Technical Aspects and Prescription of Peritoneal Dialysis in Children

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Introduction

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

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

Update on PD Connection Technology

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

Catheter-to-Transfer Set Connectors

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

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

Transfer Set-to-Container Connection

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

Transfer Sets

The ideal transfer set should be characterized by:

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

Several types of transfer set have been developed over the years.

Straight Transfer Set (the Standard Oreopoulos System)

When introduced by Oreopoulos [1], this transfer set made the connection considerably easier and reduced the incidence of peritonitis in CAPD patients. One significant limitation of this system was that the PD fluid was infused into the abdominal cavity immediately after the connection which increased the risk for potential bacterial contamination. Furthermore, the patient had to carry the bag and transfer set until the following exchange.

The Y-Set

The Y-set [2] was developed to free the patient from the need to remain attached to the empty bag between exchanges and allow a flush-before-fill phase after the connection. The priming of the tubing with a small amount of fresh dialysis solution, followed by the discharge of the spent dialysate into the drainage bag, together with the injection of a disinfectant solution into the Y-set lumen after the exchange to sterilize it, was able to dramatically lower peritonitis rates [3]. Precautions were still required to flush the antiseptic solution completely before instilling fresh dialysis solution.

A further evolution of the Y-set was represented by the double bag system [4], where the Y-set is already attached to the dialysis solution bag and to an empty bag, eliminating the spiking procedure. The Y-set is connected to an adapter tubing during the exchange and is discarded after each use. The patient flushes the system after breaking color-coded frangible seals, drains the dialysate effluent, and then fills the peritoneal cavity with the dialysis solution. With this system, the patient has to wear only a small adapter tubing, without any antiseptic solution inside, between the exchanges.

In the absence of a disinfectant inside the transfer set after the exchange, touch contamination at disconnection may lead to significant growth of bacteria before the following exchange.

Here, the flush-before-fill procedure could fail to completely wash out the contaminating microorganisms, especially those with high adhesiveness to the plastic of the devices (e.g., *Staphylococcus aureus*, *Pseudomonas* sp.). For this reason, at the end of the exchange, the transfer set is closed with a disinfectant-containing cap (MiniCap®, Baxter Healthcare Corporation, McGraw Park, Illinois, USA). The povidone-iodine contained in the disconnect caps of these sets has the potential to be a contributing factor to thyroid function changes such as hypothyroidism. Patients most at risk to be potentially affected are primarily infants and children with small peritoneal dialysate fill volumes, where high dialysate concentrations of iodine may result [5]. In such patients, thyroid function should be monitored. In order to minimize iodine exposure, the contents of the peritoneal cavity should be drained prior to the initiation of the subsequent fill cycle whenever possible.

In another connecting device, disconnection takes place without opening the system (A.N.D.Y. Plus®, Fresenius Medical Care, Bad Homburg, Germany), since the line is clamped very close to the catheter and then broken; the plastic clamp perfectly fits the line causing complete occlusion.

Another device developed to increase the safety and ease of the line connection is represented by a connector that has a rotating gear with a fixed position for any phase of the exchange (Dianectan®, Laboratoire Aguettant, Lyon, France); in this system, when the cap is positioned, the catheter has already been automatically closed.

In a further development, a polyolefin-made plasticizer-free system (stay•safe®, Fresenius) may reduce potentially harmful exposure to phthalate esters [6].

The development of safe and simple-to-use connecting devices has contributed to simplifying and shortening patient and caregiver training, with an associated reduction in peritonitis episodes due to touch contamination both in adult [7, 8] and in pediatric patients [9] (see also Chap. 16).

Peritoneal Dialysis Prescription

The strategic process of determining a PD prescription for pediatric patients with ESRD requires a tailored treatment schedule to meet the needs of each individual child, according to a series of parameters including age, body size, associated nonrenal diseases, residual renal function (RRF), clinical condition(s), blood pressure, nutritional status, and peritoneal membrane (PM) transport characteristics [10, 11]. At the same time, potential negative effects of chronic PD on the patient's metabolism and on the anatomical and functional integrity of the PM should be taken into account. Finally, the socioemotional burden of PD treatment should be minimized to allow for a satisfactory level of psychological and social rehabilitation for the patient and his/her family

The selection of chronic PD modality and treatment prescription should be based on knowledge of PM physiology in parallel with an accurate assessment of individual patient PM transport characteristics. Therefore, a basic description of the PD system and of the driving forces of solute and water exchange will be briefly presented, and the issue of PM function tests will be addressed.

The Peritoneal Dialysis System

The PD system has three major components: the peritoneal microcirculation; the PM; and the dialysis fluid [12].

Peritoneal Microcirculation

Peritoneal capillary blood flow has been reported to vary between 50 and 150 mL/min in adults [13]. Blood flow through the peritoneal membrane is usually preserved to allow solute removal even in moderately hypotensive subjects [14]. Peritoneal blood vessel density decreases with age, from the highest levels in infancy; thus, solute removal rates decrease proportionately [15]. In addition to blood flow, the peritoneum has

an active lymphatic system, which includes specialized structures (*lacunae*) located on the undersurface of the diaphragm.

Peritoneal Membrane

The PM lines the inner surface of the abdominal and pelvic walls (parietal peritoneum), covers the intraperitoneal organs, forms both the visceral mesentery and the omentum, and connects loops of the bowel (visceral peritoneum) [16].

The PM is the barrier that solutes and water must cross during dialysis. It is a complex structure composed of:

- *The capillary wall*. Peritoneal capillaries are mainly of the continuous type, with less than 2% of fenestrated capillaries [17]. Peritoneal capillary endothelial cells are linked to each other by tight junctions and surrounded by a basement membrane. Healthy endothelium thus plays a central role in the control of PM vascular permeability [18].
- *The interstitium*. The PM interstitium is composed of extracellular matrix, containing a limited number of cells (fibroblasts, mononuclear cells) and lymphatic vessels. Hyaluronan, a major component of the extracellular matrix, has been reported to be an important determinant of the resistance to fluid and solute transport [19].
- *The layer of mesothelial cells.* These cells have a system of tight and gap junctions, microvillus projections at the free surface, and several organelles in their cytoplasm. Mesothelial cells have been reported to participate in glucose transport and regulation of water and solute fluxes through tight junction modulation, but their actual role as a rate-limiting barrier to PM transport is still debated [20, 21].

Dialysis Fluid Compartment

Both the composition of the PD solution and the modalities of its delivery influence the peritoneal exchange. PD solutions contain an osmotic agent to produce the osmotic gradient required to obtain ultrafiltration (UF), a buffer to correct the patient's metabolic acidosis, along with balanced concentrations of calcium, magnesium, and electrolytes. Dialysis fluid is infused into the peritoneal cavity in an amount that is scaled to the patient's body size and clinical conditions.

Driving Forces of Solute and Water Exchange

The driving forces of solute and water exchange across the PM, between the dialysis solution and the capillary blood and surrounding tissues, are represented by diffusive transport, UF, and convective mass transfer [21].

Diffusive Transport

Diffusion consists of passive solute exchange between two solutions (blood and dialysis fluid) separated by a semipermeable membrane. Main factors affecting the rate of solute diffusion are represented by:

- *The solute concentration gradient between blood and dialysate*. Because blood flow through the PM is relatively stable and apparently well preserved even in unstable patients who are moderately hypotensive, the concentration gradient is best maintained by replacing the dialysis fluid in the abdomen as often as is feasible.
- *The molecular weight (MW) of the solute.* Since diffusion is a size-selective process, small molecules (urea, creatinine) diffuse more rapidly than larger molecules (vitamin B_{12}, "middle molecules," higher-MW proteins). Low-MW compounds such as urea are preferentially removed by diffusion. Each compound is characterized by a specific PM permeability coefficient. Phosphate transport is lower than that of urea and creatinine since its molecules are surrounded by an aqueous layer which increases their effective MW. Moreover, phosphate transport is influenced by active transmembrane transporters.

- *The effective surface area and permeability of the PM.* The PM is a dynamic dialysis membrane [11], and it is the functional and not the anatomic peritoneal surface area that is important in peritoneal exchange. The peritoneal vascular exchange surface area is determined by the peritoneal vascular mesenteric perfusion and the density of the functional pores of the perfused capillaries available for dialytic exchange [22, 23]. This area can be estimated by means of the so-called three-pore permeability model [24]. According to this model, the peritoneum is characterized as a heteroporous three-pore membrane with few (~1–2%) water-exclusive ultrasmall pores (aquaporins, radius 2–4 Å), a small percentage (~5%) of large pores (radius 200–300 Å), and a majority (~90–95%) of small pores (radius 40–60 Å). Hydrophilic small solute transport occurs primarily by diffusion across the small pores, while the movement of proteins and other macromolecules occurs across the large pores and is driven by hydrostatic forces. Fluid transport can occur across all three pathways and is determined by crystalloid and colloid osmotic pressures. The total membrane pore area that is engaged in exchanges is dynamically affected by different factors; for example, fill volume (with a progressive increase in functional PM area recruitment taking place until the fill volume approximates 1400 mL/m^2 body surface area in children 2 years of age and older), patient posture (with positive recruitment occurring in the supine position), and PD fluid composition [25–28]. The impact of dialysate volume is felt to rest on the principle of geometry of diffusion [29], which simply states that the larger the dialysate exchange volume, the longer the transperitoneal concentration gradient will persist to drive diffusion. The permeability of the tissue between the capillary lumen and the peritoneal space can be altered by illness – increasing during acute peritonitis or progressively decreasing with peritoneal fibrosis.
- *Residual peritoneal volume from previous exchanges.* The concentration gradient and hence diffusive transport are also impacted by the presence of a residual peritoneal volume from previous exchanges. Small solutes in the residual fluid will likely have equilibrated with serum; this will lead to a time "zero" solute concentration that is much greater than zero, despite the fact that the instilled dialysate concentration of a solute was zero. This will impact fluid flux and solute transport. Residual peritoneal volume can be substantial and of clinical relevance in children [30].

Ultrafiltration

UF is the bulk movement of water along with permeable solutes across the PM. In the PD system, the driving force for UF is primarily represented by the osmotic pressure, which can be the result of either crystalloid (i.e., generated by diffusible solutes such as glucose in the dialysis fluid) or colloid (i.e., generated by nondiffusible solutes such as icodextrin in the dialysis fluid and albumin in plasma). The effects of the hydrostatic pressure gradient resulting from the difference between intravascular pressure and intraperitoneal pressure (IPP) are usually of minor importance in PD unless exceedingly high levels of IPP are reached [31]. Other factors that can affect UF are membrane surface area and hydraulic permeability. The flux of water (J_F) across the membrane can be expressed by the following equation [32]:

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

where K_f is the peritoneal membrane permeability coefficient, P_c is the hydraulic pressure in the capillary, s_f is the osmotic pressure of the peritoneal fluid, p_c is the oncotic pressure in the capillary, and P_f is the hydraulic pressure of the fluid under flux.

In the course of the PD dwell, fluid is lost from the peritoneal cavity both directly into the surrounding tissues and via lymphatic vessels and capillaries. Net UF results from the balance between osmotic UF and peritoneal fluid absorption. High peritoneal fluid absorption can be clinically important in some patients in whom net UF can be substantially reduced and the absorption

of macromolecules into the lymphatics increased. Lymphatic absorption has been estimated to account for 20% of net fluid absorption from a PD exchange [33]. Fluid is believed to move primarily into interstices in the peritoneal cavity and to be driven by intraperitoneal hydraulic pressure [34]. The limited data on lymphatic absorption in children are conflicting [33, 35].

The peritoneal fluid absorption rate can be determined when a PD exchange is modeled using the three-pore model. In one pediatric study, the absorption rate increased with body size in absolute terms but decreased when normalized to body size. The decrease was slight when scaled to body surface area (BSA) but marked when scaled to body weight (BW) [36].

Glucose is the most frequently used osmotic agent in standard PD solutions. It exerts its crystalloid osmotic effect through aquaporins, and its absorption from the dialysate to the plasma leads to a time-dependent dissipation of the osmotic gradient. In some patients, the rate of glucose absorption makes glucose unsuitable for maintenance of UF during a long dwell [37]. Conversely, PD solutions containing a polymer of glucose with an average MW of 16,200 Dalton (Icodextrin® Baxter, Deerfield, IL) exert a more sustained colloid osmotic effect through the small pores and have been shown to maintain UF over a prolonged exchange dwell time [38–40].

Convective Mass Transfer

Convective mass transfer occurs when water moves from capillaries to peritoneal cavity down a pressure gradient, "dragging" dissolved molecules along with it ("solvent drag"). The convective transport of a solute depends on the amount of fluid removed by UF and on membrane permeability. Permeability of a membrane to a given solute can be expressed by the sieving coefficient and calculated by dividing the concentration of solute in the ultrafiltrate by its concentration in plasma water (in the absence of a concentration gradient). The sieving of sodium reflects aquaporin function and thus free water transport [41]. During PD exchanges, the contribution of convection to solute removal is limited for small molecules but significant for high-MW compounds such as the "middle molecular weight" uremic toxins [42, 43].

Peritoneal Membrane Function Tests

Peritoneal solute and fluid transport may vary considerably from patient to patient and in the same patient during different phases of PD treatment, as a consequence of the recurrence and/or severity of peritonitis episodes, or of the exposure of the PM to PD solutions and materials. Moreover, inherited genetic variants could affect the transport capacity of the PM through the regulation of specific mediators [44]. Therefore, PM transport characteristics should be assessed at the beginning of chronic PD (usually, 1 month after the start of dialysis treatment) and then monitored two to four times per year. Additional monitoring may be required in case of recurrent or particularly severe peritonitis episodes or following other clinical events that may cause changes in PM transport capacity [42, 45]. In this way, intraindividual changes in the functional status of PM can be detected, and adjustments in PD prescription can be made.

PM function tests represent the first step in the process of tailoring the PD prescription to individual patient needs and characteristics. The application of these tests to the pediatric patient population has long been hampered by a lack of standardization of dialysis mechanics during the test. Appropriate scaling for body size plays a central role in this standardization and for the calculation of PM function parameters. While in infants the peritoneal surface area per unit BW is twice that of adults, the relationship between BSA and PM surface area is constant and age independent. In early pediatric transport studies, standardization of exchange volumes by BW contributed to the false perception of differences in peritoneal permeability between children and adults, with an enhanced transport function in the youngest patients. Further analysis revealed that the apparent enhanced solute transfer in children

was due to faster solute concentration equilibration with blood associated with the use of relatively small dwell volumes scaled on BW [46]. On the contrary, scaling the exchange volume by BSA maintains the relationship between dialysate volume and PM surface area across populations and makes comparison of peritoneal transport properties between patients of different body sizes possible [47, 48]. BSA can be calculated by means of mathematical formulas from the patient's weight and height (see Section "Monitoring PD Adequacy in the Clinical Setting"). An exchange volume of 1100 mL/m^2 BSA approximates the standard 2000 mL exchange volume applied to adult patients.

Mass Transfer Area Coefficient

Diffusive permeability of the PM can be expressed by means of the mass transfer area coefficient (MTAC), which describes the maximal clearance theoretically achievable at a constantly maximal gradient for diffusion, that is, when dialysate solute concentration is zero. MTAC is independent of dialysate glucose concentration. Determination of MTAC helps to model both long and short PD dwells and to individualize the dialysis prescription and can be performed with the help of computer technology that gives reliable results in pediatric patients. Comparison of MTAC values obtained in patients of different age and body size is possible when exchange volume has been standardized to BSA [30, 49]. A small but significantly greater solute transport capacity has been reported in infants, as a consequence of higher peritoneal permeability or larger effective surface area of the PM [30].

Peritoneal Equilibration Test

The peritoneal equilibration test (PET) remains the most widely employed means of characterizing PM transport capacity in adult and pediatric patients [30, 45, 50, 51]. The PET measures the rate at which solutes, usually creatinine (Cr), urea, and glucose, come to equilibration between the blood and the dialysate. PET results provide the clinician with data to adapt the dwell time to the individual PM function characteristics and provide the opportunity to evaluate prescription changes over time during the PD treatment. To reach a satisfactory level of reproducibility of PET results, a standard PET in children can be performed with a dwell volume of 1100 mL/m^2 BSA using a 2.5% dextrose PD solution. In pediatric patients, comparable results have been obtained by using 2.5% dextrose [30] or 2.27% anhydrous glucose PD solutions. Dialysate-to-plasma (D/P) ratios of Cr and urea and dialysate glucose concentration to initial dialysate glucose concentration at time 0 (D/D$_0$) are calculated at 2 and 4 h of the test. A blood sample is obtained at time 2 h. If dialysate Cr concentration is determined colorimetrically (and not enzymatically), it must be corrected for the interference of the high glucose levels in the dialysate by the formula:

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

The correction factor should be determined in the laboratory of each dialysis center, by dividing measured Cr of a fresh, unused PD solution by the measured glucose concentration. Small solute concentrations in plasma should be expressed per volume of plasma water (aqueous concentration) instead of per volume of whole plasma by dividing solute concentrations measured in whole plasma by 0.90 [52].

PET can be also performed by using a 4.25% dextrose or 3.86% anhydrous glucose PD solution to obtain more accurate information on UF capacity and assess sodium sieving, or the maximum dip in dialysate over plasma sodium concentration, which typically occurs during the initial 30–90 min of the dwell [53, 54]. In this way, free water transport capacity through the aquaporins can be evaluated, and UF failure can be more easily detected [11].

Cr and urea D/P ratios and dialysate glucose D/D$_0$ calculated at 2 and 4 h of the PET can be compared to the results from a large pediatric

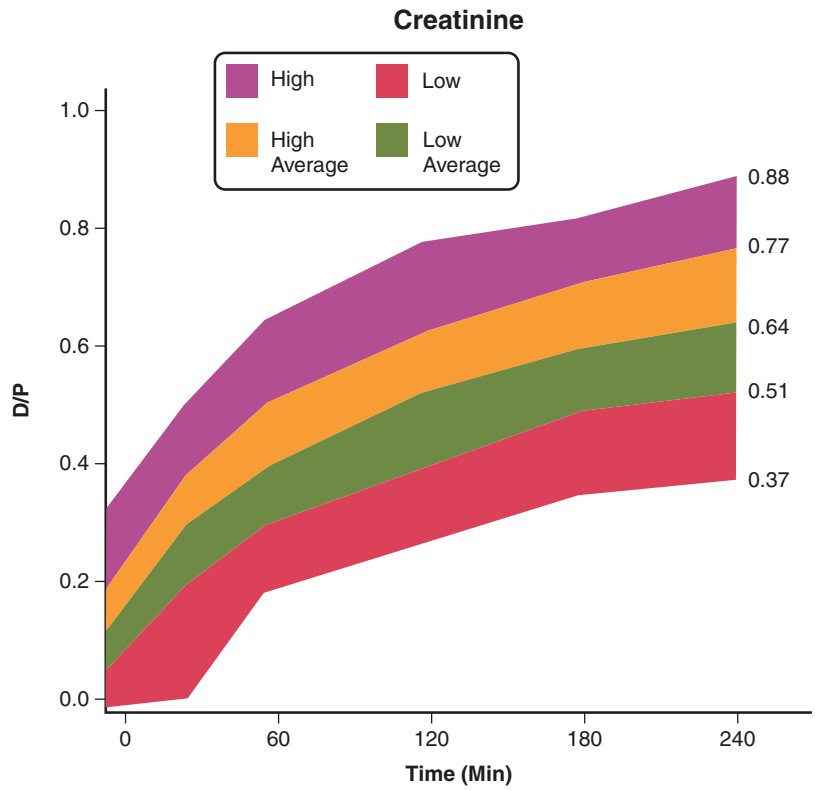

Fig. 13.1 Peritoneal equilibration test results for creatinine. *Colored* areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population. (Modified from Ref. [30])

study in which the same PET procedure was adopted (Figs. 13.1 and 13.2) [30]. Thus, patients will be characterized as having a high, high average, low average, or low solute transport capacity (Table 13.1). Similarly to what is reported in adult patients, the high transporter status may be associated with poor treatment outcome and has been identified as a significant risk factor for inadequate weight control, poor statural growth [55], and low-turnover bone disease [56]. Studies comparing PET parameters obtained with PD solutions of different osmolality did not show any effect of the dialysate glucose concentration on the D/P creatinine or the categorization into a transport group [53, 54]. Conversely, the preceding dwell composition and duration can influence small solute transport and net UF significantly. Higher D/P creatinine ratio was reported after a long dwell with icodextrin compared with a dwell with 2.27% glucose, even when a rinsing procedure with glucose was performed before the PET [11, 54]. Therefore, the same PD solution should be used for the PET and for the dwell of the preceding night.

Warady and Jennings reported that the PET results obtained at 2 and 4 h, based on either creatinine or glucose transport in 20 children who had been on PD for a period of 7 months or less, provided identical characterization of PM transport capacity for the same solute [57]. The authors proposed the use in pediatric patients of a simplified, 2-h PET procedure, the so-called short PET, as already described in adult patients [58]. Since the short PET is more convenient for patients, families, and nursing staff and is associated with cost savings, the adoption of this procedure may help in performing the evaluation of PM transport characteristics on a more routine basis among pediatric PD centers [59, 60].

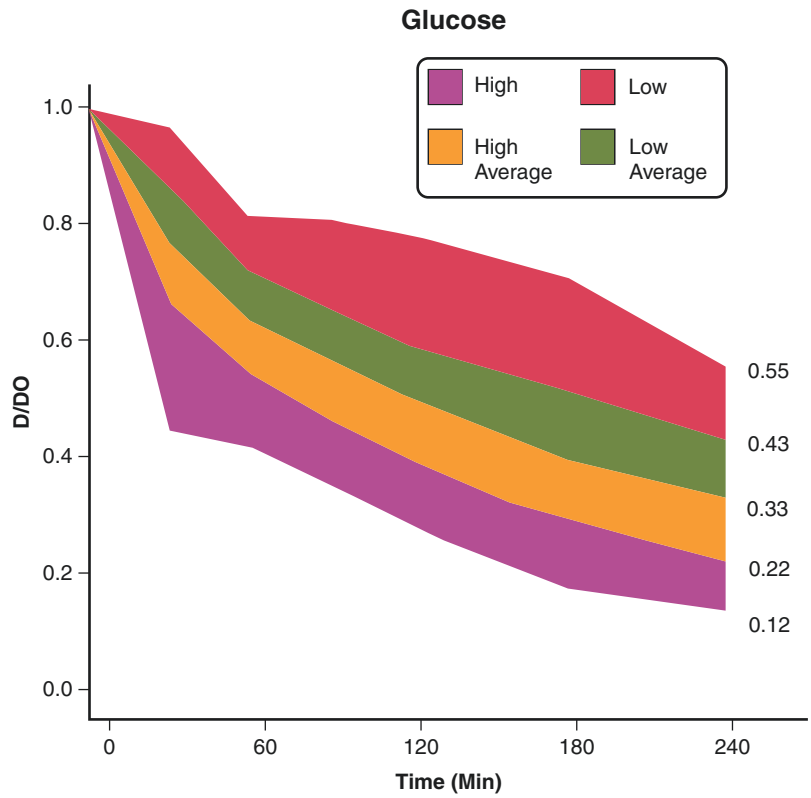

Fig. 13.2 Peritoneal equilibration test results for glucose. Colored areas represent high, high-average, low-average, and low peritoneal transport rate categories for the reference pediatric population. (Modified from Ref. [30])

Table 13.1 Classification of peritoneal transport capacity according to the results of urea and creatinine dialysate-to-plasma ratio (D/P) and of dialysate glucose/initial dialysate glucose concentration ratio (D/D_0) at 4 h dwell of a peritoneal equilibration test performed with 1100 mL/m^2 body surface area of a 2.5% dextrose dialysis solution [30]

Category of peritoneal transport	D/P urea	D/P creatinine	D/D_0 glucose
High	0.91–0.94	0.77–0.88	0.12–0.21
High average	0.82–0.90	0.64–0.76	0.22–0.32
Low average	0.74–0.81	0.51–0.63	0.33–0.42
Low	0.54–0.73	0.37–0.50	0.43–0.55

The four categories of peritoneal transport are bordered by the maximal, mean +1 standard deviation (SD), mean, mean −1 SD, and minimal values for the study population of pediatric patients (Data adapted from Ref. [30], used with permission)

Standard Permeability Analysis

Standard permeability analysis (SPA) and the PD capacity test (see below) are two other PM function tests that have given reliable results in adult and pediatric patients but are less frequently employed than the PET in the clinical setting and are mainly performed for research purposes. SPA can be considered an adaptation of PET, where polydisperse dextran-70 is added to the PD solution in order to obtain the simultaneous measurement of transcapillary UF, the marker's clearance rate (to assess lymphatic reabsorption), and intraperitoneal volume (IPV) [61, 62].

Personal Dialysis Capacity Test

The personal dialysis capacity (PDC) test [24] is based on the three-pore model of solute and fluid transport across the peritoneum. The PDC test describes the PM transport characteristics by functional parameters, which are calculated from data obtained from several exchanges of different duration and performed with PD solutions of different glucose concentration over a day. The PDC protocol includes five exchanges to be performed in 24 h using different dwell times and

two glucose solutions for patients on CAPD; a simplified protocol for patients on APD is also available [36]. The effective peritoneal surface area, final rate of fluid reabsorption, and large pore flow are calculated in this model [63]. The PDC test has been successfully employed in children to model individual PM function [36]. In one pediatric study, D/P or D/D_0 ratios derived from PET analysis were used to estimate effective peritoneal surface area by using a specific computer program [25].

Prescription of Peritoneal Fill Volume

As previously described, scaling IPV by patient BSA has become a standard in pediatric PD prescription and allows an accurate assessment of membrane transport capacity [23, 42, 45]. IPV and patient posture dynamically affect the recruitment of effective PM area available for PD exchange, which corresponds to the unrestricted pore area over diffusion distance as determined using the three-pore model [24, 25]. Raising IPV from 800 to 1400 mL/m^2 BSA leads to maximization of peritoneal vascular surface area [25]. On the other hand, a too large IPV may cause patient discomfort, pain, dyspnea, hydrothorax, hernia, emesis, gastroesophageal reflux, and loss of UF due to increased lymphatic drainage. These complications may lead to reduced patient compliance to the PD regimen prescription and are primarily related to an elevated IPP [11]. Hydrostatic IPP is a reproducible patient-characteristic parameter, and its measurement helps evaluate fill volume tolerance in the individual patient [31]. In the supine position, a fill volume leading to an IPP of 14 cm H_2O in children above 2 years of age, and of 8–10 cm H_2O in infants, is considered the maximum tolerable IPV, above which abdominal pain and a decrease in respiratory vital capacity may occur, and a higher risk of hernia and leakage is reported [23]. Increasing IPV above this peak volume can result in reduced PD efficiency. An IPV of 1400 mL/m^2 BSA seems to be suitable to ensure optimal recruitment of vascular pore area in children; however, this should be considered as a maximal limit, the safety of which has not been validated in children. In infants, the target fill volume is generally 600–800 mL/m^2 BSA until 2 years of age [45, 64]. In many cases fill volume prescription is based more on individual patient's tolerance than on a theoretically optimal exchange volume [11].

In clinical practice, peritoneal fill volume can be increased in steps toward the maximum limit of 1400 mL/m^2 BSA (or 800 mL/m^{2}BSA in infants) for a night exchange, while the patient is lying down, according to clinical tolerance and IPP measurement, in order to ensure as high recruitment of vascular pore area as possible and achieve adequate solute removal and UF [23]. Bedside measurement of IPP, i.e., of an objective parameter of abdominal filling, can be performed following the procedure described by Fischbach et al. [31]. Measured IPP levels can be compared with age-dependent normal values in children above 2 years of age [65].

Prescription of Dwell Time

Dwell duration is an important determinant of PD efficacy and should always be determined according to the individual patient's transport status [23, 42, 45]. Short exchanges lead to satisfactory clearance of small solutes (like urea) and UF, which can be further enhanced by increasing dialysate glucose concentration. High transporter patients benefit from short exchanges, due to the dissipation of the osmotic gradient by fast glucose absorption. Infants usually require shorter dialysis cycles than do older children to maintain the osmotic gradient and achieve adequate fluid removal. Long exchanges favor the removal of solute of relatively higher MW, such as Cr and phosphate. Phosphate clearance is clinically important owing to the contribution of hyperphosphatemia to metabolic bone disease and cardiovascular morbidity. It should be considered that while performing a PET, the time needed to obtain a D/P for phosphate of 0.50–0.60 is three to four times longer than it is for urea [11, 31, 66]. On the other hand, a long dwell time exchange can be associated with the risk of

impaired UF or dialysate reabsorption while using glucose-based solutions. An icodextrin-based solution is more appropriate for such long dwells (see also Chap. 14) [67].

A potentially useful way to individualize dwell duration in pediatric patients on APD according to peritoneal transport capacity is the calculation of the so-called APEX time. While performing a PET, APEX time corresponds to the point at which D/P urea and D/D_0 glucose equilibration curves cross and should represent the optimal length of APD cycles.

The abovementioned prescription principles should be applied to the delivery of different PD regimens, which will be described in the following section.

Peritoneal Dialysis Methods and Regimens

Chronic PD can be performed either manually (CAPD = continuous ambulatory PD) or utilizing an automatic dispenser of PD solution, commonly called a "cycler" (APD = automated PD). The PD regimen can be continuous, with dialysis solution present in the peritoneal cavity evenly throughout 24 h, or intermittent, with an empty abdomen for part of the day, usually during daytime (Fig. 13.3). Continuous regimens allow complete equilibration of small solutes as well as removal of middle-sized molecules. The presence of a large volume of dialysate in the abdomen during the day can be associated with patient discomfort, the occurrence of abdominal hernias (especially in infants and young children), and problems of body image (especially in adolescents). Moreover, continuous absorption of glucose from the dialysate compromises appetite and aggravates uremic dyslipidemia.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD represents a continuous regimen of manual PD in which dialysis solution is present in the peritoneal cavity continuously, 7 days per week (Fig. 13.3). The short interruptions at the time of the 3–5 daily exchanges do not disqualify the regimen as continuous if they do not exceed 10% of total dialysis time [68].

In the CAPD exchange, a double-bag PD solution container with a Y-set disconnect system is currently employed. CAPD solution, as well as the solutions for any other form of PD, is usually warmed to body temperature prior to inflow, to avoid uncomfortable lowering of the body temperature and shivering. Drainage of spent dialysate and inflow of fresh dialysis solution are performed manually, relying on gravity to move fluid into and out of the abdomen. CAPD products fulfill the requirements of ease of use and a simple interface that should be characteristic of a home-based, self-care treatment. CAPD has the undoubted advantage of a limited cost of the equipment.

As described, the prescription of the fill volume per exchange should be scaled for BSA rather than BW. According to the guidelines of the European Committee on adequacy of the pediatric PD prescription [42], the initial fill volume can be 600–800 mL/m^2 during the day and 800–1000 mL/m^2 overnight. If an increase in the dialysis dose is indicated, the fill volume can be gradually increased according to patient tolerance and to IPP measurements [31]. When there is inadequate UF overnight due to rapid glucose absorption, an icodextrin-based PD solution can be employed for the prolonged nighttime exchange.

CAPD is usually effective in patients who still have RRF, while it may provide inadequate solute and fluid removal in children with poor RRF and in infants when their high nutritional requirements are achieved by liquid formula [69]. In all CAPD patients, RRF should be closely monitored, together with the UF capacity and the patient's dry BW. Patients with a low-average or high-average peritoneal transport status as per the PET [30] can be maintained on CAPD, with close monitoring of the dialysis adequacy indices. A limitation of CAPD is that in order to further enhance the delivered dialysis dose there is no other means than increasing the number of exchanges. If increasing the number of exchanges

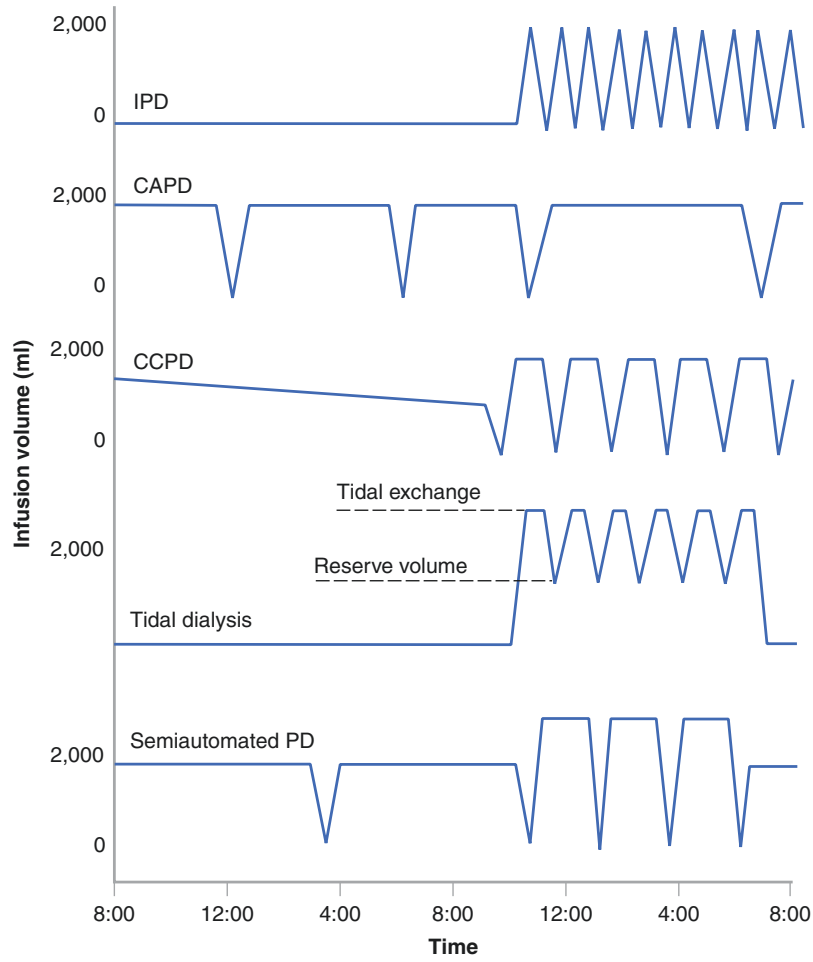

Fig. 13.3 Schematic representation of various peritoneal dialysis (PD) regimens based on a standard fill volume of 2000 mL of dialysis fluid. *IPD* nightly intermittent PD, *CAPD* continuous ambulatory PD, *CCPD* continuous cyclic PD

to obtain adequate UF and solute removal represents an excessive burden upon the patient and the family, a shift of the patient to an APD modality should be considered.

Automated Peritoneal Dialysis (APD)

APD represents the PD modality of choice for children and has largely replaced CAPD in the treatment of this category of patients, at least in those countries where its use is not limited by cost constraints [70–73]. Financial and technical problems still represent a limitation to the use of APD for many units in developing countries. The preference for APD as the dialytic modality of choice for children with ESRD has largely been a lifestyle choice; indeed, nighttime APD treatment enables children to attend school full-time and reduces the impact of dialysis treatment on the way of life of the patients and of their families [74]. Therefore, APD can ensure a higher level of psychological and social rehabilitation of children with ESRD when compared to other forms of chronic dialysis. The option of an empty abdomen during the day, or a half-volume daytime dwell, has the potential to reduce the interference with nutritional intake and minimize the incidence of abdominal hernias. At the same time, performing the nighttime exchanges in the lying position allows the use of larger fill volumes. Sequential measurements of IPP in children showed that in the supine position, an IPV up to 1400 mL/m^2 BSA was not associated with an unsafe increase of IPP. However, such a high fill volume is infrequently prescribed, due to prob-

lems of patient tolerance [75, 76]. Increasing the nocturnal fill volume allows more effective contact between dialysate and the PM, with the recruitment of a larger functional peritoneal surface area (i.e., the area available for the diffusive transport of solutes) and a higher permeability × surface area product, frequently referred to as solute diffusive transport coefficient (KoA) [77]. In addition, the small solute KoA has been reported to be higher in the supine position than during the ambulatory upright position. Another important reason for using APD in pediatric patients is that with the range of treatment options which are available through this modality, the dialytic prescription can be tailored to the individual patient's age, body size, clinical condition, growth-related metabolic needs, and PM transport status. APD is the preferred PD modality also in the treatment of infants: 71% and 85% of infants initiating chronic PD in Europe (between 1991 and 2013) and in the United States (between 1990 and 2014), respectively, started on APD [78, 79]. The flexibility of exchange frequency provided by the cycler allows frequent exchanges with short dwell times in anuric infants who require high ultrafiltration rates, or longer dwell times in infants with polyuric renal failure [11, 64].

Mathematical modeling software programs have been developed to calculate kinetic parameters to mathematically simulate the results of the APD regimens and to rapidly find the best personalized dialysis schedule, thus avoiding long trials for the patient [80]. Such programs are based on specific kinetic models and the individual patient's peritoneal function test. Two of these software programs have been validated and applied to pediatric patients [36, 49, 81]. Both of these software programs have a user-friendly interface, a mathematical model describing the PD system, and a specific individual peritoneal function test as data entry. The accuracy of these mathematical models in predicting the results of different APD schedules is greater for solute removal than for UF, owing to inability of kinetic modeling to account for changes in residual dialysate volume, the marked variability of UF in different exchanges and on different days, even in the same patient, the large variability of daily fluid intake, and the confounding effects of residual diuresis in non-anuric patients [82, 83]. A certain amount of error is almost always a component of modeling biologic systems as well; moreover, since mathematical modeling refers to perfect and virtually uneventful APD sessions (no alarms, no delay in the drain and fill phases), the simulations may at times be too "optimistic." However, computer-assisted kinetic models can be regarded as useful tools for the calculation and normalization of kinetic indices and for mathematical simulation of the various APD regimens. They can help determine the optimal dose of dialysis for each patient, but in the individual patient, direct measurement of solute clearances and UF remains necessary.

Finally, the choice of the proper APD regimen through which the individual dialytic prescription could best be accomplished is currently based not only on patient clinical and metabolic conditions and peritoneal transport but also on lifestyle considerations.

A description of the main characteristics of the various APD regimens will follow.

Nightly Intermittent Peritoneal Dialysis (NIPD)

NIPD is an intermittent PD modality consisting of a number of short nocturnal cycles performed every night by an automated cycling machine in the patient's home, without a daytime dialysate dwell (Fig. 13.3). The presence of a dry peritoneal cavity during the day is the crucial feature distinguishing NIPD from other models of APD. The reasons why children with ESRD represent a patient group that may likely benefit most from a "dry" day have been already discussed and are summarized in Table 13.2. The reduced exposure of the PM to glucose and glucose degradation products, together with the reduced deposition of advanced glycosylation end products (AGE), has been reported to be beneficial for long-term PM preservation [84]. The prescription of a small fill volume during the daytime is frequently adopted in an attempt to lessen

Table 13.2 Advantages and limitations of nightly intermittent peritoneal dialysis

Advantages	Limitations
No glucose absorption during the daytime	Not recommended in patients with poor residual renal function
Daytime normal intraperitoneal pressure	Inadequate small solute clearance in patients with low and low-average transport
Preservation of body image (for adolescents mainly)	Inadequate middle-sized molecule clearance
Reduced loss of proteins and amino acids Better preservation of the peritoneal membrane integrity	No flush of the catheter and lines at the start of the night session (increased risk of infection)

the risk of peritoneal infection due to touch contamination through the preventive effect of a "drain before fill" phase with the flush of the peritoneal catheter and of the lines at the start of the night APD session [85].

The major limitation of NIPD may be that the absence of a daytime dwell reduces solute clearance compared to continuous PD modalities; the negative impact on the clearance of middle molecules is even more pronounced. The evaluation of peritoneal transport status is mandatory while selecting patients for NIPD. NIPD is primarily indicated in patients characterized by a high transport PM, who show rapid equilibration of solute concentrations and adequate UF only with rapid exchanges and/or patients with significant RRF. NIPD may be not suitable for children with low and low-average peritoneal transport or for anuric patients. This frequently represents the initial mode of PD employed in children with RRF [42]. A typical initial prescription can be formulated as follows:

- Nine to 12 hours of total treatment time.
- A fill volume of 800–1000 mL/m^2 exchanged five to ten times (young infants frequently require more cycles); an exchange dwell time of approximately 1 h represents a typical choice for the initial APD prescription in pediatric patients [11].
- Dialysis solution should contain 1.36% (1.5% dextrose) glucose or higher concentrations depending upon UF requirements. Solutions with different concentrations can be mixed by the cycler to titrate tonicity of the infused solution according to the patient's individual needs.

In the course of treatment, the NIPD regimen can evolve according to clearance and UF requirements, which are mainly dictated by the decline of urine volume. In particular, the importance of the control of fluid balance on patient outcome should be emphasized [83, 86, 87]. An increase of the efficiency of NIPD can be obtained by:

- Maximizing the dwell volume, according to patient tolerance and IPP limits [23, 25, 31].
- Increasing the number of exchanges in patients with high and high-average PM transport capacity. This should be done up to a point, beyond which clearance and UF decrease since the non-dialytic time, corresponding to the fill and drain phases, becomes more important than the benefit of further increasing dialysate volume.
- Increasing the total treatment time, as the patient's compliance and social life allow. The number of exchanges can be kept constant in patients with low and low-average PM transport capacity.
- Increasing dialysate tonicity in order to enhance UF rate. Since solutions from dialysate bags are proportionally mixed by the cycler (provided they are positioned at the same level), the tonicity of the dialysate can be titrated by choosing different tonicity for the various bags; the most common glucose concentrations used are 1.5%, 2% (obtained from equal mixing of the other two concentrations), and 2.5% [86].

If a sufficient increase of solute and water removal is not achieved with these adjustments of the NIPD schedule, the patient may be at risk for inadequate treatment and would benefit from consideration of a different APD regimen.

Continuous Cyclic Peritoneal Dialysis (CCPD)

CCPD, just like CAPD, represents a continuous regimen of PD (Fig. 13.3). In the morning, at the end of the overnight PD session, the patient disconnects from the cycler, leaving in the abdomen a fresh exchange of dialysis solution, ranging in volume from 50% (more frequently in children) to 100% of the night fill volume. In the classic form of CCPD, this daytime exchange is drained at bedtime when the cycler is reconnected, so that patient involvement is reduced, as with NIPD, to one session for preparation of the equipment and solutions and a very short period for disconnection. The long daytime dwell makes a very significant contribution to solute removal and to UF; moreover, clearance of middle-sized uremic toxins that is poorly influenced by short cycles of APD with high-flow regimens is much more dependent on total dialysis time and favorably influenced by prolonged exchanges [88]. Since complete saturation of the dialysate with small solutes over a long dwell exchange is often achieved, daytime clearance is also dependent on the net UF (convective transport), that in turn can be influenced by the choice of the osmotic agent, the fill volume (which results in various IPPs), and the membrane transport status[1] [89].

A continuous PD regimen is recommended when RRF has become negligible and/or the desired targets of solute and fluid removal cannot be achieved any longer by a NIPD regimen. Consideration of PM transport characteristics is also important for the choice of the optimal schedule of CCPD [90, 91]. Patients with high-average transport rates often do best on CCPD (Table 13.1).

During a long daytime dwell, glucose is largely absorbed, while a sustained net UF can be achieved with the use of the icodextrin-based PD solution (ICO). Available data on the use of this alternative osmotic agent in pediatric patients show that over a 12–14-h dwell, net UF obtained with ICO is similar to that obtained with a 3.86% (4.25% dextrose) glucose solution, and significantly greater than that reached with a 1.36% (1.5% dextrose) glucose solution both in adult and pediatric patients [92, 93]. The evaluation of the intraperitoneal volume-to-time curve during a 14-h dwell with icodextrin solution in children showed a gradual increase in net UF [38]. From the results of the mathematical modeling of the UF profile obtained with icodextrin solution, and based on the kinetic parameters of 396 adult patients, no separation between the PET transport categories was found [94]. By comparing the results of two 4-h PETs, performed in nine pediatric patients using 3.86% (4.25%) glucose and 7.5% icodextrin as a test solution, Rusthoven et al. [40] found that the two solutions had different effects on the change in IPP. During the PET performed with a 3.86% (4.25%) glucose solution, the increase in IPP was positively correlated with transcapillary UF and inversely correlated with patients' BSA; conversely, while by using an icodextrin solution, IPP demonstrated minimal rise during the 4-h dwell, and no correlation was found with fluid kinetics or patient BSA.

If a further increase in solute clearance is required, and/or net UF is still insufficient for a patient's clinical needs, as is often seen in patients with a low-average transport status treated with CCPD, more than one diurnal exchange can be used. With this optimized APD schedule (continuous optimal peritoneal dialysis, COPD), an exchange of the dialysate is performed at midday or after school, using the cycler in a disconnectable manner (Fig. 13.3), and the length of each dwell is optimized according to the patient's peritoneal transport rate and the type of osmotic agent employed [42, 88]. This modality requires more patient participation but allows the patient to achieve small solute dialysate-to-plasma equilibration during both of the two daytime exchanges.

[1]It should be noted that reliance on membrane transport assessments based on mass transfer of urea or creatinine ignores the difficulty and importance of phosphate clearance. Phosphate PD clearance is usually insufficient to obtain a satisfactory control of hyperphosphatemia, and there is a continued need for dietary restriction and phosphate binder administration. Phosphate removal by PD can be improved by increasing dwell time [89] and by optimizing exchange duration through the calculation of the so-called phosphate purification dwell time (PPT) from a PET [66].

Tidal Peritoneal Dialysis (TPD)

TPD is an automated PD technique in which an initial infusion of solution into the peritoneal cavity is followed, after a usually short dwell time, by drainage of only a portion of the dialysate, leaving an intra-abdominal reserve volume (Fig. 13.3). The tidal drain volume is replaced with fresh dialysis fluid to restore the initial IPV with each cycle. At the end of the dialysis session (sometimes also once in the middle of the session), the whole dialysate volume is drained. The amount of ultrafiltrate expected to be generated during each cycle must be estimated and added to the drain volume. Otherwise, the intra-abdominal volume will become progressively larger, thus affecting the efficiency of dialysis and the patient's comfort.

TPD can be performed for the following indications:

- Increasing clearances as a result of the continuous contact between dialysate and PM, with a sustained diffusion of solutes
- Improving the efficiency of the dialysis technique by reducing inflow and outflow dead times (during which the peritoneal cavity is almost empty), particularly at high dialysate flow rates
- Avoiding repeated cycler alarms of low flow rate due to peritoneal catheter malfunction
- Reducing pain during the last part of the drain cycle

The major determinants of TPD efficiency are the total volume of delivered PD fluid and the individual peritoneal transport rate. Only high transport patients can reach adequate solute clearances with nightly performed TPD (NTPD), while high-average transport patients would benefit from one or more daytime dwells, thus undergoing continuous TPD (CTPD).

The results of studies on pediatric patients showed that TPD efficiency was equal to or higher than standard APD but required larger total session dialysate volumes [95, 96].

Optimization of TPD may be obtained by adapting the tidal volume to the individual drainage profile, thus reducing the fill and drain dead times to the minimum [97]. The peritoneal catheter drainage profile can be accurately evaluated by looking at the information on peritoneal fluid drainage during each cycle of an APD session recorded by the software of the new cyclers. Catheter drainage does not demonstrate a linear behavior, since a high flow rate is only maintained until a critical IPV is reached. After this critical point (also called the breakpoint), the flow rate drops, and the final part of the drainage can take more than twice the time of the previous segment. During this slow-flow portion of drainage, the peritoneal cavity is almost empty, and solute clearance is significantly reduced [76, 98]. Since the critical IPV is an individual characteristic, tailoring the tidal volume to the drainage profile of each patient reduces idle time, thus improving the overall efficiency of the system. This optimization would be particularly indicated in patients without an optimally functioning catheter.

Adapted APD

The need to combine adequate ultrafiltration and solute removal, especially in anuric children and infants with a mostly liquid diet, has led to the development of a new approach combining short dwells with a relatively small volume of PD fluid to maximize UF with long dwells using a larger fill volume to enhance solute removal [99]. This APD schedule is called adapted APD and is performed by means of new-generation cyclers that can deliver short exchanges with small fill volume in the first part of the APD session, followed by longer exchanges with larger fill volume. With the use of adapted APD, a significant increase of urea, creatinine, sodium, and phosphate removal combined with improved UF was obtained in a randomized, prospective crossover trial conducted in adult patients [99]. An additional crossover trial in adults and a pilot study in children suggest that sodium and fluid removal are increased by adapted APD, leading to improved blood pressure control when compared with conventional PD [100].

Such results were achieved applying the same total amount of glucose (and glucose exposure) and dialysate volume during the same total dialysis time (and treatment costs) than in the standard APD session. PET results and IPP measurement data can be used to define dwell time and fill volume, respectively [101].

Concluding Remarks

For each regimen of chronic PD delivered to pediatric patients with ESRD, the dialysis prescription should be adjusted and monitored following the guidelines of the European Pediatric Dialysis Working Group [42] and the 2006 update of the NKF-KDOQI clinical practice recommendations for pediatric PD adequacy [45]. In the absence of definitive results from large randomized controlled studies on the correlation between solute removal and clinical outcome in pediatric patients treated with PD, current clinical opinion supports the recommendation that the target delivered solute clearance should meet or exceed adult standards. In patients with RRF, the contribution of renal and peritoneal clearance can be added for practical reasons. Regular assessment of the prescribed PD schedule should be performed, taking into account not only targets of small solute depuration but all the parameters involved in the definition of adequacy of dialysis treatment in childhood, such as adequate growth, blood pressure control, and nutritional status; avoidance of hypovolemia and sodium depletion; and adequate psychomotor development [42, 45, 55]. These issues will be specifically addressed later in this chapter and elsewhere in this text.

Peritonitis in APD Patients

Some peculiar aspects of the diagnosis and management of peritonitis in APD patients deserve a brief discussion owing to the clinical relevance of this complication, which significantly affects PD treatment among pediatric patients. (For an in-depth discussion of this topic, please also see Chap. 16). A number of factors can make the diagnosis of peritonitis more difficult in APD than in CAPD: (1) peritoneal effluent is not readily available for inspection, owing to the use of a nontransparent effluent bag or effluent drained directly to a household outlet; (2) the shorter dwell times and the high volume and continuous flow of the dialysis fluid would result in lower white blood cell (WBC) number and less effluent cloudiness; and (3) the abdomen is frequently (although not necessarily) dry during the day. For these reasons, the presence of a cloudy effluent, which is an early sign of peritonitis, may be missed initially. Similarly, the dialysate WBC count may be lower than the value currently considered indicative of peritoneal infection. Moreover, short dwell times and a large dilution factor of the dialysate may increase the possibility of a false-negative culture [102]. In view of these issues, the use of a reactive test strip (Combur^2 Test® LN, Roche) which is sensitive to granulocyte peroxidase, can be helpful for the early diagnosis of peritonitis. In some centers, when a positive Strip-Test of the drained fluid from the daytime dwell or from the first APD cycle is observed, and no other signs and/or symptoms of peritonitis are present, the patient is instructed to obtain a fluid sample for culture and to program the cycler so as to leave an amount of dialysate equal to at least 50% of the night fill volume at the end of the night APD session and for at least a 4-h dwell. Then, a new sample for WBC count and culture is obtained from the effluent of this dwell, and laboratory diagnosis in the usual manner is conducted. When the positivity of the Strip-Test performed at the beginning of night APD session is associated with at least one other sign or symptom of peritonitis (such as abdominal pain or fever), an effluent sample is immediately obtained for culture, and an empiric regimen of intraperitoneal antibiotic therapy is started. In general, during peritonitis the daytime dwell that contains antibiotics should be a full exchange as long as antibiotic treatment is continued.

Evaluation of the Adequacy of Peritoneal Dialysis Treatment

Historically, the first studies on the correlation between the delivered dialysis dose and the adequacy of dialysis treatment were performed in hemodialysis patients and were mainly based on urea kinetic modeling. Therefore, the concept of "adequate" dialysis was initially adopted to define a minimum hemodialysis dose, below which a clinically unacceptable rate of negative outcomes might occur. The most frequently used outcome measures were represented by patient hospitalization, morbidity, and mortality. As a consequence, the influence of small solute clearance on the outcome of PD patients was a major focus of interest during the 1990s. The results of observational studies in adult patients treated with CAPD suggested that better patient survival and lower morbidity and mortality were associated with higher clearances of low-MW molecules, such as urea and creatinine [103, 104]. Small solute clearance was considered the key criterion of PD adequacy in the clinical practice guidelines developed in year 2000 by the Kidney Disease Outcomes Quality Initiative (KDOQI), which defined dialysis adequacy by certain minimum urea and creatinine clearance values [105]. In the following years, a reanalysis of the data from the original CANUSA study as well as the results of prospective randomized interventional trials did not demonstrate any clear advantage for patient survival by further increasing peritoneal small solute clearances beyond a minimal "adequate" level but showed that RRF is a much stronger predictor of survival than peritoneal clearance [106–108]. Failure of increased PD dose to significantly improve patient outcomes could be due to higher IPP associated with larger exchange volume, failure to increase clearance of middle molecules, and increased exposure of the PM to glucose-based dialysis fluids [109]. Moreover, some recommendations for higher clearance proved difficult to be fully applicable in clinical practice, especially among pediatric patients.

In children, even more than in adults, adequacy of PD treatment cannot be exclusively defined by targets of solute and fluid removal. Clinical assessment of adequacy of PD treatment should also take into consideration a comprehensive series of clinical, metabolic, and psychosocial aspects, the most important of which are listed in Table 13.3.

Table 13.3 Clinical, metabolic, and psychosocial aspects that should be taken into consideration in the assessment of the adequacy of chronic peritoneal dialysis treatment in pediatric patients

Hydration status
Nutritional status
Dietary intake of energy, proteins, salts, and trace elements
Electrolyte and acid-base balance
Calcium phosphate homeostasis
Control of anemia
Blood pressure control
Growth and mental development
Level of psychosocial rehabilitation

Clearance of Small Solutes

In the literature, there are no definitive outcome data indicating that any measure of dialysis adequacy is predictive of well-being, morbidity, or mortality in pediatric patients on chronic PD. Therefore, the 2006 KDOQI guidelines [45] simply stated that by clinical judgment the target delivered small solute clearance in children should meet or exceed adult standards.

A minimal delivered dose of small solute clearance should correspond to a Kt/V_{urea} of no less than 1.8 per week. Data from pediatric and adult studies found the serum albumin level to be a predictor of patient survival and a Kt/V_{urea} of 1.8 or greater in adult PD patients has been associated with better serum albumin values [45, 110]. This target should be intended as total clearance (i.e., the arithmetical sum of peritoneal clearance and renal clearance) or peritoneal clearance alone in patients without RRF (defined as a renal Kt/V_{urea} of less than 0.1 per week). Even if peritoneal clearance and renal clearance have a different impact on patient outcome [106–109], they can be added to determine total clearance in clinical practice. The term *delivered* refers to the

actual dose the patient is receiving based on direct measurement, not to an estimated value obtained by using a kinetic modeling program. Solute clearance should be measured within the first month after the start of chronic PD treatment and at least once in every 6 months thereafter in a clinically stable patient. More frequent measurements should be conducted when:

- Dialysis clearance may have been compromised (e.g., 1 month after the resolution of a peritonitis episode).
- There is a rapid loss of RRF.
- There is clinical evidence of inadequate dialysis.

In any case, if a patient is not doing well and no other cause of the worsening of his clinical conditions than kidney failure can be identified, a trial of increased dialysis dose is indicated [45].

The 2006 KDOQI guidelines [45] recommended the use of Kt/V_{urea} as a surrogate for adequate dialysis, at least in CAPD patients. Historically, both Kt/V_{urea} and creatinine clearance (CrCl) have been employed to evaluate PD clearance. It has been proposed that the ratio of these two parameters should be 1:30 [11, 42]. A discrepancy between urea and creatinine-based PD adequacy parameters has historically been reported in adults [111, 112] and in children [42].

In APD patients, for whom targets of CrCl have recently been published, the relationship between CrCl and Kt/V_{urea} is much more variable than in patients on CAPD [11, 113]. Indeed, urea clearance is mostly related to dialysate volume and number of exchanges, while CrCl is predominantly affected by the duration of the dwell time (i.e., the duration of contact of the peritoneum with dialysate, which is currently called "contact time") and by RRF. The finding of adequate values of Kt/V_{urea} associated with inadequate values of CrCl can be related to a hyperpermeable PM state, or a too low IPV, since both of these conditions are associated with a greater removal of urea than creatinine [11, 55, 113]. Finally, scaling of Kt/V_{urea} to BW and CrCl to body surface area may differently influence values obtained in the calculation of these parameters in infants and small children as a result of a higher ratio of BSA/weight [42]. The 2006 KDOQI recommendations stated that the determination of dialysis and urine Kt/V_{urea} alone for follow-up was preferred mainly due to the simplicity of its calculation and the observation that studies on adult PD patients have not provided evidence of a benefit in terms of patient outcome when expressing clearance in any manner other than Kt/V_{urea} [45, 112].

Since Kt/V_{urea} is scaled for urea distribution volume (V), which is assumed to equal total body water (TBW), accurate estimation of TBW is a critical component of dialysis dose measurement. The gold-standard isotope dilution technique to determine TBW is laborious, costly, and not widely available; therefore, anthropometric prediction equations based on height and weight are commonly used to estimate TBW. Equations derived from healthy children [114] systematically overestimate TBW in pediatric patients receiving PD. In this patient population, anthropometric TBW prediction equations have been developed and validated by comparison with the determination of TBW by means of a heavy water (H_2O^{18} or D_2O) dilution technique [115]. These formulae are based on an anthropometric parameter called *height times weight*, which correlates linearly with TBW when both values are log-transformed and are as follows:

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

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

Hyperphosphatemia and elevated calcium times phosphorus product are associated with calcifying large-vessel arteriopathy, which develops even in young patients with childhood-onset ESRD [116, 117]. Schmitt and coworkers [118] raised the issue whether dialytic phosphate removal might provide a more reliable direct measure of dialysis efficacy than urea and creatinine clearance. By studying peritoneal phosphate kinetics and daily dialytic and renal phosphate elimination in 35 pediatric patients receiving chronic APD, these authors found that the peritoneal transport state defined by the creatinine equilibration pattern is poorly predictive of daily

phosphate clearances; this finding suggests that a specific evaluation of the D/P phosphate ratio should be done to define an individual's phosphate transport category. The efficacy of phosphate elimination by means of a standard APD regimen is limited and independently predicted by total fluid turnover, the number of cycles, 2-hour D/P phosphate, dwell time, and achieved ultrafiltration [118].

In summary, numerical targets of small solute clearance, as defined by currently available guidelines, should be interpreted cautiously and in the context of patient clinical assessment. Neither K_t/V_{urea} nor CrCl are the perfect indices to predict outcome in PD patients; however, they provide complementary measurements of dialysis dose. Indeed, these targets should be included as a part of global patient care. Failure to achieve them should not be considered an indication to abandon PD if all other aspects of patient care are successfully addressed by PD treatment.

Clearance of Middle-Sized Molecules

Failure to achieve adequate clearance of the so-called middle-sized molecules (from 300 to 5000 daltons of MW) is one of the possible explanations for the failure of increased dialysis dose to improve patient survival [109]. Small solute and middle-sized molecule clearances respond differently to changes in the PD prescription, since the former is mainly determined by the frequency of exchanges and total volume of dialysate, while the latter depends more on the dialysate/PM contact time [119, 120]. The transport rate of middle-sized molecules is much slower than that of small solutes and more dependent on the convective component of transmembrane solute movement [121]. In practice, the removal of middle-sized molecules and low-MW proteins, such as β_2-microglobulin and leptin, mainly depends on RRF [122, 123]. Moreover, an increase in the restriction coefficient for macromolecules was reported in relation to time on chronic PD, which is associated with increased size selectivity and reduced peritoneal permeability for higher-MW solutes [62]. Hence, particular attention should be paid to middle molecule clearance, especially in children on NIPD and in all PD patients as RRF is declining. In these cases, a continuous PD regimen (CCPD or CAPD) should be adopted even if small solute clearance is above the target without the longer dwell [45]. Increased β_2-microglobulin and leptin clearance have been reported in patients receiving a long dwell with icodextrin solution [124].

Fluid Balance

Systematic adjustment of the PD prescription should be planned in order to achieve and maintain fluid balance and normal blood pressure. PD has been considered an optimal approach to reach this therapeutic result thanks to its continuous nature, which avoids fluctuations of the total body volume and offers better hemodynamic stability than intermittent therapies. Nevertheless, PD population surveys show a high prevalence of hypertension and cardiovascular mortality with inadequacy of UF as a significant predictor of mortality in anuric adult PD patients [87, 125]. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [126] showed that 57% of nearly 4000 pediatric patients on dialysis had blood pressure (BP) values higher than their age-, sex-, and height-specific 95th percentile; moreover, 20% of patients had blood pressure values at or above the 95th percentile while receiving antihypertensive medication. In Europe, systolic or diastolic BP higher than the 95th percentile was reported in 35.5% of 851 pediatric PD patients, irrespective of the use of antihypertensive medications [127]. As reported by the International Pediatric Peritoneal Dialysis Network (IPPN), 48% of 507 pediatric PD patients treated in 55 centers had echocardiographic evidence of left ventricular hypertrophy (LVH) [128]. Hypertension and cardiac impairment were most frequently found in the younger and nephrectomized PD patients [129]. Even if the cause of hypertension is multifactorial, volume overload is likely to play an important etiologic role in a relevant percentage

of patients on PD therapy [45, 130]. Chronic fluid overload represents an important clinical problem in pediatric PD patients, especially when RRF is decreasing.

Routine monitoring of volume status and daily UF volume, along with periodic assessment of residual urine output, are therefore essential in the process of attaining adequate fluid balance on PD [42, 45]. In the absence of validated, readily applicable indicators of volume status, the assessment of patient target weight mainly relies on clinical judgment and assessment of vital signs. In clinical practice, the desirable target weight of a patient on chronic PD can be reasonably approximated as that weight at which the patient is edema-free and has a blood pressure within the limits of the normal range for age and gender, with minimal need for antihypertensive medications. Since fluctuations in patient weight secondary to growth and to changes in nutritional status may occur, repeated evaluations of target weight at regular intervals are mandatory in all patients.

In order to increase the efficacy of the PD prescription to attain an adequate UF rate, a series of factors that can affect the maintenance of patient fluid balance should be considered, together with the related recommended interventions:

PM transport characteristics. PM transport characteristics affect net fluid removal at a given dwell time by determining the osmotic gradient time curve of each individual patient. As already mentioned, a modification of the standard PET utilizing 4.25% dextrose solution can be employed to better evaluate the UF kinetics and the maximum dip in D/P sodium, which reflects the sodium-free water transport [82, 83]. For instance, if the patient has a fast transport, as a result of either a large peritoneal surface area or a too low prescribed fill volume, improved UF will be obtained by increasing the fill volume as tolerated and/or by shortening the dwell time. In patients with decreased sodium-free water transport and no dip in D/P sodium after 1–2 h of the dwell, there will be no benefit from the use of a high dialysate glucose concentration; in these cases, a long exchange with an icodextrin PD fluid (daytime dwell on APD; nighttime dwell on CAPD) may enhance their UF capacity [11]. La Milia and colleagues [131] suggested calculation of the exact volume of free water transport by measuring the amount of sodium transported through the small pores over a 1-h dwell; since the total ultrafiltered volume is known, subtracting the small pore transport from the total transport will give the amount of water transported through the water channels. Smit and coworkers [132] added to this method the use of a volume marker, so that free water transport could be calculated at each time point. From both studies, the contribution of free water transport appeared to be about 40–50% in the first hour of an exchange performed with an hypertonic PD solution [132].

Peritoneal surface area available for the exchanges. An extremely limited vascular surface area might be the consequence of postinfectious or postsurgical adhesions, peritoneal fibrosis, or peritoneal sclerosis.

Dwell time and PD solution tonicity. These two parameters are interrelated and should be considered jointly. For instance, low dialysate dextrose concentration and prolonged dwell time will inevitably lead to inadequate fluid removal in high transport patients [83]. An increase of dextrose tonicity is associated with enhanced UF, but the osmotic gradient dissipates over time; therefore, adjusted concentration dextrose solutions are indicated for short dwells, while for the nighttime dwell in CAPD and the daytime dwell in APD, icodextrin solution may be more appropriate. A potentially useful rule of thumb to define the optimal dwell duration in children on APD according to peritoneal transport characteristics is the so-called APEX time during a PET. As already mentioned, this is the time point at which the D/P urea and the D/D_0 glucose equilibration curves cross. APD cycle length should be equivalent to the APEX time [66].

Lymphatic absorption. A high effective lymphatic absorption rate may be the conse-

quence of a marked elevation in IPP [133]. A reduction of the fill volume may help reverse the propensity for fluid reabsorption by decreasing IPP.

Mechanical complications. Low drained dialysate volumes can be the consequence of peritoneal catheter malfunction, leading to incomplete dialysate drainage, especially after prolonged dwells on CAPD and CCPD, or dialysate leakage through the catheter tunnel or from the peritoneal cavity to the pleural space.

Fluid and sodium intake. Dietary counseling on sodium and fluid restriction should take into account renal and/or dialysis-related sodium losses, since sodium depletion may result in hypotension and impaired growth, especially in infants. Compliance with dietary recommendations should be regularly assessed.

Residual diuresis. The use of loop diuretics can be considered with caution in children with RRF (see the following paragraph).

In summary, practical strategies to alter PD prescriptions with the aim of improving the UF rate can include:

- *During short dwells of APD*: Increase the number of cycles and/or overall treatment time and/or glucose concentration; however, every effort should be made to employ the lowest possible dextrose concentration required to achieve the desired UF rate.
- *During prolonged dwells*: Utilize icodextrin solution; if needed, replace single long exchange with two or more exchanges.

The Role of Residual Renal Function in Treatment Adequacy

Prospective randomized trials of dialysis adequacy and observational studies in adult patients confirmed that RRF is a much stronger predictor of patient survival than peritoneal clearance [106–108, 134, 135]. In pediatric populations, no data from large-scale trials on the correlation between RRF and patient outcome are currently available. However, a single-center observational study on pediatric PD patients [136] reported that growth velocity was higher in a group of children with RRF than in children without RRF, even if the same mean total solute clearance was achieved in the two groups. In a nationwide analysis on the incidence of arterial hypertension among children undergoing chronic dialysis in Poland [137], residual urine output was higher in normotensive patients. Furthermore, when reviewing cardiovascular risk in a group of 59 pediatric PD patients, residual diuresis was negatively correlated with diastolic dysfunction [138]. In the IPPN data, oliguria (diuresis <0.5 L/m2 BSA per day) was associated with LVH [128].

The rate of RRF decline in pediatric patients on PD was reported to be slower than in patients on HD, and high urine volume at start of chronic PD is predictive of sustained diuresis [139, 140]. It is still not clear if there is any difference in the rate of preservation of RRF between patients on CAPD and patients on APD [141, 142]. A single-center, retrospective study of 30 children treated with CAPD or APD showed a better preservation of RRF in CAPD patients whose primary renal disease was a glomerulopathy or a familial or hereditary renal disease [143].

The PD prescription should be aimed to preserve RRF as long as possible, by gradually increasing the dialysis dose in steps, accurately targeting UF rate to maintain the patient's dry BW, and using the lowest possible dialysate glucose concentration required to achieve the desired UF volume [45, 140]. Loop diuretics can be used to increase urinary water and salt excretion without detriment to renal function in the peritoneal dialysis patient [144].

Efforts to preserve RRF also involve the prevention of such nephrotoxic insults as the following [45]:

- Exposure to nephrotoxic medications; in particular, aminoglycoside antibiotics should be employed in the treatment of PD-related peritonitis only when taking into account their

nephrotoxicity, as well as ototoxicity and vestibular toxicity.
- Exposure to radiocontrast agents.
- Extracellular fluid volume depletion.
- Urinary tract obstruction and infection.

The use of angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB) to preserve RRF has been studied in adult patients on chronic PD [145, 146]. A systematic review and meta-analysis of randomized controlled trials on this issue showed that there are only limited data supporting the efficacy of these medications in slowing the decline of RRF [147]. Experience on the effect of these agents on RRF in children on chronic dialysis is still limited; while this issue is worth investigating further, close monitoring for the occurrence of hyperkalemia is recommended, especially in anuric patients in whom peritoneal potassium excretion may be adversely affected [148] and if dual blockade is employed [149].

In summary, interventions that may contribute to the preservation of RRF in the course of chronic PD treatment should be adopted whenever possible [45]. At the same time, RRF should be routinely measured by means of an accurate 24-h urine collection, and PD prescription should be adjusted accordingly and in a timely fashion, in order to prevent inadequate treatment.

Clinical Evaluation of PD Treatment Adequacy

Large-scale, prospective outcome studies in children treated with chronic PD are lacking owing to the small number of patients per center, the relatively short period of time on dialysis prior to renal transplantation, and the, fortunately, low patient mortality rate. Nevertheless, some pediatric studies have effectively addressed the issue of the correlation between PD dose and selected clinical aspects.

Growth is a potentially valuable outcome measure specific to pediatrics and can be used to evaluate the efficacy of PD depuration. Multivariate analysis of the data of a multicenter study [55] showed a weak positive correlation of height standard deviation score (SDS) with dialytic creatinine clearance and a negative correlation with peritoneal transport status, since children with high transport on PET had a lower change in height SDS. Accelerated height velocity was reported in 62% of the patients who met or exceeded DOQI target clearances [150]. Chada et al. [136] suggest that growth correlates with renal solute clearance but not with peritoneal clearance. Similar to adult studies, these data may confirm that peritoneal and residual renal small solute clearances are not equivalent. IPPN data showed that among children who initiated chronic PD at <24 months of age, length SDS, adjusted for age and length at study entry, age at PD start, and region of residence did not change significantly with time; however, growth was significantly better in patients receiving biocompatible PD fluid and in those receiving rhGH for at least 6 months [151].

Nutrition is an issue of particular interest in pediatric PD, since it can significantly affect growth and development of children. Children on CPD commonly suffer from protein and calorie malnutrition with loss of muscle mass and protein stores, and this condition is associated with increased morbidity and mortality [152]. Compared with normal healthy children, pediatric patients receiving chronic PD have significantly lower energy intake, as well as diminished height, weight, triceps skinfold thickness, and mid-arm muscle circumference [152, 153]. In these patients, dietary protein intake is inconsistently correlated with delivered Kt/V_{urea} [154–156]. However, the relationship between Kt/V_{urea} and the normalized protein equivalent of nitrogen appearance (nPNA) has often been criticized as merely being the result of mathematical coupling [157]. Finally, a higher Kt/V_{urea} was associated with a lower serum albumin level in children, suggesting that enhancing PD dose may reach a point of no further benefit (i.e., a Kt/V_{urea} value of more than 2.75/week), owing to an increased loss of albumin in the peritoneal effluents [158].

A study of 18 children on PD showed that increasing weekly Kt/V_{urea} and CrCl was positively correlated with cardiac function and

inversely with left ventricular mass [159]. In an already mentioned study on the assessment of cardiovascular risk conducted in 59 pediatric PD patients, Kt/V_{urea} was a significant predictor of carotid intima-media thickness [138].

Monitoring PD Adequacy in the Clinical Setting

Regular assessment of the delivered dialysis dose can be performed following the NKF-DOQI clinical practice guidelines [45], with some adaptations to specific problems of childhood, and the European guidelines on adequacy of the pediatric PD prescription [42]. This assessment is fundamentally based on the direct measurement of dialytic and renal clearance, through a 24-h collection of dialysate and urine. For practical reasons, peritoneal and renal clearance can be added to determine total clearance, even if they have a different impact on patient's outcome. All dialysate discharged during 24 h should be accurately collected, including the daytime exchange(s) if present, total volume precisely measured, and a sample obtained after mixing effluent thoroughly. The same attention should be paid to performance of a complete 24-h urine collection. Urine collection requires a preservative, such as thymol, to be added to the collection or refrigeration to inhibit the growth of bacteria that can degrade urea; dialysate does not require refrigeration or preservative.

Weekly peritoneal Kt/V_{urea} can be calculated with the following formula [160]:

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

where D/P represents the dialysate-to-plasma urea concentration ratio and V the distribution volume of urea that is assumed to equal TBW, which can be calculated from the already reported formulas [115].

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

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

CrCl calculation is normalized to BSA, which can be calculated from weight and height by the the use of the Gehan and George formula [161]:

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

The following formula can be employed to calculate dialytic CrCl per week [160]:

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

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

$$\text{Solute clearance}\left(\text{mL/min}\right) = \frac{\left(24-\text{h urine Volume in mL} \times \text{urine solute concentration}\right)}{\left(1440\,\text{min/day} \times \text{serum solute concentration}\right)}$$

This calculation is then normalized to patient's BSA.

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

lent of nitrogen appearance (nPNA), taking dialysate protein losses into account.

Body composition of children on PD can be evaluated by means of bioelectrical impedance analysis (BIA). Specific equations to predict fat-free mass (FFM) and TBW from BIA data have been provided and are as follows [162]:

$$\mathrm{FFM}\left[\mathrm{kg}\right] = 0.65 \times \left(\mathrm{height}^2 / \mathrm{impedance}\right)\left[\mathrm{ohms}/\mathrm{cm}^2\right] + 0.68 \times \mathrm{age}\left(\mathrm{years}\right) + 0.15$$

$$\mathrm{TBW}\left[\mathrm{L}\right] = 0.144 \times \left(\mathrm{impedance} / \mathrm{height}^2\right)\left[\mathrm{ohms}/\mathrm{cm}^2\right] + 40 \times \mathrm{weight}\left[\mathrm{kg}\right] + 1.99.$$

The first measurement of PD dose can be obtained as early as 1 week after the patient is stabilized on a defined PD prescription. Subsequently, PD dose measurements can be completed every 3 months and in the event of any significant change in clinical status and/or in the amount of residual diuresis. A PET can be performed 1 month after chronic PD initiation and then repeated every 12 months or earlier in case of unexpected changes in delivered PD dose or if any clinical condition that could permanently affect the peritoneal transport properties occurs, such as recurrent or persistent peritonitis.

In the clinical setting, routine clinical and biochemical outcome evaluations in pediatric patients on stable chronic PD can be organized according to the following timetable.

Every Month
- Clinical and physical examination
- Height/length
- Weight
- Head circumference (in infants and toddlers)
- Blood pressure
- Blood urea nitrogen and creatinine
- Sodium, potassium, acid-base status
- Hemoglobin/hematocrit
- Serum albumin, serum calcium, phosphorus, and magnesium
- Daily urine volume and UF

Every 3 Months
- Serum ferritin
- Serum iron
- Total iron binding capacity
- Alkaline phosphatase
- Parathyroid hormone
- 25-Hydroxyvitamin D
- Kt/V_{urea} and CrCl from a 24-h dialysate and urine collection

Every 12 Months
- Ambulatory blood pressure monitoring
- Echocardiography
- Hand and wrist x-ray for bone age
- Neurodevelopment assessment (every 6 months in children <2 years of age)
- Peritoneal equilibration test

In the course of PD treatment, attention should be paid by the patient's parents, dialysis nurses, and physicians to potential manifestations of inadequate dialysis. In practice, the signs and/or symptoms that should be regularly recorded and evaluated are the following:

- Clinical manifestations of overt uremia (uremic pericarditis, pleuritis)
- Clinical and/or biochemical signs of malnutrition
- Hypertension/hypervolemia
- Hyperkalemic episodes
- Hyperphosphatemia and/or excessive calcium times phosphorus product
- Kt/V_{urea} and/or CrCl values below the minimal recommended targets
- Clues of patient and family noncompliance.

It should be stressed again that numerical targets of small solute removal must be interpreted cautiously and in the context of patient clinical assessment; failure to reach these targets should be regarded as a warning sign for treatment failure, requiring careful reevaluation of each constituent of the therapeutic program. The contribution of RRF to the adequacy of PD treat-

ment is extremely important and tends to deteriorate with time on chronic dialysis, albeit at a slower rate in PD than in HD patients. Therefore, RRF should be regularly measured, although this may be difficult to do accurately in young children, requiring good cooperation by caregivers. While RRF is declining, adaptation of the PD prescription by increasing dialysis should be performed in a timely manner in order to anticipate and prevent the occurrence of the abovementioned signs and/or symptoms of inadequate treatment.

Machines for Automated Peritoneal Dialysis

The rapid evolution that APD has experienced has been closely linked to the development of new automatic machines, which are referred to as cyclers, which have been also adapted for pediatric needs.

Characteristics of Cyclers for Automated Peritoneal Dialysis

Advances in the fields of electronics and computer technology generated substantial modifications of the old cyclers employed for high-flow intermittent PD (IPD), to machines that are now smaller, lighter, more user-friendly, less expensive, and increasingly reliable. Since APD is performed by the patient or caregiver at home, the most important requirements that cyclers should fulfill are the following:

- Small size, light weight, and easy portability, which have been obtained by means of component miniaturization
- Simple interface with unequivocal messages and/or symbols (touch screen)
- Safe, accurate, and reliable functioning in the patient's home setting

Patient satisfaction should therefore be one of the leading design criteria for an APD machine [163]. At the same time, the technology incorporated in the cycler should be so advanced as to allow one to:

- Individualize the dialytic prescription.
- Measure the delivered dialysis dose and net UF.
- Monitor patient adherence to the prescribed treatment schedule.
- Detect excessive IPP.
- Detect peritoneal catheter malfunction.
- Fulfill the basic requirements of safety according to local and global standards.

Moreover, the overall cost of treatment must be contained, although proportionate to the expected level of patient well-being and rehabilitation.

Some of the technical options incorporated in modern cyclers for APD are:

- Online warming of dialysate.
- Pressure monitors to assess IPP.
- Gravity-assisted roller or diaphragm pumps to infuse and/or drain the dialysate; the pumps do not operate directly on the peritoneal cavity but on the heater and drain bag.
- Cassette receptacles for the tubing set, to simplify the procedure and minimize operator errors and risk of contamination, thus facilitating a quick and safe connection.
- Bar code readers to match the prescription with the PD solution selected by the patient.
- Automated connecting devices to facilitate the connection between the bags and the tubing manifold.
- Ad hoc connectors to perform one exchange of dialysate during the day.
- Newer generations of cyclers are incorporating voice-led instructions for ease of training and improved caregiver troubleshooting at home. Furthermore, there is a significant potential for integration of cycler data to the electronic medical record (see "Registration and Transmission of Treatment Data") with current advances in cycler technology.

The machine interface is typically characterized by an easy and clear display with unequivo-

cal messages, through which trained personnel and patients can easily set up the prescribed dialysis schedule. Usually, there are various levels of access to code protected programs so that scheduled changes can be programmed only by the operator. The access to the prescription and control level of the cycler is usually protected by a password that is known only by authorized personnel, while data of the ongoing treatment can be easily visualized on the display of the cycler.

The miniaturization of most components allows full portability by means of both reduced dimension and light weight.

In particular, cyclers to be used for the treatment of children should have a specific pediatric mode designed to:

- Accurately deliver even a small volume of dialysate (as low as 60 ml per exchange in the newer cyclers), with the possibility of very small increments.
- Have a low recirculation volume set (20 mL or less) for low fill volume PD regimens.
- Allow peritoneal effluent inflow and drainage at low flow rates and pressure, which can be physiological for infants and small children, without alarming (low fill volume mode).
- Allow programming of individualized minimum drain volume and minimum drain time for each patient, according to the desired PD schedule and peritoneal catheter function. The factory default setting of the patient fill volume can be adopted initially; then, an individualized, optimal drain percentage should be determined. Attention should be paid that if the minimum drain volume percentage is set too low, an incomplete drain could result, and this could lead to an overfill of solution that in some circumstances may cause injury to the patient. On the contrary, if the minimum drain volume percentage is set too high, an increased number of alarms and a loss of dwell time could result. Usually, a nontidal drain phase ends, and the system moves on to the next fill when a minimum volume has been drained, a minimum drain time has elapsed, and the system has determined the patient to be empty.

In general, the ideal cycler for APD should be able not only to perform all treatment schedules in an accurate and safe way but also to optimize the performance of the selected PD regimen [164]. Future directions may enhance cycler development to utilize machine learning – taking the recorded treatment information to suggest, or even automatically attempt, an improved regimen. Examples of such self-programming of the cycler are the following:

- Dialysate inflow and outflow time could be adjusted on the basis of the flow rate that has been registered during the previous exchange.
- Online detection of net UF, related to fluid osmolarity, dwell time, and fill volume, could serve as the basis for an automatic feedback on the PD fluid composition in the following cycle (profiling of glucose concentration throughout the dialysis session). Bedsides production of dialysis solution could individualize PD treatment with respect to osmotic agent, buffer, sodium, and calcium contents [164].

Registration of Treatment Data

The introduction of microchips and computer technology has led to greater programming flexibility of the cyclers, as well as to the possibility of recording on an electronic device the patient's prescription, medical history, and treatment events. This system provides information on the home dialysis treatment and a means of monitoring patient compliance. This also provides a patient-specific database of therapy information. The cycler system includes a data card (memory card) which can store up to 60–90 days of actual treatment data. This database of therapy information can be downloaded from the memory card of the cycler when the patient goes to the dialysis unit for a visit or can be retrieved remotely as needed.

One example of the potential utilization of this recording system is the evaluation of peritoneal catheter functioning. The pattern of the peritoneal catheter's flow during each treatment cycle can be

analyzed with the help of graphs and charts and any catheter malfunction detected even if it has not yet caused cycler alarms or clinical symptoms. The PD prescription can be adapted to the drainage profile of each individual patient's catheter, thus minimizing the fill and drain dead times and the occurrence of minimum drain volume alarms. An application of this adaptation process is represented by optimization of tidal volume to the individual drainage profile, which eliminates the flow rate drop occurring beyond the so-called breakpoint of the drainage curve [97].

The recording of a PD session may also reveal an excessive incidence of cycler alarms during the nightly treatment, resulting in sleep deprivation and an impairment of the quality of life to both patient and caregiver [165]. Tube kinking and catheter malfunction are the most frequent causes of drain alarms. In some cases, unsuitable setting of alarm limits (e.g., the default adult settings of the cycler – such as low drain – may not be appropriate for a small pediatric patient) may generate the occurrence of an excessive number of useless and disturbing alarms.

The memory card of the cycler can be reprogrammed by the physician or the dialysis nurse to address patient prescription changes; when the patient inserts the card back into the cycler, all the settings are updated. Therefore, the use of these electronic devices eliminates the need for patients to program and manually record APD treatment data, thus shortening the training time and simplifying data collection and management by the dialysis team.

Transmission of Treatment Data

The possibility of a remote Internet connection between the home cycler and the dialysis unit makes the so-called teledialysis possible. APD treatment data can be visualized and monitored by the staff in the dialysis unit online (while the treatment is being administered at a patient's home) or offline in the morning after the end of the night APD session. Alternatively, data can be transferred electronically from the cycler's memory card to the personal computer of the dialysis unit on a regular basis (e.g., every 7–10 days). This provides ease of data review should there be any concerns observed by the patient or the caregiver related to cycler function or peritoneal catheter function. Information stored in the file of each patient should be examined and evaluated by the physician and dialysis nurse on a routine basis. Data can be organized in charts and graphs and statistically elaborated. Recently, a two-way technology has become available that allows for remote data monitoring and therapy adjustment from the dialysis unit – specifically, this provides a cost-effective opportunity to change a patient's PD prescription setting remotely [166]. Integration of advanced technology allows for early detection of therapy problems and provides the opportunity to facilitate APD prescription changes that may help reduce the need for hospitalization [167]. Furthermore, technology-based integration with dialysis teams and families may also reduce the feeling of isolation and detachment that the patient and family may experience in the course of long-term home PD, especially should they live a significant distance from the dialysis center.

There is limited data on the use of telemedicine in the pediatric PD program setting; however, one study [165] did demonstrate that the so-called telePD allowed timely identification of clinical and psychosocial problems and increased patient and family satisfaction with home PD treatment. Such problems were represented, for instance, by an imperceptible but progressive decrease of UF rate or by a prolongation of the drainage phase due to catheter malfunction that is still too small to release cycler alarms. A teledialysis system can also be integrated by videoconferencing equipment (digital camera; ISDN [Integrated Services Digital Network] line) to give private videoconferencing and video capture of images; thus, the dialysis and the exit site care procedure can be followed by the dialysis center server or by the physician's personal computer [168, 169]. Contrasting data on the use of telecare in a pediatric program suggested that the employed videophone equipment showed technical limitations and was not cost-effective [170]; therefore, this technology deserves further evaluation in pediatric home PD.

Monitoring of Patient Adherence to the Prescribed APD Treatment

Nonadherence is an important obstacle to achieving adequate PD therapy and a significant cause of morbidity, patient hospitalization, and dialysis technique failure. In a pediatric single-center analysis, at least some degree of nonadherence to the prescribed PD regimen was reported in 45% of patients [171]. Several methods to assess patient adherence to the PD prescription have been proposed, based on comparison of measured versus predicted creatinine excretion [172], home visits to check dialysis solution supply inventories [173, 174], patient self-report confidential questionnaires [175], or the comparison of self-reports of compliance with the rate of predicted versus measured Kt/V_{urea} and CrCl [176]. Given that no single method is able to provide a complete assessment of nonadherence in patients on home PD, these assessments should be used in an integrated way.

The electronic data registration system of the cyclers for APD provides an objective means to monitor patient adherence to the prescribed treatment. Comparison of the prescribed versus the actually delivered therapy shows any change the patient and/or caregiver may have made in the prescribed dialysis schedule on his or her initiative. Most frequently reported changes in the setting of nonadherence made by the patients or caregivers include changing session length or fill volume [171, 175] but can include all of the following:

- Skipping treatment cycles
- Shortening overall treatment time
- Manually changing treatment parameters
- Bypassing therapy phases or cycles
- Reducing fill volume by performing manual drains

In summary, recording and transmitting PD session data through an electronic device on a regular basis can enhance patient adherence to PD prescriptions, since the awareness of the recording makes the patient feel more confident of treatment control and the doctor-patient communication more explicit. It also helps the dialysis staff understand the reasons for inadequate depuration and accordingly change the PD prescription.

Strategies to Enhance Patient Adherence to PD Prescriptions

An approach to increasing the compliance of patients and caregivers to the prescribed PD schedule should be considered an essential component of the prescription process and a key factor in achieving the expected therapeutic results. Effective strategies to increase compliance require a structured, comprehensive care model with a team-based focus including the patient, caregiver(s), and dialysis staff.

Patient- and family-targeted interventions are mainly based on their active involvement in the choice of dialysis modality and on their education to perform home dialysis treatment [177].

Patient selection should include the following action points:

- Early patient/family referral to dialysis staff
- Evaluation of patient's clinical needs and patient and family lifestyle
- Structured, unbiased information on the available dialysis modalities
- Evaluation of physical and psychological ability of the caregiver(s) to perform dialysis tasks
- Assessment of patient home environment

Patient and family preparation for home PD [178] should:

- Start well before dialysis initiation.
- Involve a multidisciplinary team including nephrologist, renal nurse, renal dietitian, psychologist, social worker, school teacher, and child life staff.
- Make use of appropriate written information and other teaching aids.
- Encourage contacts with similar-aged children on home dialysis.
- Include a home visit and a liaison with the nursery/school/college and the family doctor.

Training for home PD procedures should involve two family members and could potentially be completed in the home environment by dialysis units with a well-organized home training program.

Ultimate goals of patient and family education are:

- To achieve an adequate level of knowledge, understanding, and participation in the choice of PD modality and in the process of PD prescription
- To reduce patient and family anxiety and stress by increasing awareness of the disease process and treatment options
- To convince the patient and family of the appropriateness and beneficial effects of the prescribed treatment and that adherence to the prescription will improve the outcome

Once PD treatment has started, regular contact (telephone, electronically, and/or telehealth) and support for the family should be planned; moreover, acquired knowledge and skills of performing home PD should be assessed at regular intervals.

Dialysis staff-targeted interventions to address the issue of patient adherence should increase staff ability to:

- Individualize the PD prescription and evaluate results.
- Explain the reasons for prescription changes.
- Manage treatment complications as much as possible on an outpatient basis.
- Test and recognize signs of patient noncompliance.

Dialysis staff education about compliance should be monitored and regularly updated.

Conclusions

PD therapy has experienced a remarkable evolution during the past 30 years in parallel to the development of safe and simple-to-use connecting devices, more biocompatible dialysis materials and solutions, and automatic machines for PD delivery that utilize computerized technology for improved prescription accuracy. All of these achievements have provided dialysis staff valuable tools to improve the overall efficacy and tolerability of PD treatment in children.

For CAPD, the use of an integrated Y-set, double-bag system, with a disinfectant-containing cap and a "flush before fill" mode, has been associated with a reduction in the incidence of peritonitis episodes due to touch contamination and has simplified PD connecting maneuvers, thus shortening patient and partner training.

Individualizing the PD prescription is routinely performed by the characterization of PM transport capacity, assessed by means of well-standardized functional tests that have been validated in pediatric patients. Early controversy over the approach to prescribing fill volume has given way to generally accepted guidelines for scaling to BSA according to clinical tolerance and IPP measurement, in order to ensure maximal recruitment of peritoneal exchange area.

Fluid balance is increasingly recognized as a crucial aspect of PD patient management, as the efficiency of water and salt removal has been clearly associated with patient outcome, especially in anuric patients. UF failure is an important cause of PD abandonment with conversion to hemodialysis.

Prospective randomized trials of dialysis adequacy and observational studies in adult patients have confirmed that RRF is a much stronger predictor of patient survival than peritoneal clearance. The PD prescription should be aimed to preserve RRF as long as possible, by gradually increasing the dialysis dose in steps, accurately targeting UF rate to maintain the patient's dry BW, and using the lowest possible dialysate glucose concentration required to achieve the desired UF volume. Prevention of RRF loss also involves avoidance of nephrotoxic agents. The potential role of angiotensin-converting enzyme inhibitors and ARB requires further investigation in children on PD. As RRF declines over time, the PD prescription should be adjusted to its decline in a timely fashion to prevent the adverse effects of chronic fluid overload. The ultimate goal of PD

modality selection and prescription is to identify, and possibly achieve, the optimal PD dose for each individual patient; this can be regarded as determining the amount of dialysis above which the additional expected benefit does not justify the increase in the burden on patient and family and of financial costs.

The evolution of APD has been closely linked to advances in the technology incorporated in the new cyclers, which has made APD delivery safer and more efficient. While the currently available cyclers can monitor technical parameters, there remain limitations with current dialysis technology that limit real-time data transfer from the cycler to the primary team. Teledialysis may help increase patient and caregiver confidence in performing therapy at home and reduce the need for patient hospitalization, thus improving academic/psychosocial outcomes and patient compliance with therapy.

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