements in technique and patient survival among children on maintenance PD [4–7]. However, mortality for children on dialysis remains unacceptably high and notably higher than for children who receive a kidney transplant [2, 3, 7]. Ongoing efforts to further improve outcomes in children on maintenance PD must include prescribing, monitoring and adjusting the dialysis treatment to meet the unique needs of the child [8, 9]. This chapter focuses on the principles involved in developing and monitoring the PD prescription, establishing a functioning access to perform the dialysis procedure and the infectious and non-infectious complications seen in children on maintenance PD. Kidney failure is an incredibly complex condition and therefore comprehensive care of the child on maintenance peritoneal dialysis must not only include tailoring the PD prescription to provide optimal solute and fluid removal, but also maximizing growth and neurocognitive development, managing anemia, minimizing bone and mineral metabolism disorder and cardiovascular disease, and addressing the psychosocial well-being of the child and their family [8, 9]. Each of these important topics is therefore covered in a separate chapter of this book.

The Peritoneal Dialysis Prescription

The directly modifiable components of the PD prescription include the composition and volume of the dialysis fluid and the schedule by which that fluid is instilled and removed from the peritoneal cavity. Although empiric recommendations for prescribing maintenance PD in children are often used when initiating dialysis, optimal care requires that the PD prescription be modified to meet the unique needs of the individual child or adolescent with kidney failure [8–10]. This requires a basic knowledge of the physiology of dialysis which, in turn, relies on an under-

A. M. Neu (✉)
Division of Pediatric Nephrology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: aneu1@jhmi.edu; aneu@jhmi.edu

B. A. Warady
Division of Pediatric Nephrology, Children's Mercy Kansas City, Kansas City, MO, USA
e-mail: bwarady@cmh.edu

F. Schaefer
Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany
e-mail: franz.schaefer@med.uni-heidelberg.de

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standing of the peritoneal membrane as the primary barrier to solute and fluid transport. This chapter therefore begins with a brief overview of the structure of the peritoneal membrane, followed by a discussion of the physiology of dialysis, that is, the driving forces for the exchange of solute and fluid across the peritoneal membrane. The application of these principles to guide selection of the modifiable components of the PD prescription is then presented.

The Peritoneal Membrane

The peritoneal membrane is a thin structure lining the inner surface of the abdominal wall and the majority of visceral organs. It is lined by the mesothelium, a continuous layer of flattened epithelial cells covered with numerous microvilli, and includes a dense network of capillaries distributed within a thin interstitium [11–13]. The pathway for the solute and water exchange between the plasma in the peritoneal capillaries and the dialysate in the peritoneal cavity of the child on PD includes the continuous capillary endothelium, the peritoneal interstitial space, and the mesothelium [14]. Of these, the capillary endothelium appears to be the primary determinant of resistance to transport, and microvascular density is therefore a major determinant of transport characteristics [11, 15–18]. The permeability of the endothelium lining the peritoneal capillaries has been functionally described by the three-pore model proposed by Rippe and colleagues [19]. In this model, the major route for small-solute and water movement is represented by the spaces between the endothelial cells, the so-called small pores, which have a radius of 40–50 Å, slightly larger than albumin (36 Å) [12, 19]. Ultrasmall pores, with a radius of approximately 2.5 Å, are the most abundant type of pores and are involved in sodium-free water transport [12, 19]. Several lines of evidence have demonstrated that the water channel aquaporin-1 corresponds to the ultrasmall pore [20, 21]. The third group of pores is the transendothelial 'large pore' pathways, which have a radius of approximately 250 Å, and which account for only 0.01% of the total population of capillary pores and through which macromolecules are transported [19].

The Physiology of Dialysis

The driving forces for exchange of solute across the peritoneal membrane include diffusion and convective mass transfer through the small pores in the capillary endothelium. The rate of solute movement by diffusion is determined by the concentration gradient of the solute between the dialysate in the peritoneal cavity and the plasma in peritoneal capillaries, the effective surface area of the peritoneal membrane in contact with the dialysate, the so called "wetted membrane," and the permeability of the peritoneal membrane to that solute, which, in turn, is influenced by the molecular weight of the solute [13, 22]. Convective mass transfer occurs as water moves through small pores from capillaries to dialysate, "dragging along" dissolved solutes. The amount of solute removed by convective mass transfer is, therefore, determined by the amount of water removed and by the membrane permeability, or sieving coefficient for that solute. While small molecular weight solutes, like urea, move by both diffusion and convective mass transfer, the movement of larger molecular weight compounds, including the uremic "middle molecules," is driven primarily by convective mass transfer [23].

The bulk movement of water, or ultrafiltration, is driven by Starling forces, i.e. osmotic and hydrostatic pressure [12, 23]. Figure 65.1 depicts the Starling forces (P, hydrostatic pressure; Π, oncotic or osmotic pressure) that operate across each of the pore types in the three-pore model [12]. Movement of water through the ultrasmall pores is driven by the osmotic gradient between the plasma in peritoneal membrane capillaries and the interstitium and, ultimately, the dialysis fluid in the peritoneal cavity. The osmotic pressure in the plasma is generated primarily by albumin, whereas osmotic pressure in the dialysate is typically generated by crystalloid, i.e. glucose, or the glucose polymer icodextrin. This "water only" movement through the ultrasmall pores explains the transient decrease in dialysate sodium concentration during the early phase of a dialysis dwell, which is referred to as sodium

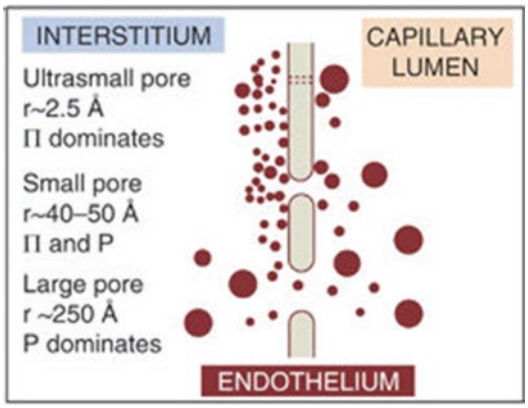

Fig. 65.1 The Starling forces (P, hydrostatic pressure; Π, oncotic pressure) operating across each type of pore in the three-pore model of peritoneal membrane capillary permeability. *Å* angström, *r* functional radius. (From [12], with permission)

sieving. Movement of water through small pores is influenced by both hydrostatic and osmotic forces (Fig. 65.1) [12]. In simplest terms, hydrostatic forces in plasma and osmotic forces in the dialysate promote ultrafiltration, while osmotic forces in plasma and hydrostatic pressures in the peritoneal cavity oppose it [24]. Several factors contribute to the generation of these forces; however, the critical component for ultrafiltration during PD is the difference in osmotic pressure between the dialysate and the plasma, which, in turn, is largely dependent on the osmotic agent present in the dialysate [24]. The amount of water removed from the person on PD, or net ultrafiltration, is also influenced by water movement from the peritoneal cavity back to the capillaries in the late stages of a dwell, when the osmotic gradient generated by dialysate glucose may have dissipated, and by uptake of water from the peritoneal cavity into tissue and lymphatics [25, 26]. The contribution of water movement through the relatively rare large pores to net ultrafiltration is felt to be minimal [12].

These principles of solute and fluid movement during PD should be used to guide selection of the various components of the dialysis prescription, including dialysate composition, fill volume and the schedule by which dialysis is instilled and removed from the peritoneal cavity (PD modality/dwell time), to optimize solute and fluid removal.

Determination of Fill Volume

As discussed above, the movement of solutes and water during PD is intrinsically dependent on the amount of peritoneal membrane surface area available for exchange, or the "wetted membrane" [13]. Although the peritoneal membrane has an estimated surface area of 1 m^2 in adults, computed tomography studies in people on maintenance PD have demonstrated that only 30–60% of this anatomic area is in contact with dialysate [27]. The peritoneal membrane contact area can be influenced by position, increasing in the supine position, and by increasing the volume of the infused dialysate, or fill volume [28]. In children, where body size varies considerably, the concept of scaling the fill volume to body size is intuitive. Fill volume should be based on body surface area (BSA), rather than weight, as the relationship between peritoneal membrane surface area and BSA is constant and age-independent [29]. Body surface area can be calculated from anthropometric data, i.e. height and weight. The most commonly used equation is that of Gehan and George [30]:

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

As stated above, increasing the fill volume will promote solute and fluid removal by maximizing peritoneal membrane contact area [31]. In addition, increasing fill volume will facilitate movement by diffusion. The impact of fill volume on diffusion rests on the principle of geometry of diffusion, that is, the larger the dialysate volume, the longer the transperitoneal concentration gradient will persist to drive diffusion [32]. However, increasing fill volume also increases intraperitoneal pressure (IPP) which may lead to patient discomfort and other complications including hernia formation, hydrothorax and gastroesophageal reflux (See Non-Infectious Complications) [10, 26, 28, 33]. In addition, elevated IPP may increase lymphatic uptake of fluid, thereby reducing net ultrafiltration [10, 33]. Studies in children on PD revealed that the peritoneal membrane vascular surface area available for exchange increased by a mean of 21% as fill

volumes were increased from 800 to 1400 ml/m^2, with no further improvement as fill volumes increased to 2000 ml/m^2 [28, 34]. These data support current recommendations that, if required for solute clearance and fluid removal, the fill volume should be gradually increased to an upper limit of 1200–1400 ml/m^2 in children over age 2 years [10]. Infants may not tolerate such large fill volumes, and an upper limit volume of 800 ml/m^2 is currently recommended in this age group [10]. The maximal volume for individual children on PD should also be influenced by the child's comfort level and when indicated, an objective measure of IPP [35]. Measurement of IPP can be done at the bedside, using a manometer attached to the PD catheter. The mean IPP is calculated from the pressure measured during inspiration and expiration. Normal ranges of mean IPP for children over age 2 years have been reported to be 7–14 cmH_2O, with an upper tolerated limit of 18 cmH_2O [35, 36].

Choice of PD Fluid

Conventional PD Solutions

PD solutions typically contain an osmotic agent, a buffer and sodium, chloride, calcium and magnesium in varying concentrations, in an effort to provide not only removal of fluid and waste products, but also electrolyte homeostasis, and acid-base and calcium balance. The composition of the most widely used commercially available dialysis solutions attempt to mimic normal plasma, while allowing mass production and storage stability [37]. These constraints led to the selection of glucose in supraphysiologic concentrations as the osmotic agent and lactate alone as the buffer, with a resultant low pH of the dialysis fluid. This allows heat sterilization without caramelization of the glucose, and minimizes precipitation of calcium and magnesium from the solution, which may occur when bicarbonate is used as the buffer [37]. From the description of the Starling forces involved in water movement during PD, it follows that increasing the concentration of glucose in the dialysis fluid increases the osmotic gradient driving ultrafiltration. From a functional standpoint, because glucose is a diffusible solute, it is absorbed from the dialysate to plasma via the small pores, resulting in a time-dependent loss of the crystalloid osmotic gradient. Thus, glucose is unable to provide sustained ultrafiltration during extended exchange dwell times. In addition, absorption of glucose can contribute to anorexia and lead to elevated serum glucose and hyperinsulinemia, even in non-diabetic patients [38]. This increased carbohydrate load can predispose to abnormalities of lipid metabolism and insulin resistance (See Non-Infectious Complications) [37, 39]. In addition to the negative effects associated with glucose absorption, the heat sterilization process used with conventional PD solutions produces high levels of glucose-degradation products (GDP), which are directly toxic to the peritoneal mesothelium and are systemically absorbed [40]. GDPs also enhance production of advanced glycation end products, which along with high concentration of glucose have been implicated in the development of structural changes in the peritoneal membrane including vascular proliferation and progressive fibrosis, both of which contribute to peritoneal membrane failure [31, 37, 41, 42].

Alternate Osmotic Agents

In light of these findings, minimizing the exposure of the peritoneal membrane to hypertonic glucose is a therapeutic aim [43]. Currently, there are two commercially available PD solutions that contain osmotic agents other than glucose; one contains icodextrin and the other amino acids. Icodextrin is a glucose polymer with a molecular weight of approximately 16,000 Daltons, which exerts its osmotic effect through the small pores in the capillary endothelium. Thus, there is little to no salt-free water movement through the ultrasmall pores (sodium sieving) and sodium removal is typically higher than with glucose-based solutions [44]. Because icodextrin does not diffuse through the peritoneal membrane, the osmotic gradient, and therefore ultrafiltration, is typically sustained, and icodextrin solutions are therefore used during dialysis exchanges with a prolonged dwell time [45, 46]. The net ultrafiltration seen in individual people on PD can be variable, probably owing to variability in the peritoneal residual volume, i.e. the amount of

non-icodextrin containing fluid remaining in the peritoneal cavity from the previous exchange, which modifies the concentration of icodextrin and, therefore, the osmotic pressure difference between the peritoneal cavity and plasma [47, 48]. Another factor influencing net ultrafiltration is lymphatic absorption of icodextrin, which has been reported to be as much as 45% within 12–14 h in children on PD. [49] Reabsorption may be particularly high in infants on PD, limiting the ultrafiltration achieved with icodextrin in this age group [50]. Finally, a minimum daytime fill volume of 550 ml/m^2 has been suggested to optimize ultrafiltration with icodextrin in children [51]. Icodextrin is metabolized to maltose and a number of oligosaccharides which reach systemic steady state levels within 2 weeks of initiating treatment, and concerns about higher levels of these non-degradable compounds limits the use of icodextrin containing solutions to a single daily exchange [43, 45]. Hypersensitivity reactions have also been reported with icodextrin-containing solutions [45].

Amino acids, in a 1.1% solution, are also used as an osmotic agent in a commercially available, non-glucose PD solution. This solution is as efficient an osmotic agent as a 1.36% glucose-based solution. Amino acid-based solutions initially appeared particularly appealing for children on PD because of the potential nutritional benefit; however, studies revealed conflicting impact on nutrition, as well as increases in blood urea nitrogen and metabolic acidosis [52]. Given these findings, it is not recommended that amino acid solutions be used as a nutritional source in children on PD. [43] The benefits and potential drawbacks of each of the three solutions described here are summarized in Table 65.1 [37].

Table 65.1 Characteristics of currently available single-chamber peritoneal dialysis solutions, based on osmotic agent. Modified from [37], with permission

Buffer	Potential drawbacks	Potential benefits
Glucose	Low pH High GDP Poor peritoneal membrane biocompatibility Infusion pain Local and systemic glucose exposure	Ease of manufacture Low cost
Icodextrin	Hypersensitivity Low pH Systemic accumulation of oligosaccharides Lactate containing	Sustained ultrafiltration Preservation of RKF Hypertonic glucose replacement Reduced hyperglycemia Desirable effects on metabolic profile and body composition
Amino acid	Low pH Exacerbation of uremic symptoms and acidosis	No GDP Avoid systemic and peritoneal glucose exposure Peritoneal membrane protection Enhanced nutrition in adults

GDP glucose degradation product, *RKF* residual kidney function

Biocompatible Solutions

The supraphysiologic concentrations of glucose and the presence of GDPs are not the only contributors to the bio-incompatibility of standard dialysis solutions. Low pH is associated with infusion pain and directly induces neoangiogenesis and mesothelial cell damage [53, 54]. Even at a neutral pH, lactate-based peritoneal dialysis solutions have been associated with impaired mesothelial cell viability and function [55, 56]. The effort to provide truly biocompatible solutions therefore includes not only the use of alternative osmotic agents, but also a solution composition that results in a more neutral pH and reduced exposure to lactate. The development of multi-chamber dialysis solutions has allowed these issues to be addressed at the commercial level. These bags isolate the buffer during storage, thus allowing glucose to be stored at low pH, ensuring stability, and avoiding the creation of GDP during heat sterilization. This also avoids bicarbonate-induced precipitation of calcium and magnesium in the solution [37]. A summary of the benefits and potential drawbacks of the currently available multi-chamber PD solutions is shown in Table 65.2 [37]. All of these solutions provide lower GDP levels than standard glucose-containing solutions. Although numerous in vitro studies have supported the biocompatibility of

Table 65.2 Characteristics of currently available multi-chamber peritoneal dialysis solutions, based on buffer. Modified from [37], with permission

Buffer	Potential drawbacks	Potential benefits
Lactate alone	More physiologic, but not neutral, pH Local and systemic glucose exposure	Lower GDP levels More physiological pH Improved peritoneal membrane biocompatibility Preserved membrane defense
Lactate/ bicarbonate	Local and systemic glucose exposure Does not eliminate peritoneal lactate exposure	Lower GDP levels More physiologic pH Improved peritoneal membrane biocompatibility Preserved membrane defense Reduced infusion pain
Bicarbonate alone	Local and systemic glucose exposure	Lower GDP levels More physiologic pH Improved peritoneal membrane biocompatibility Preserved membrane defense Improved correction of acidosis

GDP glucose degradation product

these solutions, a study of peritoneal biopsies in children at the time of PD catheter insertion and then after receiving maintenance PD with neutral pH, low GDP fluids revealed a doubling of peritoneal microvascularization and exchange area within a few months of initiating PD, calling into question the ability of these fluids to preserve membrane function and structure [41]. A subsequent analysis found that the duration of dialysis and dialytic glucose exposure were the primary determinants of the alterations to the peritoneal membrane [57]. Although biocompatible fluids may, in turn, not eliminate the structural changes to the peritoneal membrane, there may be some benefit of using bicarbonate, rather than lactate, as the dialysis solution buffer. A multicenter randomized controlled trial in 37 children on PD compared two multi-chamber, neutral pH, low GDP PD solutions that differed only with regard to the buffer, lactate versus bicarbonate. This study found equivalent correction of metabolic acidosis with the two solutions, but bicarbonate-based solutions were associated with better long-term preservation of peritoneal membrane function as measured by ultrafiltration capacity [58]. In addition, data from the International Pediatric Peritoneal Dialysis Network (IPPN) revealed that young infants exposed to neutral-pH, low-GDP PD solutions exhibited significant catch-up growth, whereas patients using conventional PD fluids showed no improvement in height standard deviation scores over the same time period. These findings led investigators to speculate that reduction of the inflammatory processes associated with conventional solutions might improve growth in children undergoing maintenance PD [59]. Finally, a Cochrane Review revealed that use of a neutral pH, low GDP PD solution is associated with improved preservation of residual kidney function and urine volume in adults on PD [60]. Given these findings, use of the more biocompatible solutions is encouraged, while recognizing that cost and availability of these solutions may limit widespread use [43]. In fact, data from IPPN reveals significant regional variability in the prescription of neutral pH PD solutions among children on PD enrolled in that registry [61]. When excluding children from the United States, where neutral pH PD solutions are not approved, 8% of children from low-income countries are prescribed these solutions, compared to 68% of children in high-income countries [8, 61].

Determination of PD Modality/ Dwell Time

CAPD vs. APD

There are two major PD modalities utilized for maintenance PD, continuous ambulatory peritoneal dialysis (CAPD), in which 3 or 4 exchanges

are performed manually during the day with an exchange with a long dwell time conducted overnight, and automated peritoneal dialysis (APD), in which multiple exchanges are provided, typically overnight, by a cycler. The most commonly prescribed APD schedules are continuous cycling PD (CCPD) and nightly or nocturnal intermittent PD (NIPD). Both provide multiple exchanges overnight, but in CCPD, 50–100% of the nightly fill volume is instilled at the end of the APD session for a daytime exchange. For NIPD, no daytime exchange is used, and the person on PD is said to have a dry day with no dialysate being present in the peritoneal cavity. Other modifications can include the addition of a mid-day manual exchange, sometimes referred to as semi-automated PD, and tidal PD, where only a portion of the initially instilled fill volume is drained and replaced with each exchange overnight, with the full volume drained only at the completion of the APD session. Tidal therapy has been found to be particularly beneficial in patients who experience "drain pain."

The selection of PD modality should be individualized for each child based on a number of factors, including age, residual kidney function, nutritional status, tolerance/comfort and the preference of the child and their caregivers [8, 9]. The physiology of PD should be considered so that the modality selected meets the child's solute and fluid removal requirements. Because APD allows more exchanges to be conducted during a 24-h period than CAPD, the peritoneal membrane is exposed to a larger total volume of dialysate in this time period which may enhance clearance of small solutes. In addition, during APD the majority of exchanges occur at night, when the child is in the supine position, which optimizes peritoneal membrane contact area and minimizes increases in IPP [28]. Conversely, CAPD allows increased clearance of middle molecules, which is dependent on the duration of contact between dialysate and the peritoneal membrane [62]. The requirement for fluid removal will also impact modality selection. In CAPD, daytime dwell times are typically 4–6 h long, as more frequent exchanges may be too cumbersome for the child/caregivers to perform. These long dwell times may result in reduced ultrafiltration, due to the loss of glucose-generated osmotic gradient, and necessitate higher glucose-containing solutions to maintain that gradient. Recall that in the early part of an exchange, sodium-free water movement occurs via the ultrasmall pores. Thus, frequent exchanges with short dwell times characteristic of APD may result in a relatively higher contribution of free water transport to total fluid removal, that is, more water than sodium is removed. Conversely, an exchange with a longer dwell time, as occurs with CAPD, allows more time for convective losses of sodium, but also allows back-diffusion and back-filtration, and may result in net fluid and sodium retention [26].

From a practical standpoint, because a cycler is not required for CAPD, the training and equipment required are less than for APD. However, because APD, is performed at night, this therapy minimizes the restriction on daytime activities, such as school attendance for children and work for adult caregivers, which is a significant benefit associated with the use of this modality [63].

Empiric Dialysis Prescriptions

A typical empiric APD prescription includes 5–10 exchanges over 9–12 h overnight, with an identical fill volume and duration for each exchange. A daytime exchange is usually prescribed, particularly in children who are anuric. More recently the concept of adapted PD, with initial cycles using a relatively small fill volume and short dwell times to maximize ultrafiltration, followed by a larger fill volume with longer dwell times to promote solute clearance, has been suggested as a means of improving dialysis efficiency, and in particular sodium and fluid removal [26, 64]. Not all commercially available PD cyclers are able to provide adapted PD and further prospective crossover studies in children on PD are required for validation. As stated previously, the typical CAPD prescription includes 3–4 exchanges during the day and a long overnight exchange.

Measures of Peritoneal Membrane Function

Because peritoneal membrane transport characteristics may vary considerably between people on PD, and even in a single person over time, it is important to evaluate these characteristics to optimize the PD prescription. Pediatric guidelines recommend evaluating peritoneal membrane function within the first month of initiating PD and then

after any event that may impact peritoneal membrane transport capacity, such as peritonitis [65]. The most commonly used test to characterize peritoneal membrane transport capacity is the peritoneal equilibration test or PET, developed by Twardowski [66]. The PET measures the rate at which solutes, specifically urea, creatinine and glucose, equilibrate between the blood and the dialysate. In the PET, dialysate is infused into the peritoneal cavity using a standardized fill volume and glucose concentration. Because the fluid used in the exchange immediately preceding the PET may influence results, the solution used for the PET should also be used for the dialysis session the night prior [67, 68]. Once the dialysis solution is instilled, the concentrations of creatinine and urea in the dialysate and in plasma are measured after 2 and 4 h of dwell time to derive dialysate to plasma ratios (D/P). The concentration of glucose in the dialysate at 2 and 4 h after instillation is compared to the concentration of glucose in the dialysate at the time of instillation (D/D_0). The D/P and D/D_0 ratios are then compared to standard curves to characterize the child as having high, high average, low average or low peritoneal membrane solute transport capacity [66]. People on PD with low or low average transport capacity may benefit from exchanges with longer dwell times, which will allow maximal diffusion of solutes. Conversely, rapid diffusion of glucose in patients with high peritoneal membrane transport capacity necessitates the use of exchanges with short dwell times to achieve ultrafiltration. The crossing point of the urea and glucose equilibration curves obtained from the standardized PET, referred to as the Accelerated Peritoneal Examination (APEX) time, has been proposed as a means to identify the dwell time to be used to optimize ultrafiltration [69]. The characteristics seen with the various peritoneal membrane transport types, and the percent of children enrolled in the IPPN with each are shown in Fig. 65.2.

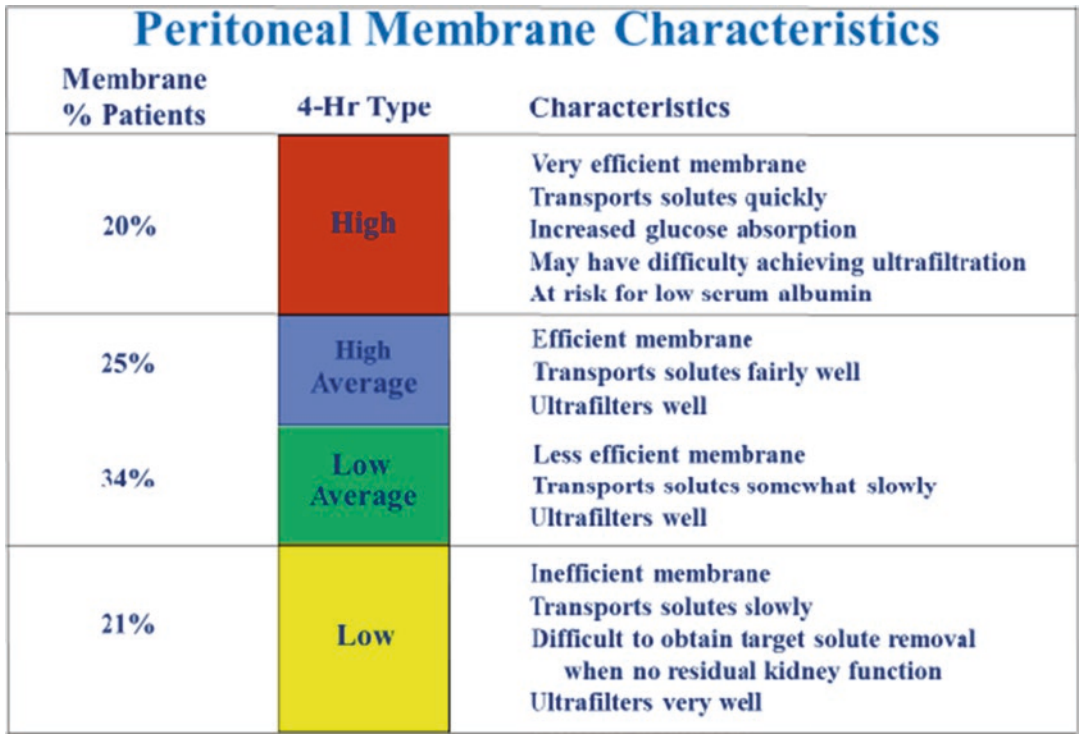

Fig. 65.2 Characteristics of the various peritoneal membrane transport types (high, high average, low average and low) and the percentage of children with each of the types enrolled in the registry of the International Pediatric Peritoneal Dialysis Network (personal communication, B Warady)

The PET has been validated in children on PD, using 2.5% dextrose, or 2.3% glucose PD solution and a fill volume of 1100 ml/m^2 [70, 71]. In infants, the fill volume used for the PET is usually the clinically prescribed fill volume [23]. Figures 65.3 and 65.4 show the standardized D/P creatinine and D/D$_0$ glucose curves, respectively, from which a child's peritoneal membrane transport capacity can be characterized [70]. In a study of 20 children on maintenance PD, nearly identical characterization of peritoneal membrane function was found with the D/P creatinine or D/D$_0$ glucose at 2 and 4 h, and it has therefore been suggested that a 2 h or short-PET may be reasonable in children on PD [72]. The sequential PET, in which the standard PET is followed by a "mini-PET," has been proposed as a method for providing more complete characterization of both solute and fluid transport [73]. The mini-PET is a modification of the

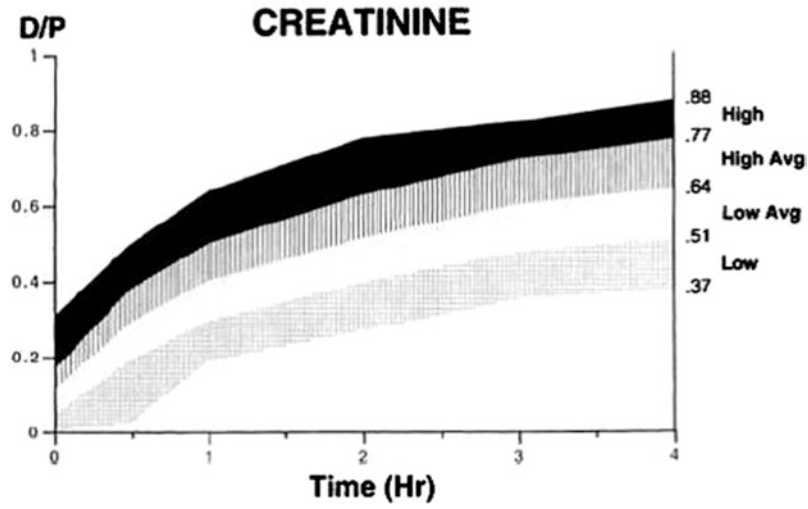

Fig. 65.3 Peritoneal equilibration test results for creatinine. Shaded areas represent high, high average, and low transport rates. The white band represents the low average transport rate. The four categories are bordered by the maximal, mean + 1 SD, mean, mean − 1 SD, and minimal values for the population. D/P, dialysate to plasma ratio. (From [70], with permission)

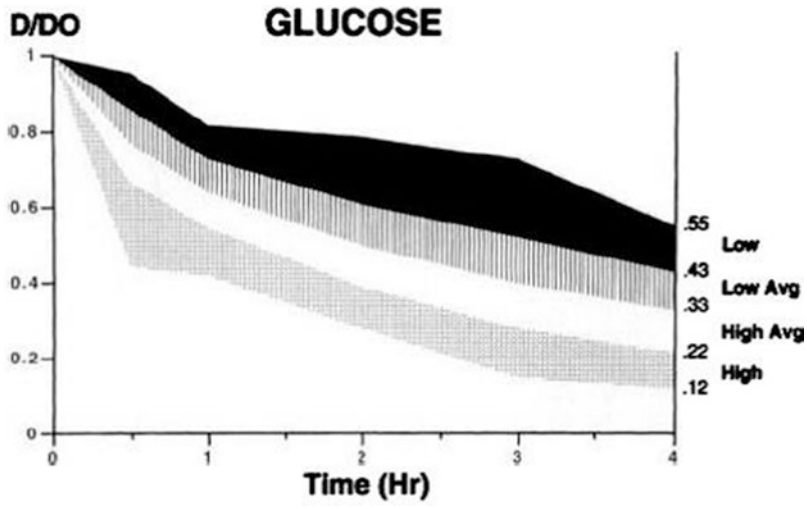

Fig. 65.4 Peritoneal equilibration test results for glucose. Shaded areas represent high, low average, and low transport rates. The white band represents the high average transport rate. The four categories are bordered by the maximal, mean + 1 SD, mean, mean − 1 SD, and minimal values for the population. D/D0, dialysate glucose to initial dialysate glucose concentration ratio. (From [70], with permission)

standard PET which uses a 3.86% glucose solution instilled for 1 h. Dialysate sodium concentration is measured just prior to infusion and after 60 min, providing more accurate information about the ultrafiltration capacity and assessment of sodium sieving [74].

Data obtained from the PET can also be used to calculate the mass area transfer coefficient (MTAC) [70, 75, 76]. The MTAC has been variably defined as the area available for solute transport divided by the sum of resistances to peritoneal diffusion. The MTAC represents the maximal clearance of a solute theoretically achievable at a constantly maximal gradient for diffusion, i.e. when the dialysate concentration of the solute remains at zero. Unlike the D/P ratio, MTAC is essentially independent of dialysate glucose or fill volume. Calculation of MTAC requires rigorously performed PD exchanges and complex mathematical equations. However, with the assistance of computer programs, data from a carefully performed PET can be used to derive MTAC. These programs, which have been validated in children on PD, can also be used to predict solute and fluid removal for individualized dialysis prescriptions [77, 78]. It must be recognized that the results predicted by these programs assume optimized conditions and therefore the actual amount of dialysis delivered by any prescription needs to be measured (See Goal-directed Approach to Prescribing PD).

Goal-Directed Approach to Prescribing PD

Solute Clearance

Historically, modification of the empiric PD prescription has been driven by the concept of achieving "dialysis adequacy," i.e. the dose of dialysis delivered is measured and adjustments are made to exceed a minimum dose below which patient outcomes are unacceptable. For decades, adequacy targets focused on the delivered dialysis dose in terms of small solute clearance. Peritoneal dialysis adequacy guidelines recommended the use of urea removal, scaled for the urea volume of distribution, Kt/V_{urea}, to monitor solute clearance and guidelines published in 2006 in the United States and internationally suggested a minimum target of a total weekly (residual kidney and dialysate) Kt/V_{urea} of 1.8 or 1.7 for adults on PD, respectively [65, 79]. These targets were largely based on studies in adults on PD which suggested improved survival with increasing small solute clearance [80, 81]. However, a reanalysis of data from a large prospective study in Canada and the United States (CANUSA) found the association between small solute clearance and mortality to be completely explained by the clearance contributed by residual kidney function, with no association between increasing dialysate small solute clearance and survival [82]. Similarly, two large prospective randomized trials did not demonstrate an association between increasing small solute clearance and mortality in adults on PD [83, 84]. A retrospective analysis of administrative data in the United States did reveal an increased risk for mortality with a $Kt/V_{urea} < 1.7$ in anuric adults on PD [85].

Although a prospective study of 171 children on PD demonstrated a positive correlation between dialytic creatinine clearance and change in height standard deviation score, and cross-sectional and retrospective studies have suggested improved growth and cardiac function with increasing small solute clearance, there are no large-scale, prospective, randomized studies of the influence of small solute clearance on outcomes in children on PD to more definitely define adequacy targets [86–88]. In light of this, the 2006 guidelines recommended that the total weekly Kt/V_{urea} in children should meet or exceed the adult standard [65].

Measurement of total weekly Kt/V_{urea} should incorporate both dialysate and residual kidney clearance [65]. This is accomplished by collecting the volume of urine from a 24-h period, as well as the peritoneal dialysis effluent from the PD exchanges during those 24 h. The volume is recorded and urea measured on each sample. Blood urea nitrogen concentration is also measured.

The total dialysate Kt/V_{urea} is then calculated by:

(24 h Dialysate/Plasma urea×24 h drained volume × 7) / Volume of distribution of urea

The residual kidney urea clearance is calculated by:

(Volume of 24 h urine in mL×urine urea nitrogen concentration)/(1440 min/day × blood urea nitrogen concentration)

From this, the residual kidney Kt/V_{urea} can be calculated as:

(Kidney urea clearance (ml/min) × 1440 min/day × 7 days)/1000 mL × Volume of distribution of urea.

The total weekly Kt/V_{urea} is the sum of the weekly dialysis and residual kidney Kt/V_{urea} [65].

The volume of distribution of urea, V, is assumed to be equal to total body water. Therefore, accurate estimates of total body water are important to accurately determine Kt/V_{urea}. The gold standard method for determining total body water, the heavy water dilution technique, is rarely applied in the clinical setting. Equations using anthropometric information (height and weight) are more commonly used to estimate total body water, and sex-specific nomograms developed in children on PD are available [89].

Guidelines for children on PD recommend that total weekly Kt/V_{urea} be measured within the first month after initiating dialysis and then at least twice yearly, and following any change in the child's clinical status that could influence solute clearance or ultrafiltration capacity [10, 90]. Given these recommendations, measurement of small solute clearance is standardly performed, and achievement of the minimal target for Kt/V_{urea} in adults and children on PD is used as a measure of the quality of care by dialysis organizations around the globe and regulatory and payment agencies in the United States. However, the data linking small solute clearance to outcomes in people on PD remains relatively weak, with no prospective intervention trials since publication of the 2006 KDOQI guidelines, and prospective cohort and retrospective studies in adults on PD only confirming that patient outcomes are more closely linked with residual kidney function than clearance of solute by dialysis [91–98]. In addition, it has been increasingly acknowledged that optimal care requires that all aspects of management, including the PD prescription, be driven by the unique needs of the person with kidney failure, and not solely by small solute clearance [8, 91]. In 2018, a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference focused on dialysis proposed a change in terminology from "adequate" to "goal-directed" dialysis, where shared decision-making between the person on PD and the care team is utilized to establish realistic care goals that allow the person on PD to meet their life goals and allow the care team to provide individualized, high quality dialysis care [99]. In this framework, solute removal targets are interpreted and implemented in the context of the overall goals and clinical status of the person on PD [99]. In alignment with this statement, the International Society for Peritoneal Dialysis (ISPD) published new practice points for prescribing high-quality, goal-directed PD in 2020, including specific practice points for children on PD [8, 9, 91]. These documents suggest that modifications to the PD prescription should be based on regular assessment of clinical well-being, volume status (see below) and other laboratory parameters, in addition to Kt/V_{urea}, with a minimum target total weekly Kt/V_{urea} of 1.7 [9]. The guidance document specifically states that children on PD with $Kt/V_{urea} < 1.7$ should not have their PD prescription modified for the sole purpose of achieving the target, if close and repeated assessment of clinical and laboratory parameters suggest that the child is otherwise doing well [9].

The 2020 ISPD guidance document for children on PD also suggests that the PD prescription be adjusted with the goal of achieving a normal serum phosphate level [9]. Because phosphate clearance is related to contact time between dialysate and the peritoneal membrane, optimizing the long daytime exchange is suggested to enhance phosphate removal [100]. It is recognized, however, that phosphate control cannot be achieved with dialytic clearance alone and dietary restriction and phosphate binders are required in most children on peritoneal dialysis [9].

Fluid Removal

Cardiovascular disease, as manifested by hypertension and left ventricular hypertrophy, is unfortunately quite common in children on dialysis, and fluid overload is a major contributor to both [4, 5, 61, 87, 101–104]. PD guidelines have therefore consistently emphasized the importance of adjusting the dialysis prescription to provide adequate salt and water removal [9, 79, 105].

Routine assessments of fluid status should be included in the care of children on PD. Casual blood pressure should be monitored, both in the clinic and at home, and ambulatory blood pressure monitoring may be performed to more accurately assess blood pressure and detect masked hypertension [106]. Central to the evaluation of fluid status is assessing the "dry" body weight of the child on PD, which should be performed routinely. However, determination of fluid overload may be inaccurate when based on clinical assessment alone and is further complicated by the expected weight gain in the growing child. Bioimpedance, if available, may be used as a component of the assessment of fluid status, and a recent study demonstrated that multifrequency whole-body bioimpedance spectroscopy successfully quantified total body water and acute changes of extracellular and intracellular water in children with chronic kidney failure, including those on dialysis [9, 107–109]. Data from the IPPN found that anemia tended to be associated with characteristics of the patient with fluid overload, including low urine output, high ultrafiltration requirements, high transport status on PET, hypertension, and left ventricular hypertrophy [101]. In addition, serum albumin and hemoglobin levels were closely associated, suggesting that fluid overload could result in dilution of both markers [101]. These findings led the authors to speculate that ESA-resistant anemia and hypoalbuminemia may be indicators of "occult" fluid overload in children on PD.

Adjustment to the dialysis prescription should, in turn, be made to achieve "dry weight" and blood pressure control. Efforts to optimize ultrafiltration while avoiding exposure to high glucose containing solutions include the use of icodextrin-containing dialysate for an extended daytime exchange, modifying dwell time using the APEX time, and potentially the use of adapted PD, as discussed previously [9, 26, 69, 110].

The amount of sodium removal required will depend on salt intake. Infants have very low sodium intake from formula or breast milk, and may have significant urinary losses of sodium associated with underlying congenital anomalies of the kidney and urinary tract. As a result, additional sodium losses from dialysis may result in hyponatremia, hypovolemia and hypotension. Therefore, infants on PD often require sodium supplementation [111]. On the other hand, older children and adolescents on PD are typically salt overloaded. In these children, the sodium gap, defined as the difference between the calculated theoretical sodium removal (plasma sodium concentration multiplied by ultrafiltration volume) and the amount actually removed (dialysate sodium concentration multiplied by ultrafiltration volume), is positive, reflecting inadequate sodium removal [112]. Most commercially available PD solutions have a sodium concentration of 132–134 mmol/L, just slightly lower than the concentration in normal serum. Studies of PD solutions containing 115–126 mmol/L sodium in adults on PD have shown increased sodium removal and a lower sodium gap, with associated improvements in blood pressure and fluid status [112–114]. However, very low sodium solutions require slightly higher glucose concentrations to maintain osmolarity and therefore may increase overall glucose exposure [112]. There are currently no studies of the impact of lower sodium-containing dialysis solutions on sodium and fluid balance in children or adolescents on PD.

Peritoneal Dialysis Access

Catheter Configuration

Successful PD requires a catheter that provides reliable, rapid dialysate flow rates without leaks or infections. The first description of placement of an indwelling catheter for maintenance PDs was in 1968 by Tenckhoff, and the Tenckhoff catheter continues to be the most commonly used

PD access in children [3, 115, 116]. Despite significant improvements in catheter design, however, the catheter has continued to be a significant barrier to successful PD because of catheter-related complications. A recent analysis of 824 incident PD catheters in the IPPN revealed that more than 20% required revision and 83% of those revisions occurred in the first year after placement [116]. Need for access revision increased the risk of peritoneal dialysis technique failure or death [116]. This section will review the currently available catheter configurations and placement techniques. Associations between the various configurations and risk for catheter-associated infectious and non-infectious complications, including catheter malfunction, are discussed later in this chapter.

The most commonly used catheters for maintenance PD are constructed of soft material, such as silicone rubber or polyurethane. There are a wide variety of catheter configurations available, which differ in their intraperitoneal configurations (curled or straight), the number of Dacron cuffs (one or two) and the subcutaneous tunnel configuration (straight or "swan-neck"). Figure 65.5 shows the most common combinations of these configurations [117]. Table 65.3 reveals the percentage of catheters with the various configurations in children on PD from large national and international collaborative projects: IPPN, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), and the Standardizing Care to Improve Outcomes in Pediatric End stage kidney disease (SCOPE) collaborative [3, 115, 116]. These data demonstrate that a curled intraperitoneal configuration is most commonly used in children on PD [3, 115, 116].

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 be located in a superficial position. The addition of a second cuff was prompted by the potential to better secure the catheter and reduce migration of bacteria into the peritoneal cavity. Early data in children on PD demonstrated a lower incidence of infection with catheters having two cuffs, rather than one [3]. Based on these data, current guidelines recommend use of a 2-cuff PD catheter in children, except possibly in the very small infant in whom it may not be technically feasible [118]. Accordingly, the percentage of children on PD with 2-cuff catheters has increased, from roughly half of children in the NAPRTCS report from 2011, to more than 70% and 80% in recent reports from SCOPE and IPPN, respectively (Table 65.3) [3, 115, 116]. If two cuffs are used, the second cuff should be located at least 2.0 cm from the exit site to reduce the risk for cuff extrusion [117, 119]. If cuff extrusion occurs, prompt

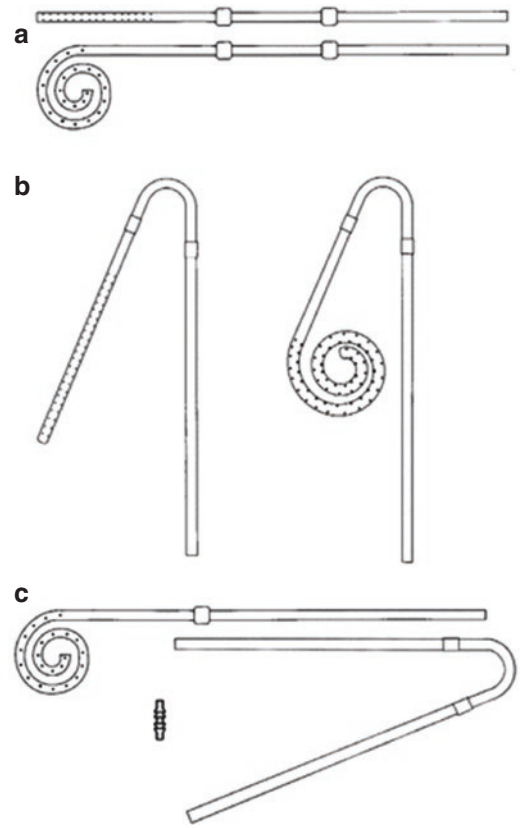

Fig. 65.5 Commonly used peritoneal catheters. (**a**) Catheter with straight tunnel segment, 2 cuffs, and straight or coiled intraperitoneal segment. (**b**) Catheter with preformed arc tunnel segment ("swan neck"), 2 cuffs, and straight or coiled intraperitoneal segment. (**c**) Extended catheter with 1-cuff, coiled-tip abdominal catheter, 2-cuff extension catheter with swan neck. Catheters with a straight tunnel segment are also available with a single cuff. (From [117], with permission)

Table 65.3 Catheter configurations from national and international collaborative registries and projects in children on maintenance peritoneal dialysis

Catheter configuration	NAPRTCS [3]	SCOPE [115]	IPPN [116]
	N (%)[a]	N (%)[a]	N (%)[a]
Number of catheters	4687 (100%)	1201 (100%)	2453 (100%)
Intraperitoneal segment			
Tenckhoff Curled	2909 (62.1%)	1070 (89.1%)	1681 (68.5%)
Tenckhoff Straight	1213 (25.9%)	66 (5.5%)	673 (27.4%)
Cuffs			
One	2375 (50.7%)	264 (22.0%)	346 (13.7%)
Two	2124 (45.3%)	873 (72.7%)	2117 (86.3%)
Tunnel			
Swan neck	1590 (33.9%)	793 (66.0%)	1542 (62.9%)
Straight	2895 (61.8%)	313 (26.1%)	911 (37.1%)
Exit-site orientation			
Up	564 (12.0%)	52 (4.3%)	346 (14.1%)
Down	1537 (32.8%)	613 (51.0%)	1299 (53.0%)
Lateral	1816 (16.4%)	459 (38.2%)	808 (32.9%)

NAPRTCS North American Pediatric Renal Trials and Collaborative Studies, *SCOPE* Standardizing Care to Improve Outcomes in Pediatric End Stage Kidney Disease, *IPPN* International Pediatric Peritoneal Dialysis Network
[a]Percentages may not add to 100% due to missing/other

shaving of the cuff off the catheter has been advocated to reduce infection risk [120, 121].

The shape of the extraperitoneal portion, or tunnel, of the catheter can be straight or have a preformed angle ("swan neck"), in which there is an inverted U-shape arc (170–180°) between the deep and the superficial cuffs (Fig. 65.5). The purpose of the catheter arc is to allow the catheter to exit the skin in a downward pointing direction, which may be associated with a decreased likelihood for the accumulation of dirt and debris within the catheter tunnel which, in turn, may reduce the development of a tunnel infection/peritonitis (see Infectious Complications) [3, 122]. In addition, the swan neck configuration allows 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 associated risk for impaired drainage [123, 124]. Since its introduction, the use of swan neck catheters has been increasing in children on PD and is now placed in the majority (Table 65.3) [3, 115, 116].

A modification of the swan neck catheter is the swan neck presternal catheter, which has a very long subcutaneous portion (Fig. 65.5). This catheter has been utilized when it is necessary to make the exit-site remote from the abdomen, such as in infants and children with incontinence, intestinal stomas, and suprapubic catheters, and the catheter exit-site is typically located in the anterior chest wall [125–127]. However, infants with complex congenital anomalies often have minimal subcutaneous tissue over the chest, which makes cuff erosion more likely in that location. One suggested approach to this problem is to place the two cuffs below the costal margin and then have the catheter exit high on the chest wall [126]. Conversely, a single cuff catheter may be used.

Preoperative Evaluation and Preparation

Careful preoperative evaluation is required for all children and adolescents prior to PD catheter placement. The preoperative evaluation should include screening and treatment of constipation, which is common in children with kidney failure and has consistently been associated with an increased risk for post placement PD catheter migration and malfunction [128]. The preoperative physical examination should include evaluation for the presence of hernias. The incidence of hernias is inversely proportional to age, with an

overall frequency of 8.0–57.0% [129–132]. The highest frequency of inguinal hernias occurs in the first year of life; they are often bilateral and all require surgical correction. Umbilical hernias can worsen in a child on PD as a result of the increase in intra-abdominal pressure generated by instillation of dialysis solution (see Non-infectious complications). As a result, some have advocated peritoneography or laparoscopic inspection for hernias at the time of catheter placement [130]. If detected, the hernias can then be fixed at the same time the PD catheter is inserted [133, 134].

A critical portion of the pre-catheter assessment is deciding upon the most appropriate location of the exit-site. In infants, 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 presence of a vesicostomy, ureterostomy, colostomy or gastrostomy will also influence the preferred exit-site location. The exit-site must be planned so that it is either on the opposite side of the abdomen from any stoma site or, as stated previously, the exit-site may be placed on the chest to increase the distance from any stoma.

Catheter Placement Technique

Since Moncrief and Popovich first reported on the use of CAPD, there have been a number of modifications of the technique for the implantation of the PD catheter [135]. The two most common PD catheter insertion techniques are open and laparoscopic. Although there are no randomized trials in children comparing outcomes in PD catheters placed using these two approaches, several case series report excellent outcomes with the laparoscopic approach, including excellent revision free survival and a lower incidence of catheter flow problems [117, 136–138]. SCOPE data reveals that more than 65% of catheters in the collaborative were placed using a laparoscopic procedure, with no statistically significant difference in placement technique (open versus laparoscopic) between children with and without peritonitis in the first 60 day after catheter placement [115].

Infectious Complications

PD-associated infections include PD catheter-related infections, i.e. infection at the catheter exit-site and/or the subcutaneous tunnel, and peritonitis. Infectious complications remain the most significant cause of morbidity and PD technique failure in children on maintenance PD [2, 3, 139–141]. In addition, infection is a leading cause of death in children on PD [2, 3, 141]. Analyses of data from large pediatric dialysis registries have revealed associations between many factors and the risk for PD-related infections in children on PD. Recognition of these risk factors is important, as they may prompt modification of care practices, which, in turn, may lower infection rates as well as the rates of patient morbidity and mortality.

Risk Factors and Prevention

Patient Age

Data from collaborative registries have consistently identified young age at dialysis initiation, and specifically age less than 2 years, as a risk factor for peritonitis [3, 122, 142–144]. It seems intuitive that the relatively close proximity of the PD catheter to the diaper region or urinary or gastrointestinal ostomy sites in a small infant would increase the risk for bacterial contamination and subsequent infection. As stated previously, efforts to maximize the distance between the catheter exit-site and the diaper area and stomas are important to decrease the risk for infection [125, 145].

PD Catheter Design, Insertion and Post-operative Exit-Site Care

As discussed previously, early studies of data from children on PD suggested a higher incidence of infection and a higher risk for relapsing peritonitis with a one cuff rather than a two cuff catheter, and current guidelines recommend a catheter with two cuffs in children on maintenance PD [3, 118, 146]. However, more recently the SCOPE collaborative has failed to show any relationship between the number of catheter cuffs

and the development of either exit-site/tunnel infections or peritonitis [122, 147]. Data in adults on PD suggest that benefit of a second cuff for infection prevention may have been reduced by widespread adoption of application of antibiotics at the catheter exit-site [117, 148].

While some studies in adults have found the use of the swan neck catheter to be associated with less frequent exit-site/tunnel infections, other studies have been unable to confirm these results [149–151]. As stated previously, one advantage of the swan neck catheter is that it allows a downward, rather than upward, pointing exit-site. Data from NAPRTCS has consistently identified an upward facing exit-site as a risk factor for peritonitis, a finding confirmed by a recent analysis of SCOPE data [3, 122]. Accordingly, current guidelines for children on PD recommend that the exit-site orientation be in the downward or lateral position [118].

Efforts to minimize the risk for peritonitis at the time of catheter placement include the provision of antibiotics prior to surgical incision [118, 152, 153]. Although vancomycin may be slightly more effective than a first-generation cephalosporin in the prevention of post-operative peritonitis, use of the latter is recommended because of concern for the generation of vancomycin resistance [118, 153–155]. The ultimate choice of antibiotic for perioperative prophylaxis should be influenced by the PD unit's antibiotic susceptibility patterns [118, 154]. Current guidelines also recommend that while securing the newly inserted catheter and minimizing movement at the exit site is important, sutures should not be placed at the catheter exit-site at the time of surgical placement, as they may increase risk of bacterial colonization and subsequent infection [118].

In the immediate post-operative period, PD catheter and exit-site care are aimed at optimizing healing and minimizing bacterial colonization [156]. Current guidelines suggest that the sterile dressing placed in the operating room following PD catheter placement remain in place for at least 7 days, and subsequent dressing changes should be performed by trained staff, using aseptic technique, no more frequently than weekly until the exit-site is healed [118, 157]. More frequent dressing changes should be performed only if the dressing becomes loose, damp, or soiled [118]. The catheter should be immobilized to optimize healing and minimize trauma [118, 158]. It is generally recommended that initiation of dialysis be delayed for at least 2 weeks following catheter placement to minimize the risk of leak at the peritoneal insertion site, although exit-site healing may take as long as 6 weeks [156–158]. In support of this, an analysis of SCOPE data demonstrated an association between use of the PD catheter for dialysis within 14 days of placement and an increased risk for early peritonitis, defined as peritonitis occurring within the first 60 days following catheter insertion [115].

Training

Because PD is a home dialysis therapy, appropriate training of the child with kidney failure and caregivers is essential to minimize the risk for infection. Unfortunately, there are no randomized controlled trials to evaluate the relationship between various training elements or the training process itself and outcomes [159–161]. Several observational studies have shown associations between shorter training time (<15 h), training in the 10 days after catheter insertion and small center size with an increased risk for peritonitis [159–164]. Current guidelines for children on PD suggest that training should include the use of a formalized teaching program that has clear objectives and criteria, with incorporation of adult learning principles [118, 159]. The training should be performed by an experienced PD nurse with pediatric training and should include core topics, including those related to infection prevention such as hand hygiene, aseptic technique, exit-site care and appropriate treatment for contamination [118, 159]. It is suggested that PD training should include no more than one child/family simultaneously [118, 159]. A syllabus for teaching PD to patients and caregivers has been published by the ISPD, and includes a checklist for PD assessment and another for PD training [165]. It remains to be determined if widespread use of this syllabus and the associated tools leads to a decrease in infection rates.

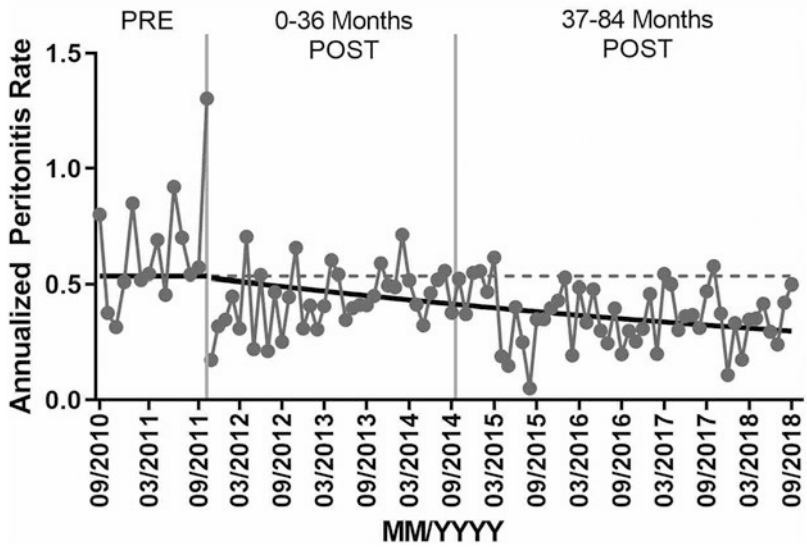

Fig. 65.6 Average monthly peritonitis rates, expressed as annualized rates, among 19 pediatric dialysis centers in the United States participating in the Standardizing Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) Collaborative from collaborative launch on October 1, 2011 through September 30, 2018. Differences between peritonitis rates in the 13 months prior to launch (pre-launch period) and the post-launch period were modeled using Generalized Linear Mixed Models techniques and revealed that the decrease in infection rate observed in the first 36 months persisted and there was a significant reduction in the average monthly peritonitis rates from 0.53 (95% CI 0.37, 0.70,) pre-launch to 0.30 infections per patient year (95% CI 0.23, 0.43) at 84 months post launch, $p < 0.001$). From [170], with permission)

Current guidelines suggest periodic retraining of the persons performing PD in the home, particularly after a peritonitis episode [118, 159]. The Trial on Education and Clinical outcomes for Home PD patients (TEACH), compared PD-related infections in adults on PD randomized to receive home visits for retraining every 1–3 months over a 24-month period compared to no re-training [166]. The study failed to demonstrate a significant difference in peritonitis rates between the two groups, although a sub-analysis demonstrated a significantly lower risk for first peritonitis episodes in patients >60 years of age who received frequent home visits [166]. The SCOPE collaborative includes a "follow up" care bundle, which requires a review of key aspects of hand hygiene, exit-site care, and aseptic technique at each monthly follow up visit in the clinic, redemonstration of competency with these procedures every 6 months, regular scoring of the PD catheter exit-site and treatment of touch contaminations according to ISPD guidelines [118, 167, 168]. SCOPE centers demonstrated a significant increase in compliance with this care bundle over the first 3 years of the collaborative, accompanied by a significant reduction in peritonitis rates [169]. A more recent analysis demonstrated that centers participating in the collaborative for 7 years were able to achieve and then maintain high level compliance with the follow up bundle and had continued reduction in center peritonitis rates over the collaborative's entire post-launch period (Fig. 65.6) [170]. An analysis of SCOPE data at the patient level also demonstrated that compliance with the follow up care bundle was significantly associated with a lower rate of peritonitis [122]. These data suggest that in addition to comprehensive training at the initiation of dialysis, ongoing review with regular testing of competency of PD catheter care and the dialysis procedure may minimize the risk for peritonitis.

Chronic Exit-Site Care

Once the catheter exit-site has healed, regular exit-site care is vital to minimize the risk for PD catheter-related infection. Current guidelines rec-

ommend regular cleansing of the exit-site with a sterile antiseptic solution and sterile gauze [118, 171]. Several cleansing agents are available and none has been shown to be superior in the prevention of catheter-related infection [118, 171]. In addition, there is no clear guidance for the optimal frequency of exit-site care, e.g. daily, every other day, or weekly [118, 171]. Not surprisingly, data from the International Pediatric Peritonitis Registry (IPPR) revealed significant variability in exit-site practices around the globe, including the frequency of exit-site care as well as the type of antiseptic agent used [172]. IPPR data also revealed that peritonitis due to *Pseudomonas* species was significantly more common at centers where exit-site care was performed more than twice weekly and where non-sterile cleansing agents (e.g. saline, soap) were used [172]. Among SCOPE participants, compliance with the specific recommendation to review exit-site care at each visit was associated with lower exit-site infection rates [147].

In addition to regular exit-site cleaning, current guidelines suggest application of a topical antibiotic during routine care, in an effort to minimize colonization of the exit-site with *Pseudomonas aeruginosa* (*P. aeruginosa)* and *Staphylococcus aureus (S. aureus),* both of which are widely accepted as risk factors for exit-site infection and subsequent peritonitis [118, 171, 173–176]. A number of observational studies, randomized controlled trials and meta-analyses have demonstrated that mupirocin applied to the skin around the exit-site reduces the risk for exit-site infections [118, 153, 171, 177–181]. However, there is concern that routine use of mupirocin may be associated with an increased risk for gram-negative infections and the emergence of mupirocin resistant *Staphylococcus* species [172, 182, 183]. Topical gentamicin is an alternative therapy, and a randomized trial in adults showed that daily application of gentamicin cream to the exit-site was not only effective in reducing exit-site infections caused by *Pseudomonas* species, but it was as effective as topical mupirocin in reducing *S. aureus* infections [180]. There are concerns, however, about the possible development of gentamicin-resistant organisms and an increased risk of fungal infections with this therapy.

Touch Contamination

Accidental contamination of the sterile portions of the PD catheter transfer set or dialysis tubing, or touch contamination, is a leading cause of peritonitis [122, 184, 185]. Current guidelines recommend that contamination prior to the infusion of dialysis fluid into the peritoneal cavity be treated with a sterile transfer set change alone, without antibiotics [118]. If the contaminating event occurs after dialysate has been infused into the peritoneal cavity, both a sterile transfer set change and antibiotic prophylaxis is recommended [118, 163]. Intraperitoneal administration of a first-generation cephalosporin for 1–3 days is typically recommended, unless the patient has a history of methicillin-resistant *S. aureus* (MRSA), in which case a glycopeptide (vancomycin or teicoplanin) should be used [118, 163]. Gram-negative coverage may be appropriate if the contamination may have included enteric organisms, e.g. from stool in a diapered infant [118]. An effluent sample should be obtained for cell count, differential and culture prior to delivery of antibiotics, if possible, and culture results and susceptibility testing used to guide any subsequent antibiotic usage [118].

Ostomies

As stated previously, ostomy sites, including gastrostomy, ureterostomy, nephrostomy and colostomy, may increase the risk of bacterial contamination of an adjacent PD catheter. In fact, data from the IPPN demonstrated an increased risk for peritonitis in the presence of any ostomy [186]. Data in children on PD have not revealed a consistent association between presence of a gastrostomy tube (GT) and risk for infection, including fungal infection; however, among infants on PD enrolled in SCOPE, placement of a GT after PD catheter placement was associated with increased risk for bacterial peritonitis [122, 144, 185, 187–190]. Although data on the subject is limited, current guidelines suggest that an open procedure should be used to place a GT in patients who are already receiving PD, while either open or laparoscopic placement may be used if the gastrostomy is placed prior to initiating PD. [118, 191]. Prophylactic

antibiotics, typically a first-generation cephalosporin, and antifungal therapy should be provided during gastrostomy tube placement in a patient with a PD catheter [118].

While an analysis of SCOPE data did not find an association between the presence of a colostomy and the risk for peritonitis in multivariable analysis, a recent study from IPPN revealed a significantly higher rate of peritonitis among patients with a colostomy [122, 192]. The number of children on PD with colostomies in these analyses was relatively small at 14 and 20, respectively [122, 192].

Antibiotic and Antifungal Prophylaxis

Although fungal peritonitis is relatively uncommon in children on PD, it is associated with an increased risk for significant morbidity and mortality [190, 193–195]. Observational data suggests that risk factors for fungal peritonitis include prior treatment with antibiotics, recurrent peritonitis, and immunosuppression [189, 190, 195–199]. Antifungal prophylaxis with either oral nystatin or fluconazole is currently recommended whenever antibiotics are administered to children on PD, although data from SCOPE reveal that this practice is not uniformly implemented, particularly when antibiotics are prescribed for infections other than bacterial peritonitis [118, 190, 200–204].

Prophylactic antibiotic and antifungal therapy should also be provided when children on PD undergo certain procedures, including gastrostomy tube placement, as previously discussed, as well as invasive dental, gastrointestinal or genitourinary procedures [118, 205, 206].

Other Factors

The risk factors listed in this section were largely derived from data collected by observational registries and quality improvement collaboratives that identified associations between various factors and risk for infection among a cohort of children on PD. There are clearly many other factors that may impact the risk for infection in individual children. The dialysis unit should perform a formal review, or apparent cause analysis, of each infection in search of causation [118, 162, 163]. This review should include nurses and physicians at a minimum. Inclusion of the child on PD and their caregivers/family, social worker, infection preventionist and infectious disease specialist is encouraged. Identification of causation will allow appropriate intervention for the individual, and potentially other children on PD in the unit.

Catheter-Related Infections

Infections of the PD catheter include exit-site and tunnel infections. PD catheter-related infections are associated with an increased risk for peritonitis. However, even without subsequent peritonitis, exit-site and tunnel infections require exposure to antibiotics with the subsequent risk for fungal infection and drug resistant organisms, both of which may require catheter removal [147, 207–209]. Catheter-related infections also carry a high risk of recurrence. In a Japanese multicenter study, 15% of all infections and 40% of MRSA infections relapsed [210].

Routine use of an objective scoring system is recommended to monitor the status of the catheter exit site and to optimize the diagnostic accuracy of exit-site infections. The pediatric Exit Site Score (ESS) considers pericatheter swelling, crust, redness, tenderness and secretion with a score range from 0 to 10 (Table 65.4) [118, 168]. An exit site infection is diagnosed by an ESS >1 in the presence of a pathogenic organism, or >3 irrespective of culture results. A tunnel infection is defined by an ESS >5 [118]. Sonographic examination may help to evaluate the extent of infection along the catheter [211, 212]. Data from SCOPE, which requires scoring of the exit-site at every monthly visit, revealed that an ESS of anything more than

Table 65.4 Catheter exit-site scoring system. From [118], with permission [168]

	0 Points	1 Point	2 Points
Swelling	No	Exit only (<0.5 cm)	Including part of or entire tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

zero is associated with an increased risk for an exit-site infection in the following month [147]. However, significant variability in exit-site scoring using this tool has been noted at SCOPE centers, and the collaborative is currently modifying the tool in an effort to promote more consistent scoring and, therefore, greater uniformity in the diagnosis of exit-site infections.

Uncomplicated catheter exit-site infections can be treated with oral antibiotics according to culture results and susceptibilities [118]. Empiric therapy for tunnel infections may be via the oral route; however, intraperitoneal or intravenous antibiotics are often indicated, particularly if signs of severe infection and/or a history of *S. aureus* or *P. aeruginosa* are present. Infections with gram-positive bacteria should be treated with a first-generation cephalosporin or a penicillinase-resistant penicillin. Intraperitoneal or intravenous glycopeptide therapy should be reserved for cases with proven MRSA infection [118]. The use of oral ciprofloxacin for infections due to *P. aeruginosa* had previously been recommended, with the addition of a second antibiotic such as cefepime, piperacillin, or a carbapenem, if resolution of the infection is slow, or there is recurrence [118]. However, recent reports from observational studies have suggested an increased risk for aortic aneurysm or dissection associated with fluoroquinolone use, particularly in the setting of other risk factors such as hypertension, which led the United States' Food and Drug Administration to issue a safety announcement (https://www.fda.gov/Drugs/DrugSafety/ucm628753.htm) [213–216].

Adjunctive therapy for exit-site/tunnel infections should include daily or twice daily dressing changes, and cautious removal of exuberant granulomatous tissue ("proud flesh") with silver nitrate.

Antibiotic treatment should be administered for a minimum of 2 weeks and for at least 7 days beyond complete resolution of the infection. Treatment for at least 3 weeks is recommended for infections caused by *S. aureus* or *P. aeruginosa*. Extension of antibiotic therapy beyond 4 weeks should be avoided. In case of persistence of symptoms or recurrence after discontinuation of antibiotic treatment, the catheter should be removed and replaced [118]. Surgical shaving of the external cuff may be an alternative to catheter removal for treatment of a persistent exit-site infection if the inner cuff is not involved [121, 217].

Peritonitis

The diagnosis of peritonitis should be considered in any child on PD with abdominal pain and/or cloudy PD effluent, with an effluent white blood cell count of greater than 100/mm^3 and at least 50% polymorphonuclear neutrophils (PMN) confirming the diagnosis [118]. For children on automated PD, the effluent white blood cell count should be obtained from an exchange with the dialysis solution instilled for at least 1–2 h [118]. In this setting, the presence of 50% or more PMN is highly suggestive of peritonitis when the clinical features of peritonitis are present, even if the total white blood cell count is below 100/mm^3. Bacterial growth in the effluent confirms the diagnosis, whereas a negative culture does not rule out a bacterial etiology. The efficiency of microbiological diagnostics can be maximized by incubating the effluent in 3–4 blood culture bottles, and by centrifuging large effluent volumes. A culture-negative rate of less than 10% should be aimed for according to consensus guidelines [218]. However, international surveys have shown that this target is far from being achieved by pediatric PD centers around the globe [172]. Data from the SCOPE collaborative revealed an overall culture negative rate of 26.6% and significant variability in the culture negative rate and culture techniques among centers, although no associations between practices and culture negative rate could be elucidated [219]. In response to these data, the SCOPE collaborative has implemented a standardized PD effluent culture bundle and has already demonstrated a decrease in the both the culture negative rate and the percentage of cultures that are negative per month (unpublished finding). Among culture-positive cases, IPPN discovered wide regional variability in causative organisms, but in general gram-positive organisms predominate, with coagulase-negative *Staphylococci* and *S. aureus* most frequently cultured [122, 172].

Empiric intraperitoneal antibiotic treatment should be initiated as soon as the diagnosis of peritonitis is considered, and include coverage for both gram-positive and gram-negative organisms

[118]. Monotherapy with cefepime may be considered for empiric therapy, while a first-generation cephalosporin or a glycopeptide combined with ceftazidime or an aminoglycoside may be used if cefepime is not available [118]. However, global peritonitis data from children on PD reveals not only significant variability in the causative organisms, but also associated antibiotic susceptibilities, prompting the additional recommendation that empiric coverage be guided by the center-specific antibiotic susceptibility pattern [172]. Specifically, the empiric use of glycopeptides should be restricted to centers where the rate of MRSA exceeds 10%. Antibiotic therapy should be modified based on culture and antibiotic susceptibility results. Dosing recommendations are given in Table 65.5 [118]. If cultures remain sterile and signs and symptoms of peritonitis are

Table 65.5 Dosing recommendations for anti-infective agents in children with peritoneal dialysis catheter-related peritonitis. Administration should be via intraperitoneal route unless specified otherwise. Intermittent doses should be applied once daily unless specified otherwise. From [118] with permission

	Continuous therapy[a]		Intermittent therapy
	Loading dose	Maintenance dose	
Aminoglycosides[b]			
Gentamicin	8 mg/L	4 mg/L	
Netilmicin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg Non-anuric: 0.75 mg/kg
Tobramycin	8 mg/L	4 mg/L	
Amikacin	25 mg/L	12 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[c]			
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg; Repeat dosing 15 mg/kg q 3–5 days
Teicoplanin	400 mg/L	20 mg/L	15 mg/kg q 5–7 days
Penicillins[b]			
Ampicillin	—	125 mg/L	—
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	—
Others			
Aztreonam	1000 mg/L	250 mg/L	—
Clindamycin	300 mg/L	150 mg/L	—
Imipenem/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 (max daily dose 1.2 g)		
Rifampin	10–20 mg/kg/day divided BID (max daily dose 600 mg)		
Antifungals			
Fluconazole	6–12 mg/kg IP, IV or PO q 24–48 h (max daily dose 400 mg)		
Caspofungin	IV only: initial dose 70 mg/m^2 on day 1 (max daily dose 70 mg); Subsequent dosing 50 mg/m^2 daily (max daily dose 50 mg)		

[a] For continuous therapy, the exchange with the loading dose of antibiotics should dwell for 3–6 h, followed by the use of the maintenance dose for all subsequent exchanges

[b] Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation

[c] Accelerated glycopeptide elimination may occur in patients with residual renal function. If intermittent therapy is used in this setting, the second dose of antibiotic should be time-based on a blood level obtained 2–4 days after the initial dose. Redosing should occur when the blood level is <15 mg/L for vancomycin, or 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum drug levels can be monitored in a timely manner

improved, empiric antibiotic therapy should be continued for 2 weeks with the exception of aminoglycosides, which should be discontinued after 72 h in culture-negative peritonitis [118].

General adjunctive measures include the reduction of the peritoneal fill volume during the initial 24–48 h of therapy in children with significant abdominal discomfort, and intraperitoneal administration of 500–1000 IU/L heparin until complete resolution of dialysate cloudiness [118].

Most children with PD-associated peritonitis achieve clinical improvement within two to three days following the initiation of antibiotic treatment [168, 185]. The initial treatment response is predictive of the functional recovery of PD and the risk of peritonitis relapse [142, 146]. Prolonged attempts to treat refractory peritonitis and to "save the catheter" should be avoided to minimize permanent injury to the peritoneal membrane [220]. In children who fail to respond clinically within 72 h of initiation of appropriate antibiotic therapy, repeat effluent cell count, differential and culture should be performed and potential sources of persistent infection should be sought. Treatment failure in peritonitis with *S. aureus* or *P. aeruginosa* points to a concomitant tunnel infection and requires catheter removal [118]. Treatment-resistant peritonitis with anaerobic bacteria or multiple gram-negative organisms is suspicious of intraperitoneal pathology (*e.g.,* ruptured appendix). Catheter removal is also recommended for any bacterial or culture-negative peritonitis that fails to resolve within 5 days of appropriate antibiotic treatment [118, 221, 222].

Ten to twenty percent of peritonitis episodes recur within 4 weeks of completion of antibiotic treatment with the same bacterial strain as indicated by identical antibiotic susceptibilities ('relapsing peritonitis') [146, 168, 185]. Repeated bouts of peritonitis are a risk factor for incomplete functional recovery and PD technique failure [146]. In relapsing peritonitis, empiric therapy should be reinitiated using an antibiotic combination covering the susceptibilities of the previous causative organism. Slime-forming bacteria can survive antibiotic therapy in a biofilm matrix or fibrinous adhesions on catheter surfaces. Accordingly, intraluminal fibrinolytic therapy may expose sequestered bacteria and render them susceptible to antibiotic activity. Local instillation of fibrinolytic agents (urokinase or recombinant tissue plasminogen activator), followed by instillation of high-dose antibiotics, has been shown to be efficacious in preventing further peritonitis relapses [223–225]. Hence, intraluminal fibrinolytic therapy should be considered in patients with a first peritonitis relapse which is not explained by extraluminal pathology such as a tunnel infection or an intraabdominal abscess. If a second relapse occurs, the catheter should be removed as soon as peritonitis is controlled by antibiotic therapy [118].

Fungal peritonitis is an infrequent but potentially serious complication of PD fraught with a high risk of PD technique failure and sometimes life-threatening, systemic infection [189, 190, 195]. Fungal infections represent 1–4% of all peritonitis episodes, although roughly 8% of peritonitis episodes reported to the SCOPE collaborative have been due to fungi [122, 185, 189, 190]. Treatment of fungal peritonitis consists of prompt catheter removal and appropriate antimycotic therapy [193, 226]. Fungi avidly grow on PD catheter surfaces, and resolution of infection is usually not possible as long as the catheter is in place. Fluconazole is the treatment of choice for most *Candida* species due to its excellent bioavailability and peritoneal penetration [227]. Alternative agents are echinocandins (e.g. caspofungin) for non-responding, non-albicans candida, and posaconazole or voriconazole for filamentous fungi such as Aspergillus [227]. Following catheter removal, effective antimycotic therapy should be administered for at least 2 weeks beyond complete resolution of clinical symptoms [118]. Reinitiation of PD following the treatment of fungal peritonitis in children has been successful [189].

Non-Infectious Complications

Non-infectious complications can result in significant morbidity, including the need to terminate PD [116, 228]. Non-infectious PD complications can be divided into catheter-related complications, and complications related to the dialysis procedure itself (Table 65.6) [229–231].

Table 65.6 Non-infectious complications of peritoneal dialysis [229–231]

Catheter related complications
Obstruction/reduced inflow or outflow
Migration of catheter out of pelvis
Catheter kinking
Catheter blockage
Fibrin
Blood clot
Omentum
Catheter compression
Stool/Constipation
Tumor or other intraabdominal mass
Peri-Catheter leak
Catheter cuff extrusion
Complications associated with the dialysis procedure
Related to increased intraperitoneal pressure
Subcutaneous leak
Gastroesophageal reflux and delayed gastric emptying
Abdominal and back pain
Hernia
Hydrothorax
Related to transfer of solutes during dialysis (electrolyte and metabolic derangements)
Hypokalemia
Hypo/hypermagnesemia
Hyperglycemia
Hyperinsulinemia
Hypertriglyceridemia
Related to exposure of peritoneal membrane to dialysis fluid
Membrane failure
Pancreatitis
Encapsulating peritoneal sclerosis

Catheter-Related Complications

Catheter-related complications include catheter malfunction, i.e. poor inflow and/or outflow, and leaks at the catheter exit-site. A recent analysis of data from the IPPN revealed a catheter revision rate of 1 per 83.2 patient-months, and the leading indication for revision was catheter malfunction, particularly in the first year after placement (Fig. 65.7) [116]. In that study, the need for access revision increased the risk of PD technique failure or death, and access dysfunction due to mechanical causes doubled the risk of technique failure compared with infectious causes [116]. The risk of access revision was associated with younger age, diagnosis of congenital anomalies of the kidney and urinary tract, coexisting ostomies, presence of a swan neck tunnel with curled intraperitoneal portion, and a high gross national income [116].

Catheter malfunction may be caused by obstruction from the omentum, kinking or migration of the catheter out of the pelvis, or blockage by fibrin or clots. Omentectomy at the time of catheter placement may reduce the risk of obstruction, and is practiced in most centers [133, 232, 233]. In practical terms, the omentectomy does not have to be complete. The remnant amount needs to be such that it cannot reach the distal catheter once it is positioned in the pelvis. However, one group of investigators, despite reporting a 20% decrease in the incidence of catheter blockage with omentectomy, calculated that eleven omentectomies would be required to prevent two omental PD catheter blockages. Therefore, the authors 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 [232].

Migration of the catheter out of the pelvis can lead to poor dialysate inflow or outflow, as well as increased pain with dialysis. As mentioned previously, constipation is a risk factor for migration and should be monitored for and treated aggressively. Once migration has occurred, interventional radiology (IR) techniques may be used to reposition the catheter, with laparoscopic repositioning if IR repositioning fails [234]. For catheters that are occluded by fibrin or blood clot, installation of fibrinolytic agents can be very effective in restoring catheter flow [235–237].

Leaking of fluid from the peritoneal cavity through the PD catheter tunnel is a significant risk for the development of peritonitis. As previously discussed, delaying use of the PD catheter for routine dialysis for at least 14 days is advised to minimize the risk for leaks, and subsequent infection [115, 118]. The use of fibrin glue in the PD catheter tunnel 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 [238, 239].

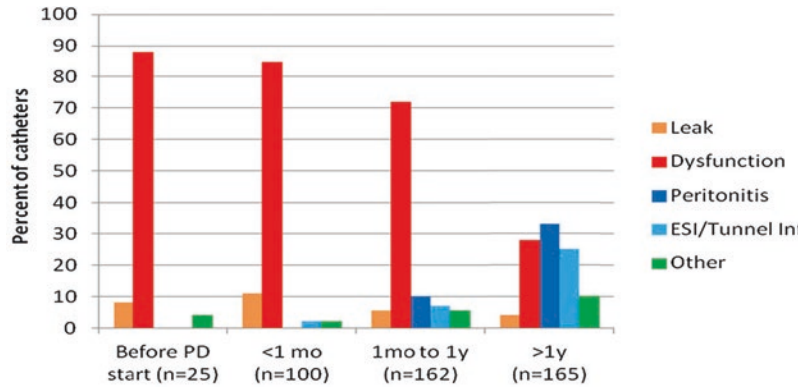

Fig. 65.7 Characterization of 452 access revisions by indication and time on peritoneal dialysis (PD) among children enrolled in the International Pediatric Peritoneal Dialysis Network (IPPN) Registry. ESI, exit site infection; tunnel inf, tunnel infection. (From [116], with permission)

Hemoperitoneum, or blood in the dialysate effluent, is common immediately after PD catheter placement and typically clears with dialysis exchanges. Heparin may be added to the dialysate to reduce the risk of clotting within the PD catheter. Strictly speaking, most cases of hemoperitoneum beyond the post-implantation period are not a complication of PD *per se*, but rather diagnosed because of the ability to visualize peritoneal fluid during the dialysis procedure. A common benign cause of hemoperitoneum in female adolescents and young adult women is menstruation. Blood may appear a few days prior to menstruation and arise from shedding of intraperitoneal endometrial tissue if endometriosis is present, or from the uterus in a retrograde fashion through the fallopian tubes [230, 231]. Hemoperitoneum can also be seen at the time of ovulation. Other causes of hemoperitoneum include trauma, bleeding disorders, anticoagulation therapy, and rupture of a hepatic, ovarian or renal cyst. Finally, bleeding into the peritoneal cavity may be associated with intraperitoneal calcifications, which may occur as a consequence of chronic kidney disease bone and mineral metabolism disorder, or in the setting of encapsulating sclerosing peritonitis (see below) [231].

Complications Related to the Dialysis Procedure

Complications related to the dialysis procedure can be divided into those due to the increased intraperitoneal pressure that arises with instillation of dialysis fluid into the peritoneal cavity, those occurring as a consequence of the transfer of solute between plasma and dialysate during the dialysis exchange (i.e. metabolic or electrolyte derangements), and those that are either directly related to or exacerbated by exposure of the peritoneum and other intra-abdominal organs to dialysis fluid (Table 65.6) [230, 231].

Complications Related to Increased Intraperitoneal Pressure

Since the efficacy of the dialysis procedure is dependent on the area of the peritoneal membrane in contact with the dialysis fluid, increasing this contact area by increasing the fill volume is a therapeutic aim. However, an increase in the fill volume is associated with an increase in the intraperitoneal pressure (IPP) [35]. Elevated IPP can lead not only to patient discomfort and intolerance of the dialysis procedure, but may also increase the risk of dialysis leaks, gastroesophageal reflux, hernia formation and hydrothorax [10, 33, 34]. While leaks at the catheter exit-site occur most frequently around the time of catheter placement, more subtle leaks may occur well after the catheter exit-site has healed [240]. These leaks typically present with accumulation of fluid in the subcutaneous tissue, weight gain, and peripheral and/or genital edema, and often resolve with reduction in fill volume, avoiding a daytime fill, or temporary cessation of PD. Complaints of back or abdominal pain and gastroesophageal reflux may be eased by efforts to lower the IPP, including a reduction of the fill volume, particularly during the day.

As stated previously, hernias are common in children and their frequency is inversely related to age. Ideally, hernias are identified and repaired at the time of PD catheter placement [133, 134, 241]. Hernias may develop after PD is initiated at the sites of surgical incisions or areas of anatomic weakness such as the umbilicus or the linea alba. Small hernias may be followed with careful monitoring for incarceration, with efforts to reduce IPP as described above. However, many hernias in children ultimately require surgical repair.

Hydrothorax in the patient on PD occurs when an elevated IPP causes fluid to enter the pleural space by way of a pleuroperitoneal leak, presumably at the site of a diaphragmatic defect [242]. This defect is almost always on the right side; the presence of the heart and pericardium may limit leak of fluid across the left hemidiaphragm. Hydrothorax usually presents with shortness of breath and chest discomfort and must be differentiated from congestive heart failure. In addition, other causes of transudative pleural effusion, including volume overload, should be ruled out. Diagnosis is typically made by measuring glucose in the fluid obtained by way of thoracocentesis, with an elevated pleural fluid glucose relative to serum glucose verifying the peritoneal dialysate origin of the fluid [231, 242]. Confirmatory tests can include CT peritoneography or a technetium scan, followed by serial imaging [243]. First line treatment of hydrothorax is transient cessation of PD, which may allow closure of the diaphragmatic defect [244]. If conservative therapy fails, chemical pleurodesis with tetracycline, talc or autologous blood may be successful [244, 245]. Other therapeutic options include thoracoscopic pleurodesis, and thoracoscopic or open diaphragmatic repair [231, 244].

Complications Related to Transfer of Solutes During the Dialysis Procedure

The bidirectional transfer of solutes between the plasma in peritoneal capillaries and the dialysate in the peritoneal cavity is the therapeutic goal of the PD procedure. However, the transfer of solutes cannot be precisely controlled and so certain electrolyte and metabolic derangements should be anticipated. The most common of these is hypokalemia, the result of potassium losses into the potassium-free dialysis solution. Liberalization of dietary intake will typically restore normal potassium, but enteral supplementation may be required, particularly in infants or young children on low potassium formulas. The possible association between hypokalemia and the risk for peritonitis should prompt attention to and correction of this issue.

Hypermagnesemia is relatively common in children with kidney failure secondary to reduced kidney clearance of magnesium. Magnesium concentrations in commercially available dialysis solutions range from 0.25–0.75 mmol/L. Elevated serum magnesium levels are typically seen with use of solutions containing 0.75 mmol/L magnesium and high magnesium levels may contribute to adynamic bone disease [246–248]. On the other hand, use of solutions containing both 0.5 mmol/L and 0.25 mmol/L magnesium has been associated with hypomagnesemia in adults on PD [246]. Given the lack of data available on magnesium homeostasis in children on PD, current recommendations suggest choosing a solution that allows maintenance of a high normal serum magnesium, i.e. 0.9–1.0 mmol/L, in this population [43].

Hyperglycemia, hyperinsulinemia and dyslipidemia are present even in the early stages of kidney failure in children [249, 250]. These conditions persist or worsen on dialysis [251–253]. The pathophysiologic mechanisms contributing to disturbances in glucose and lipid metabolism seen in children with kidney failure are quite complex, and beyond the scope of this chapter. It is important to recognize, however, that in people on PD, exposure to glucose-containing dialysis solutions provides a substantial glucose load, which induces insulin resistance and an atherogenic lipid profile [38, 229, 254]. Thus, PD may contribute to the development of disturbances of glucose and lipid metabolism, or exacerbate them if already present. These findings reinforce recommendations to minimize exposure to glucose by using the lowest dialysate glucose concentration possible, with the addition of icodextrin if required to maintain euvolemia [9, 43]. The pri-

mary therapeutic approach for dyslipidemia is lifestyle modifications, including nutrition and dietary counseling to address obesity if present. Although several pharmacologic therapies for dyslipidemia are available, given the lack of data on safety and efficacy of these agents in children, KDIGO guidelines suggest that statins or statin/ezetimibe combinations not be initiated in children less than 18 years of age with kidney failure, including those on maintenance dialysis [255].

Complications Related to Exposure of Peritoneal Membrane to Dialysis Fluid

Peritoneal membrane failure, or the inability of the membrane to provide adequate removal of fluid and/or solutes, is an important complication of PD as it typically necessitates conversion to hemodialysis. International and national registry data suggest that 4.2–8% of the children on PD in these large cohorts required transfer to HD due to membrane failure, and the percentage is as high as 27% in smaller series [3, 116, 256]. Severe, persistent or recurrent peritonitis is a significant contributor to membrane failure, but as previously discussed, an increasing body of experimental evidence suggests that exposure of the peritoneal membrane to PD solutions, and high concentrations of glucose in particular, is a predominant contributor to progressive fibrosis [41, 57, 257].

Pancreatitis in people on PD may be caused by the same precipitating factors as in people who are not on PD, such as infection, medications, hypercalcemia and hyperlipidemia. However, irritation from the peritoneal dialysis fluid and/or PD catheter has also been reported as a cause of pancreatitis in people on PD [258]. The presenting symptoms of abdominal pain, emesis and cloudy dialysis effluent may mimic peritonitis, and thus the diagnosis can be missed. The diagnosis should be considered in people on PD with sterile peritonitis, particularly if their symptoms do not improve. Most episodes may be treated conservatively, although recurrence with reintroduction of dialysate into the abdomen may prompt at least the temporary cessation of PD [231].

Encapsulating peritoneal sclerosis (EPS) is a rare, but extremely serious complication of PD defined by the ISPD as ‘a clinical syndrome continuously, intermittently or repeatedly presenting with symptoms of intestinal obstruction due to adhesions of a diffusely thickened peritoneum’ [259]. EPS has been reported in 0.7–3.3% of adult cohorts, with a mortality rate of 35–69% [259–262]. A 10-year survey of 1472 children on PD revealed a similar prevalence of EPS at 1.5% or 8.7 cases per 1000 patient-years on PD, but a lower mortality rate with 3 deaths among 22 cases after a median follow-up of 4.8 years [263]. Non-PD related risk factors for the development of EPS include previous intra-abdominal surgery, beta-blockers, and cirrhosis with ascites [259]. Among people on PD, the cause of EPS is likely multifactorial, but recurrent infection and long term exposure to dialysate are thought to be the major contributors [259, 261, 264]. As in adults, data from children on PD reveal that increasing time on PD is associated with an increased risk for EPS [263, 265, 266]. Efforts to prevent EPS, therefore, have included pre-emptive transfer to hemodialysis in people who remain on PD for more than 8 years. Ongoing treatment with PD beyond this time period can be considered if the person on PD has a stable dialysate/plasma creatinine (D/P Cr) ratio based on PET, no evidence of high peritoneal transport capacity, no requirement for frequent use of hypertonic dialysis solution, normal or only intermittently elevated serum C-reactive protein level, absence of recurrent peritonitis and clinical stability defined as “good appetite and no signs of fluid overload.” [265, 267].

People on PD with EPS typical present with symptoms of bowel obstruction, including abdominal pain, emesis, anorexia, abdominal mass, weight loss, ascites and hemoperitoneum, and EPS is almost universally associated with progressive loss of ultrafiltration [259]. The diagnosis is usually confirmed radiographically, with either ultrasound or CT demonstrating loculated/septated ascites, adherent bowel loops, peritoneal thickening, and peritoneal calcification. Treatment typically consists of transfer to HD and bowel rest with provision of parenteral nutri-

tion [261, 264]. Treatment with several immunosuppressive agents, including prednisolone, sirolimus, mycophenolate mofetil, and tamoxifen, has been reported with variable success [259, 260, 268–271]. EPS can develop in patients on immunosuppression following kidney transplantation, calling into question the role of immunosuppression in this condition [264]. In adults with EPS, surgical intervention at specialized centers has shown improvement in symptoms and survival [272, 273]. Ongoing prospective efforts to monitor peritoneal membrane function and ultrastructural changes in people on PD should provide valuable information about the risk factors for developing EPS and ultimately strategies to minimize the risk for its development [71, 274].

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